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Clinical importance of borderline proteinuria in nonazotemic cats and evaluation of other risk factors for the development of chronic kidney disease

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Abstract

Background: Borderline proteinuria is associated with decreased survival in cats with azotemic chronic kidney disease (CKD).

Objectives: Determine the clinical importance of borderline proteinuria in nonazotemic cats.

Animals: A total of 201 healthy client-owned cats ≥7 years of age; 150 nonproteinuric (urinary protein : creatinine ratio [UPC] <0.2) and 51 borderline proteinuric (UPC 0.2-0.4).

Methods: Prospective study. Cats were thoroughly screened and subsequently examined every 6 months for 2 years. Kaplan-Meier curves were compared between nonproteinuric and borderline proteinuric cats. Univariable and multivariable Cox models were fit to determine the relationship between development of renal disease and potential risk factors such as age, sex, breed, weight, dental disease, blood pressure, serum creatinine concentration (sCrea), serum symmetric dimethylarginine concentration (sSDMA), blood urea nitrogen concentration, urine specific gravity (USG), and UPC.

Results: Significantly more cats with borderline proteinuria at inclusion developed renal disease (International Renal Interest Society [IRIS] ≥ stage 2 CKD or renal proteinuria; log-rank $P = .004$) or died (log-rank $P = .02$) within 2 years, compared with nonproteinuric cats. In the multivariate analysis, IRIS stage 1 CKD (persistent USG <1.035 or sSDMA >14 µg/dL; hazard ratio [HR], 4.2; 95% confidence interval [CI], 2.0-8.8; $P < .001$), sCrea ≥1.6 mg/dL (≥140 µmol/L; HR, 2.6; 95% CI, 1.1-6.4; $P = .04$), borderline proteinuria (HR, 2.5; 95% CI, 1.2-5.2; $P = .01$), and age at inclusion (HR, 1.3; 95% CI, 1.2-1.5; $P < .001$) were significantly associated with diagnosis of renal disease 6 months later.

Abbreviations: ACVIM, American College of Veterinary Internal Medicine; BUN, blood urea nitrogen concentration; CI, confidence interval; CKD, chronic kidney disease; DLH, Domestic Longhair; DSH, Domestic Shorthair; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; GFR, glomerular filtration rate; HR, hazard ratio; IRIS, International Renal Interest Society; pCrea, plasma creatinine concentration; RCV, reference change value; RI, reference interval; SBP, systolic blood pressure; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; T4, total thyroxine concentration; UPC, urinary protein : creatinine ratio; USG, urine specific gravity.

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Conclusions and Clinical Importance: Borderline proteinuria should receive more attention in healthy mature adult and senior cats because it is associated with renal disease and death.

KEYWORDS
feline, geriatric, middle-aged, predictors, renal, urinary protein : creatinine ratio

1 | INTRODUCTION

Early diagnosis and intervention is important to slow the progression of chronic kidney disease (CKD). According to International Renal Interest Society (IRIS) guidelines, a renal diet should be considered for cats with early IRIS stage 2 CKD.[1] With persistent renal proteinuria (urinary protein : creatinine ratio [UPC] >0.4), a renal diet should be fed even with IRIS stage 1 CKD, and combined with antiproteinuric medication.[1] For cats with IRIS stage 1 CKD and persistent borderline proteinuria (UPC, 0.2-0.4), antiproteinuric measures can be considered as well,[1] because borderline proteinuria increases mortality risk for cats with azotemic CKD (plasma creatinine concentration [pCrea] >2.0 mg/dL [177 µmol/L], regardless of urine specific gravity [USG]), compared with cats that are nonproteinuric at inclusion (UPC <0.2).[2] It is not known however whether borderline proteinuria is associated with mortality in nonazotemic cats as well.

Because early identification of cats with CKD is desirable and it is often too cumbersome to perform clearance methods for glomerular filtration rate (GFR) determination, which is the gold standard to assess renal function,[3] several studies have investigated the predictive value of widely available clinical, serum and urinary variables.[4-11] If risk factors can be identified among variables that are routinely assessed during health screening in practice, cats at increased risk of developing CKD can be monitored more closely so that IRIS stage 2 CKD or renal proteinuria are noticed as soon as possible and appropriate (dietary) management can be instituted.

The first aim of our prospective study was to gain new insights about the clinical importance of borderline proteinuria in cats by investigating whether a UPC 0.2-0.4 is associated with mortality or development of renal or other disease in healthy nonazotemic cats. A second aim was to investigate other potential risk factors for the development of renal disease in originally healthy nonazotemic cats that were diagnosed with IRIS ≥ stage 2 CKD or persistent renal proteinuria during a 2-year follow-up period by analyzing data obtained during routine health examinations.

2 | MATERIALS AND METHODS

Cats were prospectively enrolled from August 2019 to December 2020 (inclusion period) as part of a health screening study[12] and data collection from confirmed healthy cats continued until December 2022 (follow-up period). This study was approved by the Local Ethical Committee of Ghent University (EC 2018/54) and owners signed an informed consent form.

Cats needed to be healthy according to the owner, meaning no changes in general behavior, stable body condition, and absence of clinical signs. Owners were asked to fast their cats for at least 12 hours before presentation; water could be given ad libitum. Cats were excluded if they had received preventive medications within 1 week or other medications within 2 months before presentation. Cats with previously diagnosed and ongoing metabolic or clinically relevant cardiovascular disease were excluded.

The investigations done at inclusion and every semiannual health check thereafter were the following: A detailed and standardized written history questionnaire was completed and a complete physical examination was performed by the first author (FM). Systolic blood pressure (SBP) was measured using Doppler ultrasonography following American College of Veterinary Internal Medicine (ACVIM) guidelines.[13] In cats with SBP >160 mm Hg, fundoscopic examination was performed and cats with signs of target organ damage were excluded from the study and treated. If fundoscopy was normal, owners were advised to have their cats' SBP rechecked within 1 month. Blood was collected from the jugular vein or, in anxious cats, the cephalic or saphenous vein, and urine was collected by ultrasound-guided cystocentesis. Macroscopic and microscopic evaluation of urine samples, USG determination using a handheld refractometer (MASTER-SUR/NM, Atago), and sediment analysis using an IDEXX SediVue Analyzer were performed on-site. Blood and urine samples were transported overnight at ambient temperature to IDEXX Laboratories where CBC, serum biochemistry profile including electrolyte, symmetric dimethylarginine (sSDMA), total thyroxine (T4) and fructosamine concentrations, and ELISA testing for feline immunodeficiency virus (FIV) antibodies and feline leukemia virus (FeLV) antigen were performed, as well as urine dipstick analysis, UPC determination, and bacterial urine culture.

Cats were confirmed healthy and included in the study if the examinations at baseline did not indicate metabolic or systemic disease such as International Renal Interest Society (IRIS) ≥ stage 2 CKD (serum creatinine concentration [sCrea] ≥1.6 mg/dL or 140 µmol/L and USG <1.035 on 2 consecutive measurements, or sSDMA ≥18 µg/dL and USG <1.035 on 2 consecutive measurements[14]; Figure 1), hyperthyroidism (T4 >4.7 µg/dL [60 nmol/L]); diabetes mellitus (serum glucose concentration >140.5 mg/dL [7.8 mmol/L] in combination with serum fructosamine concentration >51.3 mg/L [286 µmol/L]), or chronic vomiting or diarrhea and concurrent weight loss indicating potential gastroenteropathy, or clinically relevant cardiovascular

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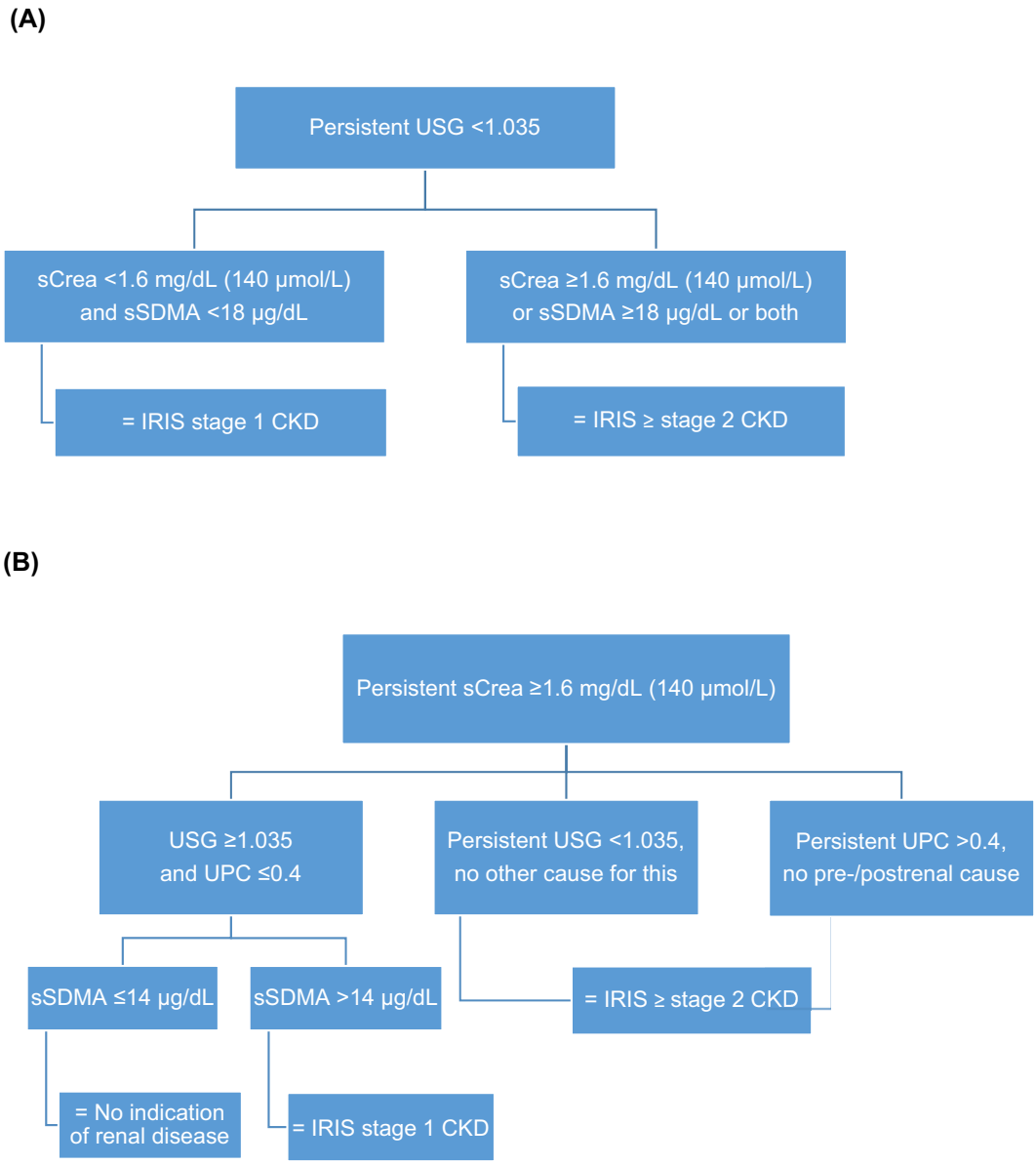

FIGURE 1 Definitions for IRIS stage 1 and IRIS ≥ stage 2 CKD, starting from (A) USG or (B) sCrea result.[35] CKD, chronic kidney disease; IRIS, International Renal Interest Society; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; UPC, urinary protein : creatinine concentration; USG, urine specific gravity.

disease such as cardiomyopathy ACVIM ≥ stage B2 or clinically relevant arrhythmias. Cats with persistent renal proteinuria (UPC >0.4 without a pre- or postrenal component) and sCrea ≥1.6 mg/dL (140 µmol/L) also were diagnosed with IRIS ≥ stage 2 CKD, regardless of USG.[14] Cats that tested positive for FIV or FeLV were excluded, as were cats with persistent macroscopic hematuria, pyuria (>5 leukocytes/high power field), bacteriuria (≥1000 colony forming units/mL[15] on 2 consecutive urine cultures 1-3 months apart), or renal proteinuria (UPC >0.4 on 2 consecutive measurements 1-3 months apart without a pre- or postrenal component).

Confirmed healthy cats were examined approximately every 6 months for up to 2 years. In cats with a combination of sCrea ≥1.6 mg/dL (140 µmol/L) and USG <1.035, or with sSDMA >14 µg/dL at any visit during the study period, re-examination of sCrea, sSDMA, and USG was scheduled 1-2 months later to allow for staging of potential CKD. During the follow-up period, hyperthyroidism was diagnosed if T4 exceeded the upper limit of the laboratory reference interval ([RI]; 4.7 µg/dL or 60 nmol/L) or if T4 exceeded the age-appropriate RI for the same laboratory (3 µg/dL or 38.6 nmol/L)[16] and had increased >34% from the cat's own baseline result at inclusion (ie, the reference change value for T4)[17-19] on 2 consecutive measurements. Cats with chronic gastrointestinal signs or unexplained weight loss during follow-up and increased liver enzyme activities, increased feline pancreas-specific lipase, decreased serum cobalamin concentration, or some combination of these were grouped under the term "triaditis." The following events were recorded during the 2-year

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follow-up period: development of IRIS ≥ stage 2 CKD (CKD ≥ stage 2), persistent renal proteinuria with sCrea <1.6 mg/dL (140 μmol/L, renal proteinuria), hyperthyroidism, systemic or metastatic neoplasia (neoplasia), triaditis, and death (by any cause). For statistical analysis, the dependent variable CKD ≥ stage 2 was assessed both separately and together with renal proteinuria (grouped as renal disease; see Table 1 for terminology). Cats were assigned IRIS stage 1 CKD when they did not fit the category of CKD ≥ stage 2, but did have persistently decreased USG (<1.035) without an identifiable nonrenal cause for suboptimal urine concentration, persistently increased sSDMA (>14 μg/dL), or both, at 2 time points 1-6 months apart (Figure 1).[14]

2.1 | Statistical analysis

Time-to-event data were analyzed using R version 4.3.2.[20] Cats were right censored at their last visit in the study. This occurred at the study end after 2 years of follow-up, or at the last visit before death or loss to follow-up. Time to CKD ≥ stage 2, renal disease, hyperthyroidism, neoplasia, triaditis, and death were studied with Cox models using procedure coxph of the package Survival.[21] The association between each outcome and borderline proteinuria at inclusion (UPC 0.2-0.4 vs UPC <0.2) was studied and the cumulative incidence in both subgroups was plotted in Kaplan-Meier graphs. Statistical comparison between both subgroups was performed using the log-rank test and significance was set at $P < .05$.

Next, univariate associations were analyzed between the development of CKD or renal disease and several potential predictive variables that are obtained during routine health examinations in cats. Age, weight, sex, and breed were added as time-independent covariates using data from inclusion (T0). Dental disease score,[5,12,22] SBP, urine dipstick protein, UPC, USG, sSDMA, sCrea, blood urea nitrogen concentration (BUN), and IRIS stage 1 CKD were added as time-dependent covariates using data from the last visit before event occurrence (T_{-6m}). The continuous covariates age, sSDMA, and USG were centered at, respectively, 10 years, 10 μg/dL, and 1.040 to facilitate interpretation. Covariates with a *P*-value <.2 in the univariate models were entered in the multivariable model. Nonsignificant ($P > .05$) covariates subsequently were removed from the model using a manual, backward selection procedure. The hazard ratios (HR) of the remaining covariates were compared at each step of the model-building process. A change in HR > 30% was considered indicative of confounding with the covariate that had been excluded from the model. Being the main predictor of interest, the categorical measure of proteinuria was forced and maintained in the multivariable models.

TABLE 1 Definitions used for the current study.

Terminology	Definition
CKD ≥ stage 2	Persistent sCrea ≥1.6 mg/dL (140 μmol/L) or persistent sSDMA ≥18 μg/dL or both, in combination with persistent USG <1.035
IRIS stage 1 CKD	Persistent USG <1.035 without an identifiable nonrenal cause for suboptimal urine concentration, persistent sSDMA >14 μg/dL, or both
Renal proteinuria	Persistent UPC >0.4 without an identifiable pre- or postrenal component, with sCrea <1.6 mg/dL (140 μmol/L) and thus no IRIS ≥ stage 2 CKD
Renal disease	IRIS ≥ stage 2 CKD or renal proteinuria or both, necessitating renal diet

Abbreviations: CKD, chronic kidney disease; IRIS, International Renal Interest Society; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; UPC, urinary protein : creatinine concentration.

3 | RESULTS

Health examination results at inclusion have been described previously.[12] After initial screening, 201 confirmed healthy cats (150 nonproteinuric and 51 borderline proteinuric cats) had at least 1 follow-up examination performed and were included in the current longitudinal study. Group characteristics of included cats and both subgroups (nonproteinuric vs borderline proteinuric cats) are presented in Table 2. Breeds represented more than once were British Short- and Longhair (n = 29), Ragdoll (n = 7), Maine Coon (n = 4), Scottish Fold (n = 3), Birman (n = 3), and Balinese (n = 2).

Serum SDMA concentration was increased (>14 μg/dL) at inclusion in 21/201 (10.4%) cats (range, 15-21 μg/dL). Reevaluation was performed within 2 months in 18/21 cats and median sSDMA decreased from 16 to 12 μg/dL (range at reevaluation, 9-19 μg/dL), with normalization of sSDMA in 16/18 (88.9%) cats. For the 3 remaining cats, sSDMA was normal at the 6-month reevaluation in 2 cats and remained increased in 1 cat with USG <1.035 on both occasions. At inclusion, USG was <1.035 in 31/201 (15.4%) healthy cats, but ≥1.035 after 1-6 months in 20/31 (64.5%) cats. Overall, 13/201 (6.5%) cats had IRIS stage 1 CKD at inclusion based on USG persistently <1.035 (n = 10), sSDMA persistently >14 μg/dL (n = 2) or both (n = 1) in combination with sCrea <1.6 mg/dL (140 μmol/L).

Two of the 201 included cats (1%) were lost to follow-up after their first reevaluation, at which time they were still healthy. The remaining 199 cats were monitored until they completed the 2-year follow-up period (180/201 = 90%) or until they died, if death occurred before the end of the study (19/201 = 9%). The cumulative incidence of events that occurred during the 2-year follow-up period is presented in Table 3.

Persistent overt proteinuria without a pre- or postrenal cause (renal proteinuria) developed in 5/201 cats (2.5%) that did not have CKD ≥ stage 2 (sCrea <1.6 mg/dL [140 μmol/L]) or another systemic or metabolic disease at that time. One of these cats had progressed to IRIS stage 2 CKD 6 months later, 2/5 cats with renal proteinuria did not develop CKD ≥ stage 2 (or another systemic disease) during the next 12-18 months, and in 2/5 cats with renal proteinuria only was diagnosed during their last study visit at 24 months.

The incidence rate for the development of CKD ≥ stage 2 was 0.07 cases per cat-year. This means that if 100 healthy cats aged ≥7 years are followed up for 1 year, 7 of them will develop CKD

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TABLE 2 Group characteristics at inclusion for all cats as well as for the nonproteinuric (UPC <0.2) and borderline proteinuric (UPC 0.2-0.4) subgroups.

	All cats (n = 201)	UPC <0.2 (n = 150)	UPC 0.2-0.4 (n = 51)
Age (years)	10 (7-18)	9 (7-16)	10 (7-18)
Sex (neutered)	122 (117) female (61%) 79 (79) male (39%)	94 (92) female (63%) 56 (56) male (37%)	28 (25) female (55%) 23 (23) male (45%)
Breed	143 DSH/DLH (71%) 58 pedigree (29%)	110 DSH/DLH (73%) 40 pedigree (27%)	33 DSH/DLH (65%) 18 pedigree (35%)
Weight (kg)	4.4 (2.2-9.5)	4.4 (2.5-9.5)	4.6 (2.2-8.7)
Body condition score	85 normal (BCS = 5; 42%) 31 decreased (15%) 85 increased (42%)	70 normal (47%) 21 decreased (14%) 59 increased (39%)	15 normal (29%) 10 decreased (20%) 26 increased (51%)
Muscle condition score	141 normal (70%) 60 decreased (30%)	109 (73%) 41 (27%)	32 (63%) 19 (37%)
SBP (mm Hg)	140 (90-200)	140 (90-200)	145 (110-180)
Dental disease score	130 none-mild (66%) 68 moderate-severe (34%)	101 (68%) 47 (32%)	29 (58%) 21 (42%)
sCrea (mg/dL) (μmol/L)	1.3 (0.7-2.1) 112 (62-184)	1.3 (0.8-2.1) 117 (68-184)	1.2 (0.7-1.8) 104 (62-156)
sSDMA (μg/dL)	11 (4-21)	11 (4-20)	11 (5-21)
BUN (mg/dL) (mmol/L)	24 (15-40) 8.5 (5.5-14.2)	24 (15-38) 8.5 (5.5-13.7)	25 (17-40) 9.1 (5.9-14.2)
USG	1.046 (1.010-1.060)	1.047 (1.011-1.060)	1.042 (1.010-1.060)
UPC	0.16 (0.05-0.39)	0.14 (0.05-0.19)	0.25 (0.20-0.39)
IRIS stage 1 CKD (persistent USG <1.035 or sSDMA >14)	13 (6.5%)	8 (5.3%)	5 (9.8%)

Note: Values are expressed as numbers (percentages) or median (range).
Abbreviations: BUN, blood urea nitrogen concentration; CKD, chronic kidney disease; DLH, Domestic Longhair; DSH, Domestic Shorthair; IRIS, International Renal Interest Society; SBP, systolic blood pressure; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; UPC, urinary protein : creatinine ratio; USG, urine specific gravity.

TABLE 3 Events in 201 confirmed healthy cats ≥7 years of age during 2-year follow-up, for all cats as well as for the subgroups of cats that were either nonproteinuric or borderline proteinuric at inclusion (T0).

Events during follow-up	All cats (n = 201)	UPC_{T0} < 0.2 (n = 150)	UPC_{T0} 0.2-0.4 (n = 51)
Newly developed diseases[a]			
• CKD ≥ stage 2	27 (13.4%)	16 (10.7%)	11 (21.6%)
• Hyperthyroidism	17 (8.5%)	11 (7.3%)	6 (11.8%)
• Triaditis	15 (7.5%)	9 (6%)	6 (11.8%)
• Neoplasia	9 (4.5%)	6 (4%)	3 (5.9%)
• Renal proteinuria	5 (2.5%)	1 (0.7%)	4 (7.8%)
Renal disease (CKD ≥ stage 2, renal proteinuria, or both)	31 (15.4%)	17 (11.3%)	14 (27.5%)
Death	19 (9.5%)	10 (6.7%)	9 (17.6%)

[a]Eleven cats developed 2 of these diseases at different time points and are represented twice.
Abbreviations: CKD, chronic kidney disease; UPC, urinary protein : creatinine ratio.

≥ stage 2. For renal disease (which also includes renal proteinuria cases), the incidence rate was 0.09, and for mortality, the incidence rate was 0.05 deaths per cat-year (Table 4).

Kaplan-Meier curves for the development of clinically relevant diseases or death during 2-year follow-up are shown in Figure 2 for cats with UPC <0.2 vs UPC 0.2-0.4 at inclusion. A significant difference was identified, with more events occurring in cats with borderline proteinuria at inclusion, for the development of renal disease (log-rank $P = .004$) and death (log-rank $P = .02$). Nonproteinuric and borderline proteinuric cats did not differ significantly with regard to the development of CKD ≥ stage 2 (log-rank $P = .05$), neoplasia (log-rank $P = .5$), hyperthyroidism (log-rank $P = .3$), or triaditis (log-rank $P = .2$).

Results of univariable and multivariable analysis are shown in Tables 5 and 6. During model building for CKD ≥ stage 2 and renal disease, the covariates IRIS stage 1 and USG (continuous variable) appeared to be confounded, as were moderate to severe dental disease and BUN >RI. The final multivariable analysis model concluded that development of CKD ≥ stage 2 was not significantly associated with borderline proteinuria at the previous visit, but was positively associated with age at inclusion, sCrea ≥1.6 mg/dL (140 μmol/L) at

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TABLE 4 Incidence rate (in cases per cat-year) for development of (A) CKD ≥ stage 2 or (B) renal disease, taking into account the number of days each cat was at risk of developing the disease (ie, until this disease was diagnosed or until death).

	Covariate categories	Visits	Days	Cases	Cases/cat-year
(A) CKD ≥ stage 2					
UPC T_{-6m}	UPC <0.2	518	95 958	12	0.05
	UPC 0.2-0.4	174	32 366	10	0.11
sCrea T_{-6m}	sCrea <1.6 mg/dL (140 µmol/L)	618	114 952	19	0.06
	sCrea ≥1.6 mg/dL (140 µmol/L)	103	18 847	8	0.15
BUN T_{-6m}	BUN ≤37 mg/dL (13.5 mmol/L)	713	132 387	25	0.07
	BUN >37 mg/dL (13.5 mmol/L)	6	1118	2	0.65
IRIS stage 1 T_{-6m}	No CKD	648	120 508	15	0.05
	IRIS stage 1 CKD	73	13 291	12	0.33
(B) Renal disease					
UPC T_{-6m}	UPC <0.2	518	95 958	14	0.05
	UPC 0.2-0.4	174	32 366	13	0.15
sCrea T_{-6m}	sCrea <1.6 mg/dL (140 µmol/L)	612	113 739	23	0.07
	sCrea ≥1.6 mg/dL (140 µmol/L)	103	18 847	8	0.15
IRIS stage 1 T_{-6m}	No CKD	647	120 341	18	0.05
	IRIS stage 1 CKD	68	12 245	13	0.39

Note: Incidence rates for variables are shown per covariate category; T_{-6m} means that data from the last visit before event occurrence were used.
Abbreviations: BUN, blood urea nitrogen concentration; IRIS, International Renal Interest Society; sCrea, serum creatinine concentration; UPC, urinary protein : creatinine ratio.

the previous visit, BUN >37 mg/dL (13.5 mmol/L) at the previous visit, and IRIS stage 1 CKD (based on persistent USG <1.035, persistent sSDMA >14 µg/dL, or both) at the previous visit ($P < .05$; Table 5). Development of renal disease (CKD ≥ stage 2 or renal proteinuria) was positively associated with age at inclusion, borderline proteinuria at the previous visit, sCrea ≥1.6 mg/dL (140 µmol/L) at the previous visit, and IRIS stage 1 CKD (based on persistent USG <1.035, persistent sSDMA >14 µg/dL or both) at the previous visit ($P < .05$; Table 6).

In cats that finally were diagnosed with CKD ≥ stage 2 (persistent USG <1.035 in combination with sCrea ≥1.6 mg/dL [140 µmol/L] or sSDMA ≥18 µg/dL), sCrea was above the threshold ≥6 months before sSDMA exceeded the cut-off value for IRIS stage 2 CKD in 18/27 (66.7%) cases. Both serum test results met the criterion for IRIS stage 2 CKD at the same visit in 6/27 (22.2%) cats, and sSDMA exceeded the threshold value ≥6 months before sCrea in 3/27 (11.1%) cats. When taking into account the age-appropriate RI for sCrea and sSDMA for the laboratory used in our study,[16] sCrea exceeded its RI (>1.89 mg/dL [167 µmol/L]) before sSDMA exceeded its age-specific RI (≥18 µg/dL) in 9/23 (39.1%) cats, both were increased at the same time in 7/23 (30.4%) cats and sSDMA increased before sCrea in 7/23 (30.4%) cats. In 4 other cats with IRIS stage 2 CKD, both serum biomarkers did not exceed the age-appropriate RI simultaneously.

When evaluating the percentage increase in sCrea (compared to baseline) in cats that were diagnosed with ≥ stage 2 CKD 12-24 months after inclusion, this increase exceeded the reference change value (RCV) of 24.7%[23] ≥6 months before CKD ≥ stage 2 was diagnosed in 7/20 (35%) cats. The sCrea had increased by >24.7% from baseline at the same visit when CKD ≥ stage 2 was diagnosed in 7/20 (35%) cats, and the RCV was not yet exceeded at the time of diagnosis of CKD ≥ stage 2 in 6/20 (30%) cats. The percentage increase in sSDMA (compared to baseline) exceeded the RCV of 61.7%[23] ≥6 months before CKD ≥ stage 2 diagnosis in 4/20 (20%) cats, at the time of CKD ≥ stage 2 diagnosis in 5/20 (25%) cats and not yet at all in 11/20 (55%) cats.

4 | DISCUSSION

Borderline proteinuria has clinical importance in healthy mature adult and senior cats because it is associated with the development of renal disease and death within 2 years, and is, therefore, a prognostic factor in cats without azotemic CKD. An earlier study showed that a UPC >0.2 in combination with sCrea >1.6 mg/dL (140 µmol/L) was associated with development of azotemia (pCrea >2.0 mg/dL [177 µmol/L], regardless of USG) in nonazotemic cats within 12 months after presentation, but cats with overt proteinuria (UPC >0.4) were included in this group as well.[4] In our study, significantly more cats with UPC 0.2-0.4 at inclusion developed renal disease (CKD ≥ stage 2 or renal proteinuria) within 2 years compared with cats with a UPC <0.2 (log-rank $P = .004$). For the development of CKD ≥ stage 2 alone, the difference between cats that were borderline proteinuric vs nonproteinuric at baseline approached but did not reach statistical significance (log-rank $P = .05$). It is possible that borderline proteinuria also would prove to be associated with development of CKD ≥ stage 2 if a larger proportion of cats with UPC 0.2-0.4 would have been included.

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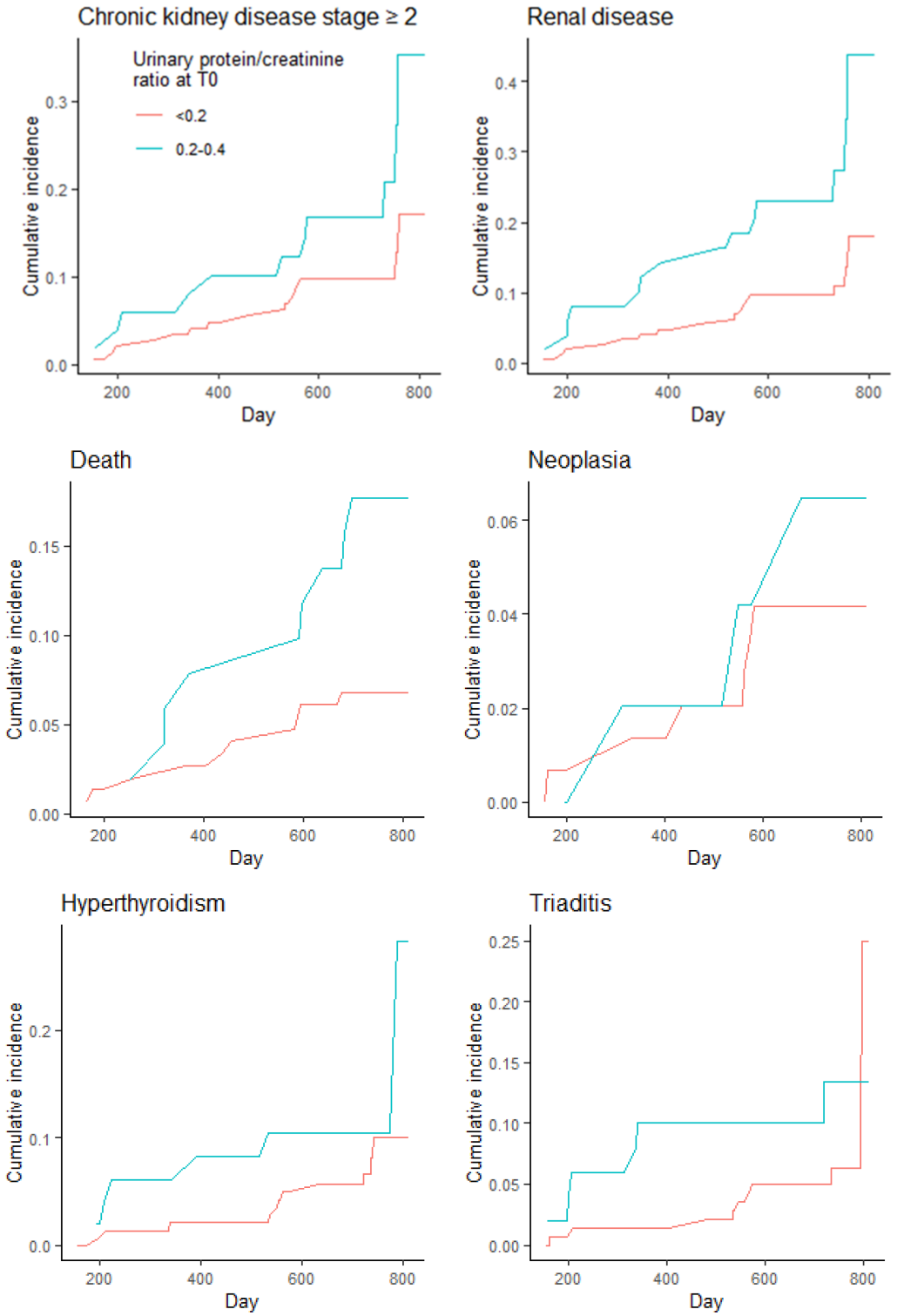

FIGURE 2 Kaplan-Meier curves for development of chronic kidney disease ≥ stage 2 (log-rank $P = .05$), renal disease (log-rank $P = .004$), death (log-rank $P = .02$), neoplasia (log-rank $P = .5$), hyperthyroidism (log-rank $P = .3$), and triaditis (log-rank $P = .2$) in 201 healthy cats within 2 years, with stratification according to baseline urinary protein : creatinine ratio in nonproteinuric cats (UPC <0.2; red) vs borderline proteinuric cats (UPC 0.2-0.4; blue).

However, when evaluating the entire group of cats that would need dietary measures (ie, cats with CKD ≥ stage 2, persistent renal proteinuria, or both), significantly more cats with borderline proteinuria at inclusion developed renal disease within 2 years. Currently, it is unclear whether this low level of proteinuria is a cause (or contributing factor) for progressive renal disease, or merely a

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TABLE 5 Results of the univariable and multivariable Cox regression analysis of risk factors for development of IRIS ≥ stage 2 chronic kidney disease in 201 healthy cats.

Covariates for CKD ≥ stage 2	Covariate categories	Univariable analysis HR (95% CI); *P*-value	Final multivariable analysis model HR (95% CI); *P*-value
Age at inclusion	Continuous: per year increase	1.5 (1.3-1.7); <.001	1.4 (1.2-1.6); <.001
Weight at inclusion	Continuous: per kg increase	0.9 (0.7-1.2); .423	–
Breed	Domestic Short- or Longhair	Ref.	
	British Short- or Longhair	0.6 (0.1-2.5); .476	–
	Other breeds	1.0 (0.4-2.3); .919	–
Sex	Female (intact or spayed)	Ref.	
	Male (neutered)	0.9 (0.4-1.9); .792	–
Dental disease T_{-6m}	Absent or mild (score 0-2)	Ref.	
	Moderate or severe (score 3-6)	3.6 (1.6-7.9); .002	–
SBP T_{-6m}	≤160 mm Hg	Ref.	
	>160 mm Hg	1.8 (0.6-5.3); .308	–
Dipstick protein T_{-6m}	Absent or trace (0 or 1+)	Ref.	
	Positive result (2+ or more)	0.8 (0.4-1.9); .649	–
UPC T_{-6m}	UPC <0.2	Ref.	
	UPC 0.2-0.4	2.6 (1.1-5.8); .022	2.1 (0.9-5.2); .090
USG T_{-6m}	Continuous: per unit increase	$2.3 * 10^{-32}$ ($3.5 * 10^{-45}$-$1.5 * 10^{-19}$); <.001	–
sSDMA T_{-6m}	Continuous: per µg/dL increase	1.2 (1.1-1.3); .001	–
sCrea T_{-6m}	sCrea <1.6 mg/dL (140 µmol/L)	Ref.	
	sCrea ≥1.6 mg/dL (140 µmol/L)	2.8 (1.2-6.3); .014	3.6 (1.3-9.9); .015
BUN T_{-6m}	BUN ≤37 mg/dL (13.5 mmol/L)	Ref.	
	BUN >37 mg/dL (13.5 mmol/L)	12.6 (3.1-52.1); <.001	4.3 (1.1-17.6); .040
$e^u/(1+e^u)$[a]	≥0.5	Ref.	
	<0.5	2.4 (0.7-7.8); .151	–
IRIS stage 1 T_{-6m}	No CKD	Ref.	
	IRIS stage 1 CKD	6.4 (2.8-14.5); <.001	3.9 (1.7-8.9); .001

Note: T_{-6m} means that data from the last visit before event occurrence were used.

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IRIS, International Renal Interest Society; SBP, systolic blood pressure; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; UPC, urinary protein : creatinine ratio; USG, urine specific gravity.

[a] e = Euler's number; $u = 6.770 - 0.201 * \text{BUN} - 0.065 * \text{sCrea} + 5 * \text{USG} - 0.928 * \text{UPC}$.[36]

marker of decreased tubular function.[2] It, therefore, remains to be determined whether it would be useful to start antiproteinuric measures as soon as cats ≥7 years of age develop persistent borderline proteinuria in order to slow further progression to CKD ≥ stage 2 or renal proteinuria. Also, significantly more cats with borderline proteinuria at inclusion died during follow-up compared with nonproteinuric cats (log-rank $P = .02$). This finding in the current healthy nonazotemic older population is similar to what has been reported for a population of mainly azotemic cats of various ages, where survival was decreased in those with borderline proteinuria as well.[2] Necropsy was not performed on any of the cats that died during the follow-up period in our study, and thus the exact cause of death remains unclear in some cases.[12] Stage ≥2 CKD was diagnosed before euthanasia in 5/19 (26%) cats that died or were euthanized and may have played a role in the decision, but was not the sole cause of death or euthanasia in any cat. Neoplastic disease can cause proteinuria,[24] which could explain the link between a higher UPC at inclusion (0.2-0.4 vs <0.2) and increased risk of death. However, borderline proteinuria at inclusion was not associated with later development of neoplasia. Other conditions that were observed during follow-up can contribute to increased urinary protein loss as well,[24] but borderline proteinuria at inclusion was not associated with later development of hyperthyroidism or chronic gastrointestinal, hepatic, or pancreatic inflammatory disease.

Multivariate models identified the following risk factors associated with development of CKD ≥ stage 2 or renal disease within 6 months: age, sCrea ≥1.6 m/dL (140 µmol/L), BUN >RI, borderline proteinuria, and IRIS stage 1 CKD. In 2 previous studies, increasing

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TABLE 6 Results of the univariable and multivariable Cox regression analysis of risk factors for development of renal disease in 201 healthy cats.

Covariates for renal disease	Covariate categories	Univariable analysis HR (95% CI); *P*-value	Final multivariable analysis model HR (95% CI); *P*-value
Age at inclusion	Continuous: per year increase	1.4 (1.3-1.6); <.001	1.3 (1.2-1.5); <.001
Weight at inclusion	Continuous: per kg increase	0.9 (0.6-1.1); .292	–
Breed	Domestic Short- or Longhair	Ref.	
	British Short- or Longhair	0.5 (0.1-2.1); .351	–
	Other breeds	1.0 (0.4-2.4); .964	–
Sex	Female (intact or spayed)	Ref.	
	Male (neutered)	1.0 (0.5-2.0); .953	–
Dental disease T_{-6m}	Absent or mild (score 0-2)	Ref.	
	Moderate or severe (score 3-6)	3.7 (1.7-7.8); <.001	–
SBP T_{-6m}	≤160 mm Hg	Ref.	
	>160 mm Hg	1.5 (0.5-4.4); .480	–
Dipstick protein T_{-6m}	Absent or trace (0 or 1+)	Ref.	
	Positive result (2+ or more)	0.7 (0.3-1.6); .392	–
UPC T_{-6m}	UPC <0.2	Ref.	
	UPC 0.2-0.4	2.8 (1.4-5.9); .005	2.5 (1.2-5.2); .013
USG T_{-6m}	Continuous: per unit increase	$2.9 * 10^{-31}$ ($1.5 * 10^{-43}$-$5.8 * 10^{-19}$); <.001	–
sSDMA T_{-6m}	Continuous: per µg/dL increase	1.2 (1.0-1.3); .009	–
sCrea T_{-6m}	sCrea <1.6 mg/dL (140 µmol/L)	Ref.	
	sCrea ≥1.6 mg/dL (140 µmol/L)	2.2 (1.0-5.0); .046	2.6 (1.1-6.4); .036
BUN T_{-6m}	BUN ≤37 mg/dL (13.5 mmol/L)	Ref.	
	BUN >37 mg/dL (13.5 mmol/L)	10.9 (2.8-42.5); <.001	–
$e^u/(1+e^u)$[a]	≥0.5	Ref.	
	<0.5	2.0 (0.6-6.4); .261	–
IRIS stage 1 T_{-6m}	No CKD	Ref.	
	IRIS stage 1 CKD	6.5 (3.1-13.8); <.001	4.2 (2.0-8.8); <.001

Note: T_{-6m} means that data from the last visit before event occurrence were used.
Abbreviations: BUN, blood urea nitrogen concentration; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IRIS, International Renal Interest Society; SBP, systolic blood pressure; sCrea, serum creatinine concentration; sSDMA, serum symmetric dimethylarginine concentration; UPC, urinary protein : creatinine ratio; USG, urine specific gravity.
[a]e = Euler's number; $u = 6.770 - 0.201 * \text{BUN} - 0.065 * \text{sCrea} + 5 * \text{USG} - 0.928 * \text{UPC}$.[36]

age also was associated with development of azotemic CKD (pCrea >2.0 mg/dL [177 µmol/L], regardless of USG) in cats in univariate analysis but not retained after multivariate analysis, possibly because cats included in those studies were already older at inclusion (≥9 and ≥10 years vs ≥7 years in our study).[4,5] A study including cats with a median age of 7 years found an HR of 1.4 (95% confidence interval [CI], 1.2-1.6) for developing CKD (sCrea >1.6 mg/dL [140 µmol/L] in combination with USG < 1.035) with increasing age,[11] which is identical to the HR for development of CKD ≥ stage 2 in our study. This observation means that, per year of age, the hazard of developing CKD increases by 40%.

Both sCrea and BUN are included in 2 models generated from a large amount of data, but it is unclear which cut-offs or formulas these models used to predict CKD in cats.[8,9] Another study found a higher risk of azotemic CKD (pCrea >2.0 mg/dL [177 µmol/L], regardless of USG) in cats with baseline pCrea >1.6 mg/dL (140 µmol/L) after multivariate analysis as well, but only in combination with a measure of proteinuria (UPC or urinary albumin: creatinine ratio).[4] Because both sCrea and BUN were independent risk factors for development of CKD ≥ stage 2 in our study, with a HR of 3.6 (95% CI, 1.3-9.9) and 4.3 (95% CI, 1.1-17.6) for cats with sCrea ≥1.6 mg/dL (140 µmol/L) or BUN >37 mg/dL (13.5 mmol/L), respectively, cats with either of these findings during health screening should be monitored more closely for future development of CKD ≥ stage 2.

Guidelines recommend intervention in the early stages of CKD, including IRIS stage 1, in an attempt to slow the progression of CKD.[1] It is not known however if IRIS stage 1 always has clinical relevance and whether and when these cats will develop IRIS ≥ stage 2 CKD.

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Various criteria can lead to a diagnosis of IRIS stage 1 disease, including abnormal renal palpation findings, renal imaging findings, renal biopsy results, renal proteinuria, increasing sCr or sSDMA on serial measurements, decreased USG without an identifiable nonrenal cause, or persistently increased sSDMA >14 μg/dL, thus representing a heterogenous group of potential risk factors for CKD.[14] In our study, cats classified as having IRIS stage 1 CKD based on persistently decreased USG or persistently increased sSDMA had an increased risk of developing CKD ≥ stage 2 within 6 months. When IRIS stage 1 CKD was diagnosed between inclusion and the 18-month reevaluation (ie, at a time point when it could be predictive of later CKD diagnosis), this finding was more often because of persistently decreased USG (<1.035 in 72%) than persistently increased sSDMA (>14 μg/dL in 34%) or simultaneously decreased USG and increased SDMA (6%). The 2 models that had processed a large amount of data from cats that developed CKD incorporated USG in their model, in addition to sCrea and BUN,[8,9] which confirms the importance of decreased USG as a predictive factor for more advanced stages of CKD. The sensitivity of these models (1 of which also included age as a fourth factor)[8] is 63-87% to predict CKD within 1 year before diagnosis. Because our study only investigated IRIS stage 1 classification because of suboptimal USG, increased sSDMA, or both, no conclusions can be drawn about the clinical importance of IRIS stage 1 CKD when diagnosis is based on other criteria (such as abnormal renal palpation, renal imaging or renal biopsy findings, or persistent renal proteinuria).[14]

The persistent decrease in USG in 36% of cats with USG <1.035 at inclusion in our study (when re-evaluated after 1-6 months) is very similar to the 38% persistence of suboptimal urine concentration found after 2 months in a younger population of healthy cats (median age, 4 years).[25] Whether IRIS stage 1 CKD also is a risk factor for CKD ≥ stage 2 development in younger cats cannot be concluded from our study in mature adult and senior cats.

The 11% persistence rate of increased sSDMA in our study when re-evaluated within 2 months after inclusion is less than the 53% persistence previously documented after 2 weeks to 18 months.[26] One potential explanation could be that cats were fasted for the semiannual health checks, whereas doing so was not required for the intermediate sSDMA measurement after 2 months, although a study in dogs found no difference in sSDMA postprandially compared to preprandially.[27]

We also found a markedly lower percentage (11%) of cats that developed CKD that had increased sSDMA before increased sCrea, compared with a previous study.[7] In the latter study, sSDMA increased (>14 μg/dL) before sCrea (>2.1 mg/dL [186 μmol/L]) in 17/21 (81%) cats aged 8-18 years at the time of CKD diagnosis. Chronic kidney disease was defined as sCrea >2.1 mg/dL (186 μmol/L), GFR >30% below the median of the study group, or the presence of calcium oxalate kidney stones. The RIs used for sCrea and sSDMA in that study were not age-specific. However, it has been shown that sCrea is lower and sSDMA higher in healthy older cats.[16,28] In our study, CKD ≥ stage 2 diagnosis was based on the cut-off values from IRIS guidelines for sCrea and sSDMA, which are used for staging of CKD in clinical practice and facilitate comparison between studies. Although not age- or laboratory-specific, the lower cut-off for sCrea (≥1.6 mg/dL [140 μmol/L]) and higher cut-off for sSDMA (≥18 μg/dL) to assign CKD stage ≥2 according to IRIS guidelines are more in line with the upper limits of the RIs for sCrea and sSDMA determined specifically for healthy aged cats (≥7 years) and for the laboratory used in our study (1.89 mg/dL [167 μmol/L] and 17.8 μg/dL, respectively).[16] The different cut-off values for sCrea and sSDMA compared to a previous study,[7] and the additional requirement of persistently decreased USG for a CKD diagnosis in our study, can explain why increased sSDMA (≥18 μg/dL) could detect IRIS stage ≥2 CKD before increased sCrea in only 11% (sCrea ≥1.6 mg/dL, IRIS guidelines) or 30% (sCrea ≥1.9 mg/dL, age-specific RI) of cases in our study.

Based on our study, closer monitoring is recommended for cats with sCrea ≥1.6 mg/dL (140 μmol/L), BUN >RI, UPC 0.2-0.4, or USG <1.035, sSDMA >14 μg/dL or both, because these cats have a higher risk of developing CKD ≥ stage 2 or renal proteinuria within the next 6 months. Owners of such cats therefore can be advised to come for a reevaluation after 6 months or even sooner, even if guidelines only recommend a complete health evaluation every 1-2 years.[29] Thus, CKD, renal proteinuria, or both can be detected in an early phase and a specific diet is prescribed (in combination with antiproteinuric medication in case of persistent overt proteinuria).

A previous study found an association between moderate or severe dental disease and later development of azotemic CKD (pCrea >2.0 mg/dL [177 μmol/L], regardless of USG)[5] and other prospective studies also documented an increased risk for development of CKD (sCrea >1.6 mg/dL [140 μmol/L] in combination with USG < 1.035) in cats that also had periodontal disease.[6,11] One of these studies found general anesthesia to be an independent risk factor for azotemic CKD,[11] and another study suggested that longer duration dental procedures in cats may carry inherent risks of kidney injury.[30] In our study, it was not routinely documented whether cats with moderate to severe dental disease underwent a dental procedure under general anesthesia. In our study, moderate to severe dental disease also was associated with both development of CKD ≥ stage 2 and renal disease in the univariable analysis, but this variable was not retained in the multivariable model. Dental disease and BUN >RI were confounded for CKD ≥ stage 2 and renal disease, and during model building, BUN >RI appeared to be a stronger independent predictor for CKD ≥ stage 2 or renal disease compared with dental disease. Moderate to severe dental disease and BUN >RI being confounding factors is in accordance with a cross-sectional study that identified a significant association between increasing severity of periodontal disease and BUN >RI in dogs with and without CKD ≥ stage 2.[31] A possible explanation for the association between dental disease and BUN is that salivary urea is hypothesized to promote dental plaque and calculus formation,[6,32] but a study in cats showed no correlation between periodontal disease and BUN.[33] Other confounding factors that became apparent during model building were IRIS stage 1 (which includes a categorical measure for USG) and the continuous measure for USG, with the latter also being deleted from the final multivariable model.

Although neutered male cats had an increased risk for development of CKD in a previous study,[6] such was not the case in our study

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and 2 other studies.[5,34] Purebred cats also were at increased risk for CKD in a previous study,[11] but breed was not associated with CKD development in our study and another study.[5] Systolic blood pressure was not associated with CKD development either, similar to what previously has been reported,[4] and neither were weight at inclusion or dipstick protein result 6 months before CKD diagnosis.

The fact that previous studies used variable definitions for CKD makes it difficult to compare the results of different studies. It would be desirable if researchers always mentioned clearly not only the cut-off value used for sCrea, but also whether USG (or other serum or urinary variables) also were taken into account for CKD diagnosis, and whether findings were based on a single measurement or multiple measurements. Interpretation of study results by other researchers and practitioners would be facilitated if scientific studies and subsequent clinical recommendations were based on the IRIS guidelines that are available at the time of study execution.

Our study had some limitations. First, most continuous variables were transformed into categorical variables for the multivariable analysis by using previously defined cut-offs (eg, laboratory RI for BUN, sSDMA, and USG, IRIS [sub]stages for sCrea and UPC). This approach was taken to facilitate interpretation by clinicians (eg, compare borderline proteinuric and nonproteinuric cats, rather than interpreting the risk associated with a 1 unit increase in UPC), but has the disadvantage of decreasing statistical power. Second, it cannot be excluded that some confirmed healthy cats already had early CKD at inclusion, because GFR was not measured. However, very strict criteria were applied for the laboratory tests that are used in clinical practice to diagnose CKD. Third, fibroblast growth factor 23 was not measured because the assay was not commercially available yet, and thus information about potential early mineral bone disorder is lacking. Fourth, several cats developed comorbidities, some of which may have complicated the diagnosis of CKD or affected UPC results (eg, hyperthyroidism and its potential influence on sCrea, USG, and UPC). This problem however is inherent to longitudinal follow-up studies in older cats and if all cats that developed a disease other than CKD were not followed further, a proportion of cats developing CKD later in the course of the study would be missed.

In conclusion, our prospective longitudinal study in a healthy nonazotemic cat population indicates that borderline proteinuria has clinical importance in healthy mature adult and senior cats, because it was associated with renal disease and death within 2 years. Additionally, risk factors for development of CKD ≥ stage 2, renal proteinuria, or both within 6 months were identified, namely age, sCrea, BUN (for CKD), borderline proteinuria (for renal disease), and IRIS stage 1 CKD. These results warrant closer monitoring of cats ≥7 years of age with sCrea ≥1.6 mg/dL (140 μmol/L), BUN >RI, UPC 0.2-0.4, or IRIS stage 1 CKD (USG <1.035 or sSDMA >14 μg/dL), so that CKD ≥ stage 2 or renal proteinuria once present can be diagnosed timely, and appropriate clinical management can be instituted.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approval granted by the Ethical Committee of the Faculty of Veterinary Medicine and the Faculty of Bioscience Engineering of Ghent University (IACUC) and the Deontological Committee of the Belgian Federal Agency for the Safety of the Food Chain (EC 2018/54).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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