Is proteinuria a rare condition in apparently healthy and sick cats? A feline practice experience (2007–2018)

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Abstract

Background: Proteinuria is assumed to be less frequent in cats than in dogs and is mainly associated with chronic kidney disease (CKD).

Aim: The current study aimed to evaluate and compare urine protein-to-creatinine (UPC) values retrospectively in cats visited for comprehensive annual health check or for presenting systemic clinical signs related to CKD.

Methods: UPC ratio was retrospectively evaluated in 112 owned cats, out of which 51 (45.5%) were apparently healthy cats according to their owners who visited for comprehensive annual health checks and 61 (54.5%) sick cats, presenting systemic clinical signs suggesting CKD, such as weight loss or polyuria/polydipsia, among others.

Results: Based on UPC, the present study found that 54.5% of all cats included were borderline proteinuric or proteinuric, having increased UPC (UPC $\geq$ 0.2), with 35.7% included in the sick group and 18.7% in the health-check group. Increased UPC was also statistically associated with azotemia and isosthenuria (urinary-specific gravity between 1,008 and 1,035) in both sick and health-check groups of cats.

Conclusion: Independent of the reason for their medical visit, it could be concluded that borderline proteinuria and proteinuria were statistically mainly related to CKD in cats. Furthermore, the measurement of UPC could be very useful in the detection and management of CKD in apparently healthy cats during a medical visit for annual health check irrespective of the age.

Keywords: Annual health check, Kidney, Urine protein-to-creatinine ratio, UPC, Urinalysis.

Introduction

Proteinuria is defined as the presence of an excessive amount of proteins or abnormal proteins in the urine (Lees *et al*., 2005; Harley and Langston, 2012). Studies conducted in the past decade have shown that proteinuria is highly related to reduced survival in both azotemic and non-azotemic cats and dogs (Lees *et al*., 2005; Syme *et al*., 2006; King *et al*., 2007; Wehner *et al*., 2008; Jepson *et al*., 2009; Littman, 2011; Bartges, 2012).

Proteinuria in cats is less frequent than in dogs due to the different pathophysiology and predisposing causes of kidney disease (Harley and Langston, 2012; Roura *et al*., 2017; Rayhel *et al*., 2020), and in the absence of active urinary sediment, it is considered a marker of renal damage or dysfunction (Lees *et al*., 2005; Harley and Langston, 2012). Furthermore, unlike what happens to cats, many other potential causes of proteinuria have been described in dogs, such as infections, neoplasms, endocrinopathies, familial or aging (Herring *et al*., 2014; Lavoué *et al*., 2015; Marynissen *et al*., 2017;

Smith *et al*., 2017; Prudic *et al*., 2018; Purswell *et al*., 2020).

Chronic kidney disease (CKD) is one of the most common diseases in adult domestic cats (Marino *et al*., 2014; Brown *et al*., 2016; KuKanich *et al*., 2021), and the main pathological feature of feline CKD consists of chronic tubular interstitial nephritis (Lawson *et al*., 2015; McLeland *et al*., 2015; Rayhel *et al*., 2020). In this setting, proteinuria is mainly secondary to tubular damage, and its increase seems associated with CKD progression and usually correlates with interstitial fibrosis, although the exact mechanisms of injury are not clearly established (Syme *et al*., 2006; Chakrabarti *et al*., 2012; Brown *et al*., 2016; Lawson *et al*., 2018). Furthermore, it seems that there is a strong association between systolic hypertension and the magnitude of proteinuria in cats with CKD (Syme *et al*., 2006). This link could be very important because proteinuria is strongly associated with survival in cats with CKD or hypertension, and managing systolic hypertension could reduce proteinuria (Syme *et al*., 2006; Jepson *et al*., 2007; King *et al*., 2007).

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Therefore, renal proteinuria is diagnostic and, especially, a prognostic factor of CKD in cats proportionally related to the risk of renal disease progression and mortality (Lees *et al*., 2005; Syme *et al*., 2006; Chakrabarti *et al*., 2012; IRIS, 2019; Giraldi *et al*., 2020). These findings have led the International Renal Interest Society (IRIS) to propose proteinuria as relevant in staging cats with CKD to properly manage the progression of this disease (IRIS, 2019). Cats with urine protein-to-creatinine ratio (UPC) < 0.2 are classified as non-proteinuric, with UPC > 0.4 as proteinuric, and with UPC between 0.2 and 0.4 to be borderline proteinuric (Lees *et al*., 2005; IRIS, 2019). The current IRIS recommendation is the treatment of either borderline and proteinuric cats to reduce the progression of kidney disease (IRIS, 2019). As descendants of solitary animals, where hiding illness is important for survival, our domestic cats display minimal behavioral signs of disease (Horwitz and Rodan, 2018). Furthermore, owners are reticent to bring cats to the veterinarian to avoid them getting stressed, or relate that it is unnecessary given the lack of evident clinical signs (Diez *et al*., 2015; Gates *et al*., 2019). Based on the above, cats should benefit from annual health checks for early detection of diseases, such as kidney disease, especially when they are getting older and urine evaluation could be a useful test to accomplish this objective (Chakrabarti *et al*., 2012; Piech and Wycislo, 2019; Mösch *et al*., 2020; Pérez-Accino *et al*., 2020).

Although some original published studies have evaluated the presence of proteinuria in cats (Syme *et al*., 2006; King *et al*., 2007; Jepson *et al*., 2009; Paepe *et al*., 2013; Rayhel *et al*., 2020), information about proteinuria in cats with and without CKD is mostly based on reviews and expert opinions (Lees *et al*., 2005; Littman, 2011; Bartges, 2012; Harley and Langston, 2012; Sparkes *et al*., 2016; Roura *et al*., 2017; IRIS, 2019; Piech and Wycislo, 2019) in contrast with the information available in dogs (Jacob *et al*., 2005; Herring *et al*., 2014; Marynissen *et al*., 2017; Willems *et al*., 2017; Prudic *et al*., 2018; Gizzarelli *et al*., 2019; Purswell *et al*., 2020).

We hypothesized that the prevalence of proteinuria in cats considered healthy, based on owners' criteria at home evaluation, was higher than in previous studies and mainly associated with CKD. So, the present study aimed to evaluate and compare UPC values retrospectively in cats visiting for comprehensive annual health checks or for presenting systemic clinical signs related to CKD.

Materials and Methods

Study design
This was a retrospective, observational, cross-sectional study.

Case selection
Clinical records, where urinalysis and UPC measured by IDEXX Laboratories should be available, of owned cats visiting a feline practice between April 2007 and December 2018 for comprehensive annual health check or for presenting systemic clinical signs suggesting CKD were selected. After this first selection, for each case to be eligible for final inclusion in the study, a complete medical record including clinical history, signalment (age, sex, neuter status, body weight, and breed), data of physical examination, total blood count, serum biochemistry, complete urinalysis with inactive sediment, UPC and systolic blood pressure (SBP), and final diagnosis, should be available for review. Moreover, if available, other additional diagnostic investigations such as feline immunodeficiency virus (FIV) and feline leukemia virus tests, serum thyroid levels, or abdomen ultrasound were also evaluated.

Data handling and statistical analysis
Cats were subdivided into two groups for statistical analysis to evaluate UPC: health-check group, which included healthy cats according to their owners visiting for comprehensive annual health check; and sick group, which included cats visiting for presenting one or more of these systemic clinical signs suggesting underlying CKD, such as weight loss, anorexia, polyuria/polydipsia (PU/PD), depression, lethargy, vomiting, diarrhea, or blindness, among others.

After carefully evaluating previous comprehensive medical information, all cats were also divided into two additional groups, CKD group and non-CKD group, depending on the final diagnosis. IRIS CKD staging guidelines (IRIS, 2019) were followed in the CKD group for statistical analyses. Finally, to evaluate an age effect, all cats were also assigned to one of these groups: 0–2 years (junior), >2–10 years (mature), and >10 years (geriatric) (Vogt *et al*., 2010).

All cats were also classified as non-proteinuric (UPC < 0.2), borderline proteinuric (UPC 0.2–0.4) or proteinuric (UPC > 0.4); increased UPC was considered when cats had values of UPC ≥ 0.2. Finally, systemic hypertension was considered when SBP measurement was 160 mmHg or higher.

Statistical analysis was conducted in R (R Core Team, 2014), and figures were generated using the package ggplot2 (Wickham, 2009). The level of significance was set at $p < 0.05$. If not normally distributed data were expressed as median (range). The relationship between continuous variables has been studied by the non-parametric approach of calculating the Spearman's rank correlation coefficient. Pearson's chi-squared test was used to examine the relationship between the presence of clinical signs and proteinuria classification. Wilcoxon signed-rank test was also used to test associations between the presence of clinical signs and UPC.

Results

During the study period, a total of 2,391 cats visited the feline practice. Of those, 403 had a complete urinalysis and UPC identified through the clinical record database

search, and 112 cats finally met the eligibility criteria. Reasons for exclusion were incomplete clinical records and active urinary sediment in 239 and 52 cats, respectively (Fig. 1).

51 out of 112 (45.5%) cats were included in the health-check group and 61/112 (54.5%) in the sick group. Furthermore, 82/112 (73.2%) cats had CKD as a final diagnosis following the IRIS guidelines, 37/51 (72.5%) in the health-check group, and 45/61 (73.7%) in the sick group. Inside the health-check group, 2/37 (5.4%) were classified as IRIS stage 1, 24/37 (64.9%) as IRIS stage 2, 11/37 (29.7%) as IRIS stage 3, and none as IRIS stage 4. Instead, within the sick group, 3/45 (6.7%) were classified as IRIS stage 1, 15/45 (33.3%)

as IRIS stage 2, 12/45 (26.7%) as IRIS stage 3, and 15/45 (33.3%) as IRIS stage 4 (Fig. 1).

Based on UPC values of all cats (Fig. 2), 51/112 (45.5%) were non-proteinuric, 24/112 (21.4%) were borderline proteinuric, and 37/112 (33.1%) were proteinuric. A UPC $\geq$ 0.2, defined previously as increased UPC, was statistically associated with cats belonging to the sick (p = 0.026) and CKD (p = 0.014) groups. Among the 61/112 (54.5%) cats with increased UPC, 48/61 (78.6%) were finally diagnosed with CKD. Furthermore, all cats diagnosed with CKD had an increased UPC (p = 0.014). However, four cats had proteinuria without increased creatinine, although the final diagnosis was hyperthyroidism in two cats of the health-check group
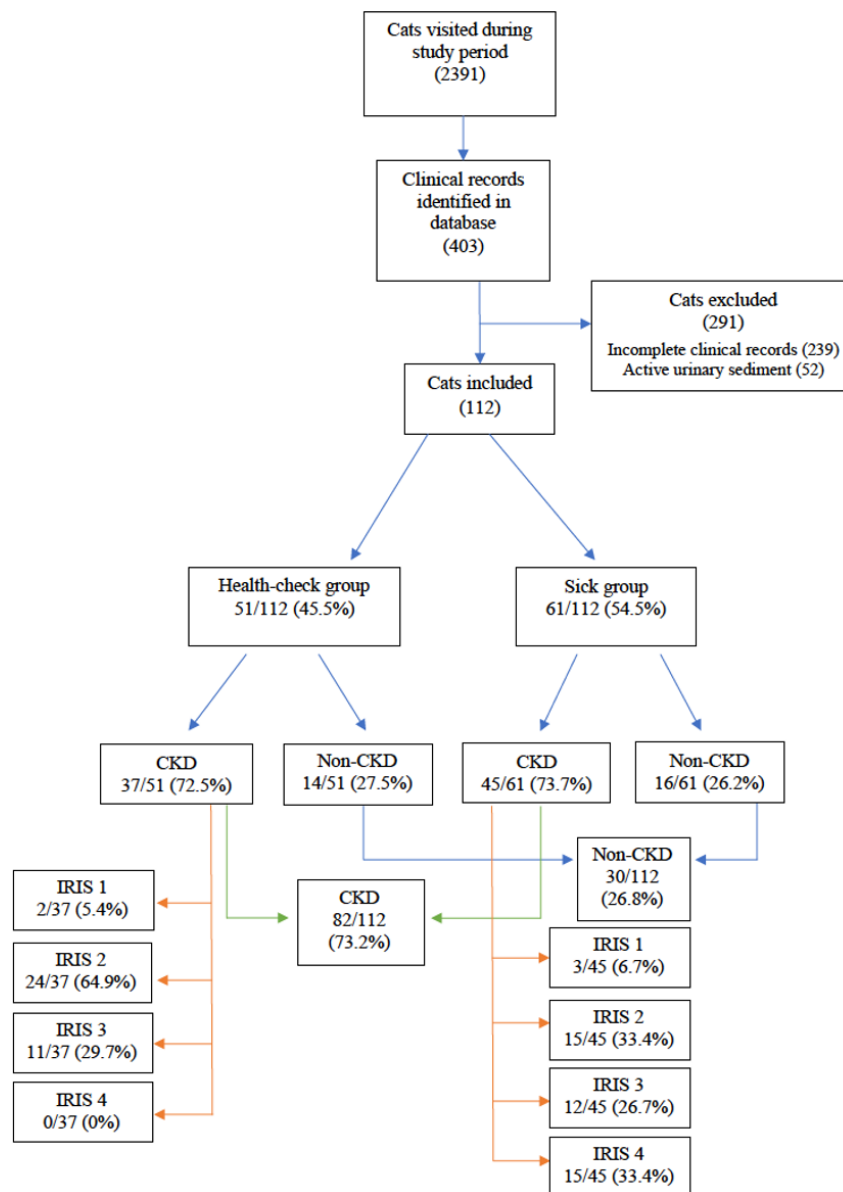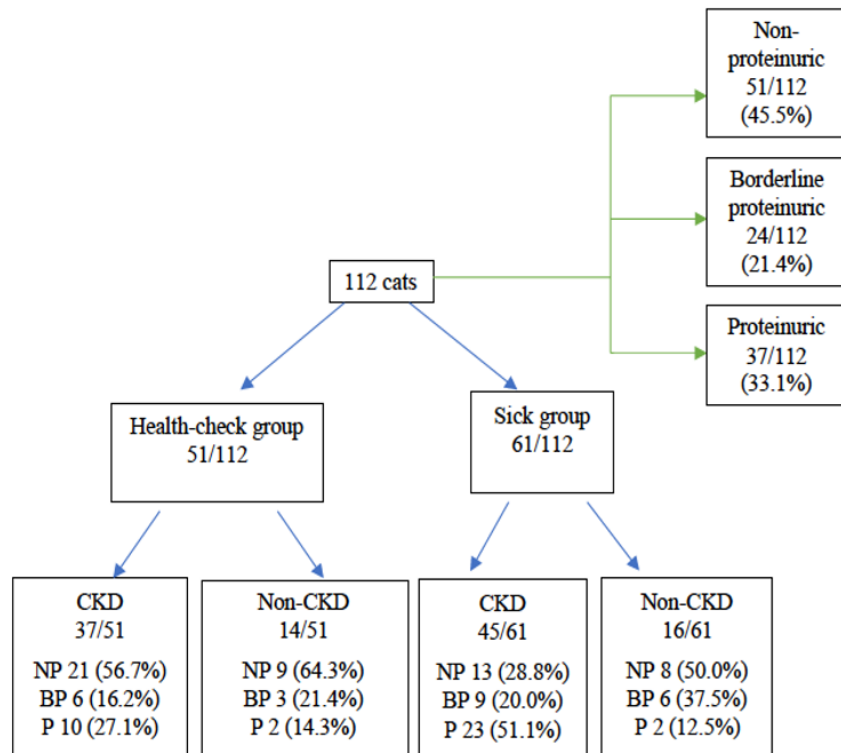

Fig. 1. Flow chart of all cats included in this study.

Fig. 2. Flow chart of UPC values of all cats included in this study. NP: non-proteinuric; BP: borderline proteinuric; P: proteinuric.

Table 1. UPC results in proteinuric cats included in this study.

Group		N	Median
Proteinuric cats		37	0.86 (0.50–3.43)
Health check	CKD	10	0.77 (0.51–3.43)
	Non-CKD	2	0.51 (0.50–0.52)
Sick	CKD	23	0.9 (0.45–2.38)
	Non-CKD	2	2.25 (2.20–2.31)

and FIV in the other two of the sick group. UPC values of all cats with proteinuria are described in Table 1.

The signalment of the enrolled cats is summarized in Table 2. In the health-check group, neither body weight ($p = 0.081$), age ($p = 0.385$) and sex ($p = 0.580$) were statistically associated with proteinuria. In the sick group, lower body weight ($p = 0.049$) was associated with proteinuria. No other statistical associations were found with age ($p = 0.176$) or sex ($p = 0.321$). Breed data were insufficient to draw conclusions.

Systemic clinical signs suggestive of CKD described in the sick group were vomiting (23, 37.7%), weight loss (20, 32.8%), anorexia (18, 29.5%), depression or lethargy (13, 21.3%), PU/PD (12, 19.7%), diarrhea (2, 3.3%), excessive vocalization (1, 1.6%), blindness (1, 1.6%), and dyspnea (1, 1.6%). Proteinuric cats

from the sick group presented the highest frequencies of all clinical signs: vomiting, lethargy, and PU/PD compared to the NP and BP cats of the sick group (Table 3). However, no statistical association was found between any specific systemic clinical sign and grade of proteinuria.

When clinicopathological alterations were evaluated in the health-check group, increased UPC was associated with higher values of creatinine ($p = 0.037$) and urea ($p = 0.009$) and lower values of urinary-specific gravity (USG) ($p = 0.018$) but did not show any statistical association with packed cell volume (PCV), potassium, phosphorous, albumin, or total protein ($p > 0.05$). Whereas in the sick group, increased UPC was associated with higher values of creatinine ($p = 0.046$), urea ($p = 0.009$), and phosphorous ($p = 0.049$), and with

Table 2. Signalment of the 112 cats included in this study.

Group	Age	Breed			Sex			Weight
		Pedigree	DLH	DSH	Male (entire)	Female (entire)		
NP (51)	9 years (1 years–17 years)	4 Siamese 2 Russian blue 1 Birman 1 Exotic 1 Siberian Forest 1 Norwegian Forest	0	41	29 (1)	22 (1)		4.5 kg (2.2–9.5)
BP (24)	9.5 years (1 years–18 years)	2 Siamese 1 Sphynx 1 Persian	1	19	8 (2)	16 (1)		3.4 kg (2.2–7.5)
P (37)	8 years (4 months–17 years)	7 Persian 3 Siamese	0	27	26 (5)	11 (2)		3.3 kg (1.2–6.6)

Age and weight data are expressed as median (range). DLH: domestic long hair; DSH: domestic short hair; NP: non-proteinuric; BP: borderline proteinuric; P: proteinuric.

Table 3. Clinical signs described in cats of sick group.

Clinical signs	Cats of sick group N	%	NP N	%	BP N	%	P N	%
Vomiting	23	37.7	9	39.1	5	21.7	9	39.1
Weight loss	20	32.8	4	20.0	8	40.0	8	40.0
Anorexia	18	29.5	3	16.7	7	38.9	8	44.4
Depression or lethargy	13	21.3	3	23.1	3	23.1	7	53.8
PU/PD	12	19.7	5	41.6	1	8.3	6	50.0
Diarrhea	2	3.3	0	0.0	1	50.0	1	50.0
Blindness	1	1.6	1	100.0	0	0.0	0	0.0
Excessive vocalization	1	1.6	0	0.0	0	0.0	1	100.0
Dyspnea	1	1.6	1	100.0	0	0.0	0	0.0

lower values of potassium ($p = 0.008$) and USG ($p = 0.018$), but did not show any statistical association with PCV, albumin, or total protein ($p > 0.05$).

15 out of 112 (13.4%) cats had hypertension (SBP $\geq$ 160 mmHg). Cats with hypertension had increased UPC compared with those without hypertension, and this difference was statistically significant ($p = 0.029$). 13 out of these 15 (86.6%) cats were finally diagnosed with CKD, and the other 2 cats were diagnosed with hyperthyroidism. To finalize the results, ultrasound alterations were found in 43 out of all cats (38.4%), but there was no statistical association between the presence of abnormalities and proteinuria ($p = 0.63$) (Table 4).

Discussion

The present study showed a high prevalence of proteinuria in apparently healthy cats according to their owners visited for a comprehensive annual health check. CKD was highly correlated with borderline proteinuria and proteinuria in cats.

This increased UPC (UPC $\geq$ 0.2) was associated with CKD in 78.6% of cats included, similar to the results recently published (Fidalgo *et al.*, 2020). Moreover, 43.3% of the cats visited during the study period as part of annual health check were diagnosed with CKD and increased UPC. Finally, the majority of cats (86.7%) included in the present study had proteinuria with UPC

Table 4. Kidney alterations revealed by abdominal ultrasound.

Ultrasound kidney alterations	N (43/112)	%
Poor corticomedullary definition	22/43	19.6
Nephrolithiasis	5/43	4.4
Irregular shape	9/43	8.0
Enlarged size	2/43	1.8
Decreased size	2/43	1.8
Pelvis dilatation	12/43	10.7
Hydronephrosis	1/43	0.9
Fluid-filled cysts	4/43	3.5

< 1.0, which is compatible with previously published data, suggesting that the main disease process occurring in the majority of these cats is chronic tubulointerstitial fibrosis rather than a primary glomerular disease (Lees *et al*., 2005; Syme *et al*., 2006). All this together points out the utility of UPC measurements in routine health check to evaluate the presence of CKD in cats without evident clinical signs according to their owners.

Furthermore, the present study found that 54.5% of cats included had an increased UPC, with 35.7% included in the sick group and 18.7% in the health-check group. These interesting results were similar to a previous feline report where 34% of sick cats and 18% of healthy cats were proteinuric (Al-Ghazlat *et al*., 2011). However, a more recent study reported that 72.7% of healthy cats analyzed were non-proteinuric, higher than the 45.5% found in the present study (Paepe *et al*., 2013). This fact could be explained because 27.5% of cats included in the healthy group, according to their owners, visited for comprehensive annual health check were finally diagnosed with CKD. The results presented here point out the importance of the urinalysis with UPC measurement in annual health check for the evaluation of chronic diseases, such as kidney disease (Chakrabarti *et al*., 2012; Piech and Wycislo, 2019). This could be important in cats due to the limitation of owners to detect subtle or even evident signs of illness in cats (Diez *et al*., 2015; Horwitz and Rodan, 2018; Gates *et al*., 2019). Furthermore, this could be especially determinant due to mild clinical signs displayed by cats with early stages of CKD such as IRIS stages 1, 2, and early 3 that were the majority in the health-check group (IRIS, 2019).

Proteinuria in cats has been associated with aging, suggesting its monitoring in geriatric cats (Paepe *et al*., 2013). However, the present study did not show this association in accordance with other previous studies (Syme *et al*., 2006). Moreover, lower weight was associated with increased UPC in the sick group, but this was not found in the health-check group. Thus, weight loss could probably be associated with the illness found in these cats, the majority with CKD,

instead of the increased UPC. Accordingly, lower body weight has been previously associated with azotemic cats (Lamb *et al*., 2017).

Increased UPC was also associated with higher creatinine values in both sick and health-check groups. This association has been previously reported in cats and can be explained by the hemodynamic consequences of declining renal function, with afferent arteriolar vasodilation, resulting in increased glomerular capillary pressure (Lees *et al*., 2005; Syme *et al*., 2006; King *et al*., 2007; Jepson *et al*., 2009; Littman, 2011). As renal function declines, the decreased number of functioning tubules is less able to reabsorb and degrade filtered protein, resulting in more intact protein molecules present in urine (Lees *et al*., 2005; Syme *et al*., 2006; King *et al*., 2007; Jepson *et al*., 2009; Littman, 2011). Moreover, in the present study, higher urea and lower USG values were associated with increased UPC in both groups, which supports the relationship between the reduction in renal function with an increased UPC. In the sick group, increased UPC was also associated with higher phosphorous and lower potassium values that could also be related to more advanced CKD IRIS stages. The present study found that hypertension was also associated with increased UPC, similarly to previously published data (Syme *et al*., 2006; Chakrabarti *et al*., 2013). However, this study just found that 15.8% of cats with CKD had hypertension, although several studies previously reported a very variable but higher prevalence of hypertension in cats with CKD, ranging from 19% to 61% (Kobayashi *et al*., 1990; Syme *et al*., 2002; Bijsmans *et al*., 2015). The lack of uniform measurement techniques, variable inclusion criteria, and inconsistent thresholds for establishing a diagnosis of hypertension in veterinary medicine could have made prevalence data difficult to interpret. However, in the present study, most of the cats were CKD IRIS stages 1 and 2, so it could explain this low prevalence of hypertension. It was previously described that the frequency of hypertension increased with an increase in the CKD IRIS stage (Hori *et al*., 2018).

Kidney ultrasound alterations such as perinephric fluid, small kidneys, hyperechoic renal cortex, loss of corticomedullary differentiation, renal calculi, and

dilated renal pelvis have been statistically associated with azotemia in cats similar to previously published study (Lamb *et al*., 2017). Furthermore, loss of corticomedullary differentiation (19.6%) and dilated renal pelvis (10.7%) were the most common ultrasound findings in the present study. However, no significant association was found between increased UPC and ultrasound alterations. A possible explanation could be that ultrasonography was recommended for the investigation of individual cats with CKD but was not recommended as a screening test for proteinuria or azotemia, probably because renal ultrasound alterations have low sensitivity and specificity for an early diagnosis of kidney disease (Sparkes *et al*., 2016; Lamb *et al*., 2017).

This study has several limitations that could produce information and selection biases. First, data were collected retrospectively, as a consequence, the authors were reliant upon the history taken at the time of presentation. Second, lack of homogeneous population and missing data for treatment applied or cause of death was also present. Finally, serum symmetric dimethylarginine was not carried out in all the cats included in this study, so it is possible that some cats had already CKD even without other markers of CKD such as an increased creatinine or lower USG.

Conclusion

The present study pointed out that proteinuria was a frequent condition in cats considered healthy and without overt clinical signs suggestive of CKD. Furthermore, UPC $\geq$ 0.2 was mainly only related to CKD in cats. Nevertheless, the results of this study were suggestive that urinalysis and UPC measurement could be warranted in the early detection and management of CKD in apparently healthy cats, irrespective of their age, during the medical visits for annual health check.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

All authors contributed to making the completion of this manuscript possible. Valentina Aybar and Juanjo Vega obtained all data and review inclusion criteria for analyses and review the paper; Alejandro Jiménez analyzed the data; Eduard Hernando and Anna Vila analyzed the data and review the paper; María C. López wrote the paper and analyzed the data; Xavier Roura and Andrea Zatelli designed the study, supervised the data, and reviewed the paper.

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