UNIVERSITI PUTRA MALAYSIA

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CERTIFICATION

It is hereby certified that we have read this project paper entitled "The Effectiveness of Telmisartan in Management of Cats with Chronic Kidney Disease" by Joyce Lim Qi Yi and in my opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement of the course VPD 4999-Project.

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Specially dedicated to all vets, my family and friends.

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LIST OF ABBREVATIONS

AAFP	: American Association of Feline Practitioners
AAHA	: American Animal Hospital Association
ACE	: Angiotensin Converting Enzyme
AKI	: Acute Kidney Injury
ARB	: Angiotensin Receptor Blocker
AT-II	: Angiotensin II
AT-1	: Angiotensin II type 1 receptor
AT-2	: Angiotensin II type 2 receptor
BCS	: Body condition score
BW	: Body weight
BSH	: British Short Hair
Crea	: Creatinine
CKD	: Chronic Kidney Disease
CLB	: Case log book
DLH	: Domestic Long Hair
DSH	: Domestic Short Hair
FIV	: Feline Immunodeficiency Virus
GFR	: Glomerular filtration rate
IRIS	: International Renal Interest Society
PU/PD	: Polyuria/ Polydipsia
RAAS	: Renin–angiotensin–aldosterone system

SBP	: Systolic blood pressure
SDMA	: Serum symmetric dimethylarginine
UP/C	: Urine protein: creatinine ratio
USG	: Urine specific gravity
UVH	: Universiti Veterinar Hospital

ABSTRAK

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 4901 -Projek.

KEBERKESANAN TELMISARTAN DALAM PENGURUSAN KUCING YANG DIDIAGNOSIS PENYAKIT BUAH PINGGANG KRONIK

Oleh

JOYCE LIM QI YI

2022

Penyelia utama: Dr. Khor Kuan Hua

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Penyakit buah pinggang kronik (CKD) ialah penyakit progresif yang lazim didiagnosis pada kucing geriatrik, akibat daripada kadar penapisan glomerular yang lebih rendah dan seterusnya kegagalan fungsi buah pinggang. Kajian ini: 1) menilai kesan telmisartan pada tahap serum kreatinin, nisbah protein urea: kreatinin (UP/C), tekanan darah sistolik (SBP), skor keadaan badan (BCS) dan berat badan (BW) dalam kucing CKD, dan 2) mengenal pasti korelasi antara nisbah UP/C kepada BW dan BCS kucing CKD yang dirawat dengan telmisartan. Rekod perubatan 48 kucing yang didiagnosis CKD yang dirawat dengan telmisartan telah dikumpulkan. Parameter klinikal (tahap kreatinin serum, nisbah UP/C, SBP, BCS dan BW) pada Hari-0 (pra-rawatan) dan selepas rawatan telmisartan pada Hari-14, -30 dan -60 telah dianalisis secara deskriptif. Ujian

Friedman digunakan untuk menentukan perbezaan signifikan parameter antara titik masa manakala ujian Wilcoxon digunakan untuk mengenal pasti perubahan paling ketara pada setiap titik masa berbanding dengan Hari-0. Korelasi nisbah UP / C kepada BW dan BCS kucing yang dirawat CKD ditentukan menggunakan ujian Spearman's rho. Telmisartan dengan signifikan ($p<0.05$) mengurangkan tahap kreatinin serum kepada normal pada Hari-60, mengurangkan nisbah UP/C pada Hari-14, menormalkan SBP pada Hari-14 dan meningkatkan BCS pada Hari-30. Walau bagaimanapun, BW tidak meningkat dengan ketara ($p>0.05$) sepanjang tempoh 60 hari kajian. Nisbah UP/C berkorelasi negatif dengan BW dan BCS, ($p<0.05$). Adalah diperhatikan bahawa semua keadaan pesakit bertambah baik dengan pemulihan selera makan walaupun mempunyai CKD. Kesimpulannya, telmisartan berkesan mengawal proteinuria dalam kucing dengan CKD, seperti ditunjukkan oleh parameter klinikal: pengurangan tahap kreatinin serum, menormalkan SBP, meningkatkan BCS dan mengekalkan BW.

Kata Kunci: CKD, tekanan darah, tahap kreatinin serum, proteinuria, UP/C, Telmisartan

ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfilment of the course VPD 4901- Project.

THE EFFECTIVENESS OF TELMISARTAN IN MANAGEMENT OF CATS DIAGNOSED WITH CHRONIC KIDNEY DISEASE

by

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Chronic kidney disease (CKD) is a progressive disease, most commonly diagnosed in geriatric cats, as a result of lower glomerular filtration rate and, subsequently kidney failure. This study: 1) evaluated the effect of telmisartan on serum creatinine level, urine protein: creatinine (UP/C) ratio, systolic blood pressure (SBP), body condition score (BCS) and body weight (BW) in CKD cats, and 2) identified the correlation between UP/C ratio to BW and BCS of CKD cats treated with telmisartan. Medical records of 48 cats diagnosed with CKD treated with telmisartan were retrieved. Clinical parameters (serum creatinine level, UP/C ratio, SBP, BCS and BW) on Day-0 (pre-treatment) and post-telmisartan treatment at Day-14, -30 and -60 were descriptively analysed. Friedman's test was used to determine significant difference of parameters between time points whereas Wilcoxon test was used to identify the most significant changes at each time point compared to Day-0. The correlation of UP/C ratio to BW and BCS of the patients was determined using Spearman's rho test. Telmisartan significantly ($p<0.05$) reduced the level of serum creatinine to normal at Day-60, reduced the UP/C ratio at Day-14, normalised the SBP at Day-60 and improved the BCS at Day-30. However, the BW was not significantly improved ($p>0.05$) over the period of 60 days observation. The UP/C ratio was negatively correlated to BW and BCS, ($p<0.05$) respectively. It was noted that all the patients' conditions improved with better appetite despite having CKD. In conclusion, telmisartan effectively controls proteinuria in cats with CKD, indicated by clinical parameters: reduction in serum creatinine, normalised SBP, improved BCS and maintenance of BW.

Keywords: CKD, blood pressure, serum creatinine level, proteinuria, UP/C, Telmisartan.

1.0 Introduction

Chronic kidney disease (CKD) is the most commonly diagnosed metabolic disease in cats, with the majority of those affected being geriatric. It is an incurable, progressive condition which often requires medical attention (Sent *et al.,* 2016). CKD is defined as a prolonged reduction in renal function over a period of at least three months (Finch, 2016). CKD is the outcome of various primary disorders when impaired nephrons result in a lower glomerular filtration rate (GFR) and eventually lead to kidney failure (Martha, 2017).

The most common clinical signs in CKD cats were lethargy, anorexia, poor body condition score (BCS) and polyuria/polydipsia (PU/PD). CKD is often diagnosed based on elevation in serum creatinine concentration (>1.6 mg/dl) that was associates with low urine specific gravity (USG) (<1.035) (Sent *et al.,* 2016). The treatment and prognosis of CKD vary according to the staging system established by the International Renal Interest Society (IRIS), which consisted of 4 stages of CKD (Brown *et al.,* 2016). The treatment for cats with CKD is primarily supportive and symptomatic, aiming to improve the quality of life of affected cats and slow down the disease progression (Sparkles *et al.,* 2016).

Study has shown that systemic hypertension associated with CKD was prevalent in 19–40% of CKD cat patients (Sparkles *et al.,* 2016). Chronic compensatory activation of the renin–angiotensin–aldosterone system (RAAS) occurs in CKD patients to sustain

GFR. This is followed by the elevation of angiotensin-II (AT-II) synthesis, with renal concentrations surpassing plasma concentrations. Due to its capacity to create glomerular hypertension, leading to glomerular damage, proteinuria, and activation of pro-inflammatory and profibrotic pathways, angiotensin-II is a key mediator of renal injury (Sent *et al.,* 2015). The angiotensin II type 1 receptor (AT1) is responsible for these AT-II actions. Nevertheless, the renoprotective actions of angiotensin II are regulated by the type 2 receptors (AT2). Hence, treating proteinuria in cats is critical, and the choice of drug in managing the condition is often Benazepril, an ACE inhibitor. Recently, Telmisartan is effective in treating hypertension and proteinuria caused by CKD in cats (Dong *et al.,* 2018).

Sent *et al.* (2015) proposed that an angiotensin receptor blocker (ARB), Telmisartan, provides beneficial effects and can be used to treat cats diagnosed with CKD. Management with ACE inhibitors lowers AT-II levels, which inhibits both AT1 as well as AT2 receptors. ARBs, on the other hand, selectively block the AT1 receptor while leaving the AT2 receptor's beneficial renoprotective properties unchanged. Vasodilation, natriuresis, and suppression of renin secretion are among the renoprotective benefits, and so are anti-inflammatory, anti-ischemic, and anti-fibrotic actions (Sent *et al.,* 2015).

Cats with CKD are very likely to lose weight. The prevalence falls between 42-82%, depending on the stage of CKD, concurrent diseases and treatment (Freeman *et* *al.,* 2016). In CKD cats, the median body condition score (BCS) of 4 was considered ideal (Tolbert *et al.,* 2017). Factors contributing to weight loss in CKD include inflammation, reduced appetite, malabsorption and increased energy requirement (Freeman 2012).

1.1 Justification, objectives and hypothesis

1.1.1 Justification of the study

Sent (2015) demonstrated that telmisartan could be administered to treat proteinuria in cats with CKD. In 2014, Boehringer Ingelheim (Canada) Ltd. launched Semintra® telmisartan oral solution to treat proteinuria in CKD cats. However, in Malaysia, Semintra was only registered and successfully marketed to be prescribed in cats with CKD in 2018 with limited availability. This study investigates the benefits and effectiveness of Telmisartan in managing CKD in cats locally.

1.1.2 Objectives of the study

The objectives of this retrospective study were:

1) To evaluate the effect of telmisartan on serum creatinine level, proteinuria, systolic blood pressure, body weight and BCS in CKD cats, and

2) To correlate the UP/C ratio to body weight and BCS of cats with CKD.

1.1.3 Hypothesis of the study

1. Ho: Telmisartan is **not effective** in the treatment of cats with CKD without reducing serum creatinine level, reducing the level of proteinuria (UP/C ratio), normalising the blood pressure, improving BCS and maintaining body weight.

   Ha: Telmisartan is **effective** in the treatment of cats with CKD without reducing serum creatinine level, reducing the level of proteinuria (UP/C ratio), normalising the blood pressure, improving BCS and maintaining body weight.

2. Ho: There is no correlation between the UP/C ratio to body weight and BCS of cats with CKD.

   Ha: There is a correlation between the UP/C ratio to body weight and BCS of cats with CKD.

2.0 Literature Review

2.1 Chronic kidney disease

Felines are susceptible to developing CKD, with a prevalence ranging between 1.6% to 20.0%. CKD is progressive in nature and characterised by an ongoing decrease in kidney function (Polzin, 2010). Although CKD affects cats of all ages, it was reported to affect up to 80% of cats over the age of 15 and, therefore, regarded as a major cause of death in geriatric cats (Chen *et al.,* 2020). Age, breed, immunisation, hypertension, proteinuria, and acute kidney injury (AKI) were among the factors that had been linked to the development of CKD (Greene *et al.,* 2014). At an early stage of CKD, affected cats may be asymptomatic or with unremarkable physical examination findings. Therefore, annual health screening is crucial to diagnose feline CKD at an early stage. This will allow any existing renal parenchymal impairment at the early stage to be identified and allows a suitable therapeutic intervention and long-term management.

CKD in cats is often detected at the later stage of the disease when renal impairment surpasses the capacity of compensatory mechanisms and significant irreversible damage to the renal parenchyma has occured (Yerramilli *et al.,* 2016). The International Renal Interest Society (IRIS) classified CKD into 4 stages. The incidence of CKD-related comorbidities, like secondary renal hyperparathyroidism, anaemia, hyperphosphatemia, proteinuria, hypokalaemia, systemic hypertension, metabolic acidosis, and uraemia, rise generally with increasing stage, and thus the prognosis and treatment differ in each stage (Boyd *et al.,* 2008).

2.2 Risk factors of CKD

A study has shown that cats reported as emaciated, and dehydrated, have recently undergone general anaesthesia, previously diagnosed with periodontal disease, cystitis and male cats are more likely to be diagnosed with CKD (Greene *et al.,* 2014). Another study identified several conditions, such as hyperthyroidism, regular vomiting and anorexia, as risk factors for CKD in cats (Barlette *et al.,* 2010). Similarly, cat breeds, including the Abyssinian, Russian blue, Maine Coon, Siamese, Burmese and Abyssinian (Lulich *et al.,* 1992), along with cats infected with the feline immunodeficiency virus (FIV) have been reported with an elevated risk of being diagnosed with CKD (White *et al.,* 2010). Screening of cat patients at risk of the disease routinely may help to identify the onset of azotaemia in felines. Identification of risk factors is crucial to monitor the disease progression and stop further kidney damage. It also allows early diagnosis of the underlying illness and treatment interventions (Finch *et al.,* 2016).

2.3 Diagnosis of CKD

The most prevalent clinical symptoms of CKD include anorexia, vomiting, polyuria, polydipsia, halitosis, weight loss and lethargy (Sent *et al.,* 2016). Upon physical examination, CKD cats usually presented with emaciated body condition score, pale mucous membrane, periodontal disease, irregular shape, and abnormal size of kidney (White *et al.,* 2006). CKD is diagnosed based on the presence of renal azotaemia with poor ability to concentrate urine (USG <1.035) (Sparkles *et al.,* 2016). Elevated blood urea nitrogen and serum creatinine driven by underlying renal dysfunction is known as renal azotaemia. Creatinine is less impacted by extra-renal factors and therefore is a more reliable indicator of the glomerular filtration rate (GFR) than urea (Paepe, 2013).

Most cats with CKD have isosthenuric urine (USG 1.007–1.015). Evidence of isosthenuric urine is a good indicator of the inability to concentrate urine in azotemic or dehydrated animals (Braun *et al.,* 2016). Moreover, low-level proteinuria findings affect a crucial prognosis indicator (urine protein: creatinine ratio [UP/C <1]) (Paepe, 2013). Proteinuria is strongly associated with a lower chance of survival in cats and dogs (Dong *et al.,* 2018).

Assessment of GFR is ideal for identifying early or non-azotaemic CKD but direct measurement of GFR is not possible in routine clinical settings. Instead, serum symmetric dimethylarginine (SDMA) as an indirect marker of GFR was used to detect early CKD as elevation of SDMA occurs earlier than creatinine and urea (Cannon, 2016). To summarise, findings such as elevation in serum creatinine, low USG, relevant clinical signs, and patient history are important elements in diagnosing CKD.

2.4 International Renal Interest Society (IRIS) CKD Staging

Following the diagnosis of CKD, the patient is then staged to monitor and indicate treatment. International Renal Interest Society (IRIS) demonstrated a CKD staging system based on fasting blood creatinine concentrations or SDMA, which reading is taken twice in a stable patient (Table 1).

Table 1: International Renal Interest Society (IRIS) of CKD Staging in cats.

Stage	Blood creatinine µmol/l mg/dl	SDMAµg/dl	Comments
1	<140 <1.6	<18	Normal, Non-azotemic, may be due to inadequate urinary concentrating ability without identifiable non-renal cause. SDMA concentration (>14 µg/dl) may be used to diagnose early CKD.
2	140-250 1.6-2.8	18-25	Mild renal azotemia. Clinical signs are usually mild or absent.
3	251-440 2.9-5.0	26-38	Moderate renal azotemia. Many extrarenal signs may be present, but their extent and severity may vary.
4	>440 >5.0	>38	Increasing risk of systemic clinical signs and uremic crises

If there is no sign of urinary tract inflammation or bleeding and regular plasma protein measurements have ruled out dysproteinemias, UP/C should be evaluated in all cats with CKD. Based on proteinuria (Table 2) and systemic blood pressure (Table 3), the patient is then sub-staged (IRIS, 2019).

Table 2: International Renal Interest Society (IRIS) of CKD Sub-staging based on UP/C in cats.

UP/C	Substage
<0.2	Non-proteinuric
0.2 - 0.4	Borderline proteinuric
>0.4	Proteinuric

The degree of risk of organ damage indicated by systolic blood pressure was used to substage the patients to evaluate whether there is a sign of abnormality or injury to the target organ (IRIS, 2019).

Table 3: International Renal Interest Society (IRIS) of CKD Sub-staging based on UP/C in cats.

Systolic Blood Pressure mmHg	Blood Pressure Substage	Risk of Future Target Organ Damage
<140	Normotensive	Minimal
140-159	Prehypertensive	Low
160-179	Hypertensive	Moderate
>180	Severely Hypertensive	High

2.5 Treatment and Management of cats with CKD

Although there is no known cure for CKD, medication can enhance and lengthen the lifespan and improve its quality of life (Sent *et al.,* 2016). The goal of therapy is to halt the progression of renal impairment, reduce the accumulation of hazardous waste products in circulation, keep patients dehydrated, address electrolyte concentration changes, provide a urinary-formulated diet, and regulate blood pressure (Sparkles *et al.,* 2016).

Cats with CKD may live longer and have a higher quality of life when fed therapeutic diets low in protein, sodium and phosphorus but rich in water-soluble vitamins, antioxidants, and fibres (Polzin, 2010). A study showed that Prescription Diet k/d feline renal health (Hills Pet Nutrition, Topeka, Kansas, USA) significantly reduces renal-related mortality and uremic episodes compared to a regular maintenance diet without causing any harmful effects (Ross *et al.,* 2006).

A study showed that systemic hypertension associated with CKD is reported to be prevalent in 19–40% of patients (Sparkles *et al.,* 2016). Renal insufficiency causes renal afferent neurons to become active and stimulate β-adrenergic from the central nervous system to release renin. The release of renin activates the renin-angiotensin-aldosterone system (RAAS). The increase of ACE and the influx of leukocytes expressing angiotensin II have both been used to indicate activation of the local RAAS (Long *et al.,* 2004).

Angiotensin-II has been identified as a key mediator of renal injury. It creates glomerular hypertension, leading to glomerular ischemia, proteinuria, and activation of pro-inflammatory and profibrotic pathways. The angiotensin II type 1 (AT1) receptor is responsible for these AT-II actions but the renoprotective actions such as vasodilation, natriuresis, anti-ischemic, anti-fibrotic and anti-inflammatory pathways are regulated by the type 2 (AT2) receptor (Sent *et al.,* 2015). The choice of drug in managing the condition is often Benazepril, an ACE inhibitor. An ACE inhibitor prevents angiotensin I from being converted to angiotensin II by inhibiting the angiotensin-converting enzyme. (Herman *et al.,* 2022)

Telmisartan, an angiotensin receptor blocker (ARB) was shown to be effective in treating hypertension and proteinuria due to CKD in cats (Dong *et al.,* 2018). A study proposed that angiotensin receptor blockers (ARBs) can benefits cats diagnosed with CKD by selectively blocking the AR1 receptor while leaving the beneficial renoprotective properties of AR2 receptors unchanged (Sent *et al.,* 2015).

3.0 Materials and Methods

3.1 Data collection

A retrospective cohort design study was carried out in University Veterinary Hospital (UVH), Faculty of Veterinary Medicine, Universiti Putra Malaysia. The clinic case log book (CLB) of cat patients between 2018 to 2021 was obtained and manually screened. The case file number of each cat diagnosed with CKD treated with telmisartan was noted and the case files were manually retrieved.

Information such as signalment (age, gender, breed, body weight and body condition score) were recorded. Findings on complete blood count, serum biochemistry, urinalysis and blood pressure measurement were reviewed and recorded.

3.2 Inclusion criteria

The inclusion criteria of CKD cats recruited in this study were; i) cats diagnosed with CKD received telmisartan as part of the treatment, ii) retrievable patient file records with complete patient signalment, iii) available complete blood and urinalysis results, and iv) blood pressure measurements. CKD cat patients with concurrent diseases were excluded from this study for analysis.

3.3 Patient signalment (age, gender, breed, body weight and body condition score [BCS])

The age (years) of cats was recorded and categorised into 6 groups according to the life stage guidelines by the American Association of Feline Practitioners (AAFP) and American Animal Hospital Association (AAHA) (2010). In this study, the age groups were categorised as follows i) Kitten (new born - 6 months old), ii) Junior (7 months - 2 years old), iii) Prime (3 - 6 years old), iv) Mature (7 - 10 years old), v) Senior (11 - 14 years old), and vi) Geriatric (>15 years old) (Refer to appendix 8.1).

The breed of cats was noted and the body weight was recorded in kilogram (kg). The body condition scoring (BCS) was recorded from 1 to 5 based on American Animal Hospital Association (AAHA) BCS system (2010) (Refer to appendix 8.2). The gender of the cat was recorded as either intact male, intact female, castrated male or spayed female.

3.4 Patient clinical pathological findings pre- and post-treatment with telmisartan.

The data collected were recorded on Day-0 (as pre-treatment) and post-treatment using telmisartan on Day-14, -30 and -60. For all the time points, the serum creatinine level and urine protein to creatinine ratio (UP/C) were recorded. Five measurements of the systolic blood pressure were obtained and averaged. The body weight and BCS were noted at all time points for each cat.

3.5 Statistical Analysis

The information and data were tabulated in Microsoft Excel. Data obtained were descriptively analysed, and normality testing using Statistical Package for the Social Sciences® (SPSS) software (IBM, USA) revealed that the data collected was not normally distributed for each parameter. A non-parametric Friedman's test was used to determine the significant parameter differences between time points. Wilcoxon signed-rank test was then used as a post-hoc test to compare the parameters at each time point to Day-0. The Friedman's test showed whether telmisartan showed a significant effect upon treatment, while Wilcoxon showed the specific time point where telmisartan showed its effect. The correlation of UP/C ratio to body weight and BCS were investigated using Spearman correlation tests. Statistical significance was accepted with a *p*-value at ≤ 0.05.

4.0 Results

A total number of 48 feline patients identified with CKD and treated with telmisartan were identified. Information such as body weight, BCS, serum creatinine level, UP/C ratio, and systemic blood pressure was recorded accordingly.

The age range of cats sampled in this study was between 4 to 18 years old with an average age of 10.8 years old. Based on the life stage, a majority of the cats were of the mature age group (n=21), followed by senior, geriatric and prime groups (Refer to Table 4).

Table 4: Age group categories of cats diagnosed with CKD (n=48).

Categories	Age Range	No. of felines sampled, n (%)
Prime	3 years to 6 years old	4 (8.33%)
Mature	7 years to 10 years old	21 (43.75%)
Senior	11 years to 14 years old	17 (35.42%)
Geriatric	15 years old and above	6 (12.50%)

There were 24 males (50%) and 24 females (50%) cats. In each group of gender, most of the cats were neutered (Refer to Table 5).

Table 5: Gender categories of cats diagnosed with CKD (n=48).

Categories	No. of felines sampled, n (%)
Intact Male	4 (8.33%)
Castrated Male	20 (41.67%)
Intact Female	2 (4.17%)
Spayed Female	22 (45.83%)

Based on the breed classified, majority were of Domestic Short Hair (n=36), followed by Persian (n= 6), Domestic Long Hair (n=2), British Short Hair (n=1), Scottish Fold (n=1), Maine Coon (n=1) and Norwegian Forest Cat (n=1) (refer Figure 1).

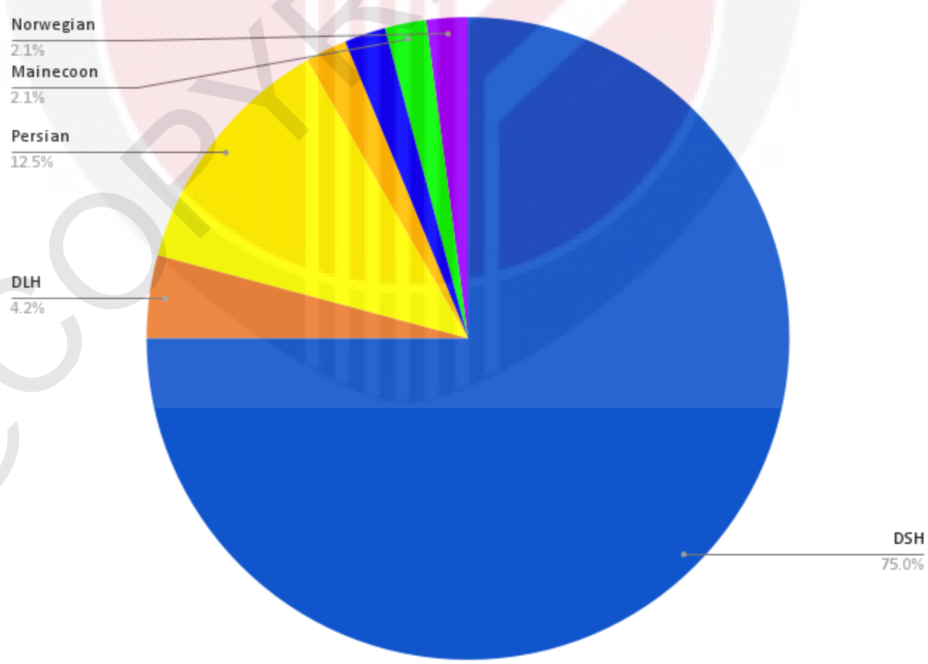

Figure 1: Breed categories of cats diagnosed with CKD (n=48).

In this study, the IRIS staging of each CKD cats were based on the serum creatinine level. Most of the CKD cats were in Stage 2 (n=28), followed by Stage 4 (n=11), Stage 3 (n=11) and Stage 1 (n=1) (refer Figure 2).

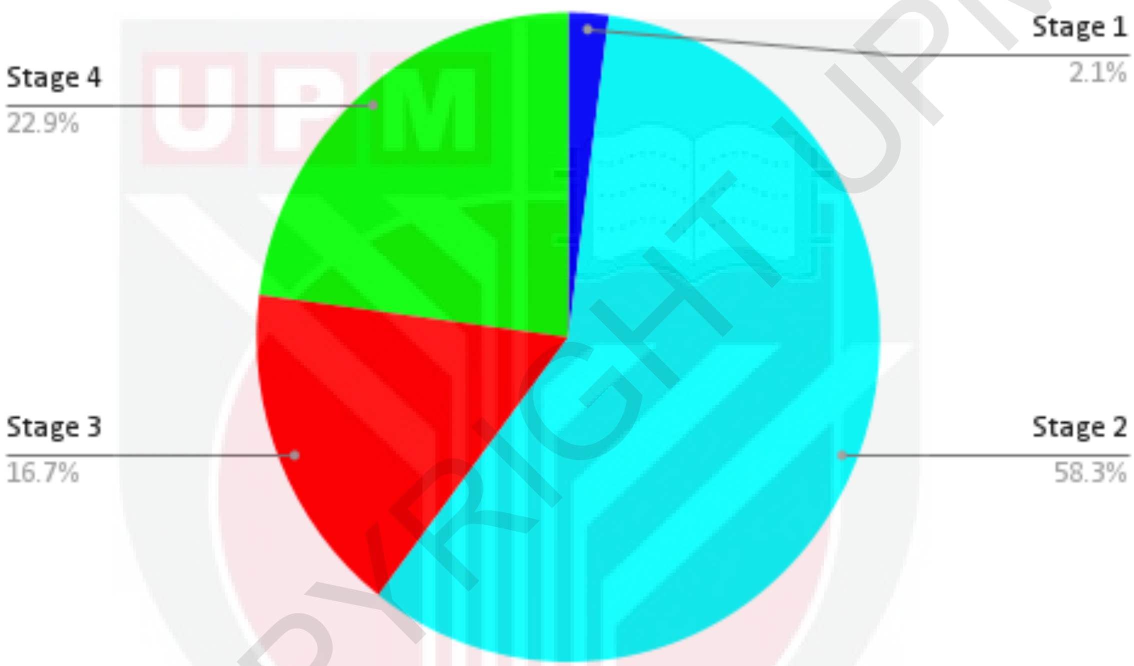

Figure 2: Staging of the cats diagnosed with CKD (n=48).

Throughout our study, the parameters that we looked into were the body weight, BCS, serum creatinine level, UP/C ratio, and systemic blood pressure. A descriptive analysis of the study parameters in different treatment time point and in CKD cats in this population were summarised and tabulated in Table 6.

Index	**Day-0**	**Day-14**	**Day-30**	**Day-60**
Bw(kg)	3.7 (2.8-4.6)	3.6 (2.6-4.6)	3.8 (4.7-5.6)	4 (3.2-4.8)
BCS	3 (2.4- 3.6)	3 (2.4-3.6)	3 (2.5-3.5)	3 (2.4-3.6)
SBP (mmHg)	144 (113.6-174.4)	132 (110-154)	129.4 (113.5-145.2)	128 (115.5-140.5)
Crea (g/Dl)	247.5 (-24.1-519.1)	226 (-73.9-525.9)	196 (6.63-385.4)	154 (43.7-264.3)
UP/C	0.4 (-1.6-2.4)	0.2 (-1.97-2.37)	0.2 (-1.43-1.83)	0.1 (-0.04-0.24)

Table 6: Descriptive analysis of the study parameters in different treatment time point and in CKD cats

All data expressed with the median value (± S.D.). Bw, body weight; BCS, body condition score; SBP, systolic blood pressure; Crea, creatinine; UP/C, urine protein to creatinine ratio.

Serum creatinine level reduced significantly after treatment with telmisartan ($p<0.05$) especially on Day 60 where its median fell within the normal range (60.0-193.0 µmol/L). The median serum creatinine level was 247.5 ± 271.6 µmol/L on Day-0 (pre-telmisartan treatment) and observed gradually decreased to 226.0 ± 299.9 µmol/L on Day-14, 196 ± 189.4 µmol/L on Day-30 and 154 ± 110.3 µmol/L on Day 60 post-telmisartan treatment (Refer figure 3).

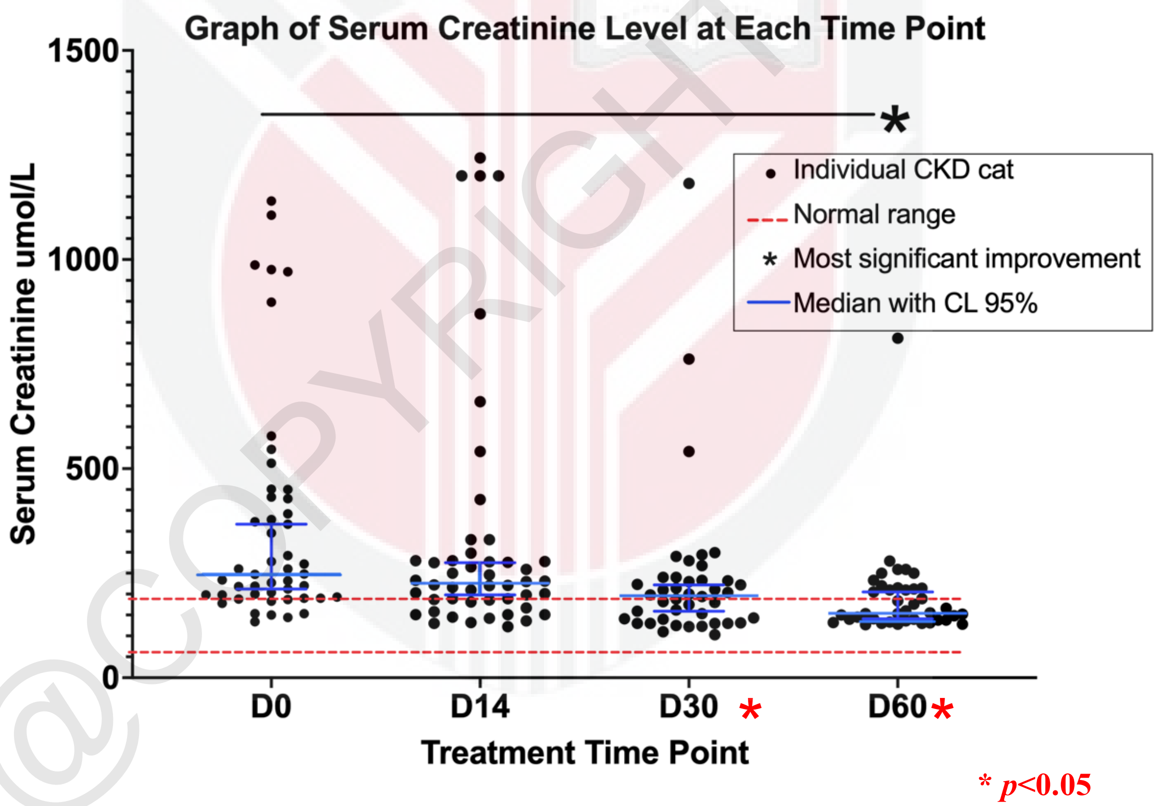

Figure 3: Graph of serum creatinine level at each time point.

Urine protein to creatinine ratio (UP/C) of the population has a median of 0.4 ± 1.9 before administration of telmisartan (Day 0), which is at borderline proteinuric to proteinuric level. Upon treatment of telmisartan, the UP/C ratio reduced to 0.2 ± 2.17 on Day 14, 0.2 ± 1.63 on Day 30 and 0.1 ± 0.14 on Day 60. The UP/C ratio reduced significantly especially on Day 60 with its median fell back to non- proteinuric (< 0.2). (Refer figure 4)

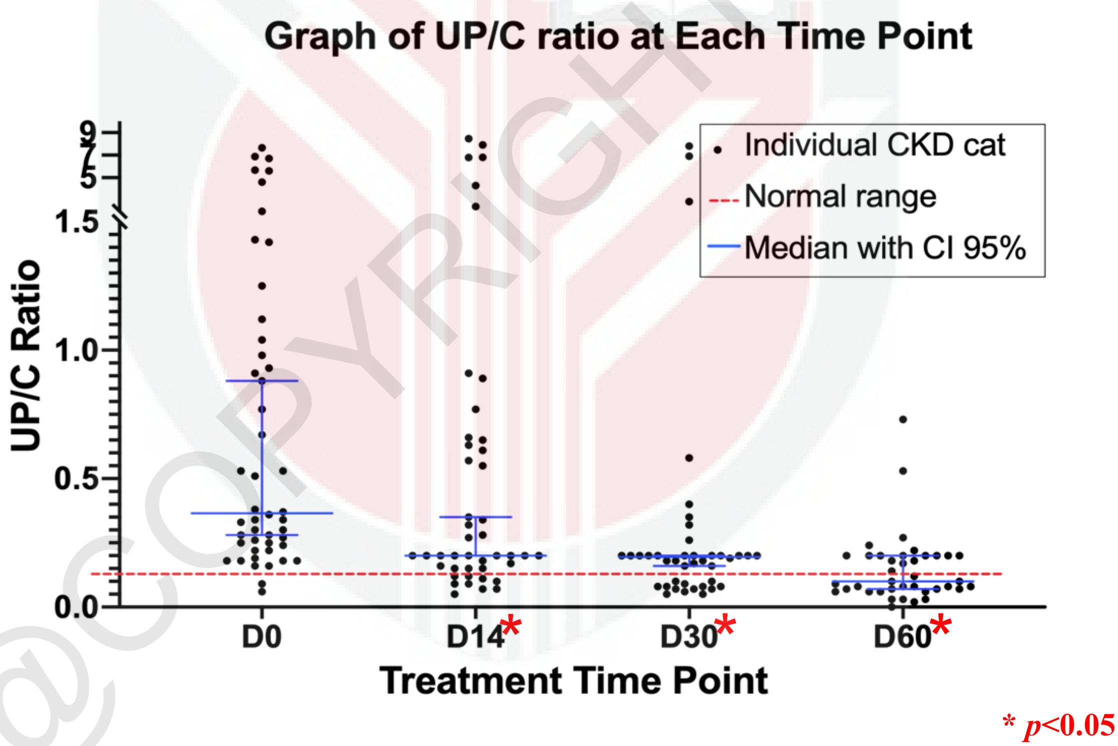

Figure 4: Graph of UP/C ratio at each time point.

The median systolic blood pressure (SBP) of the cats were 144 ± 30.4 mmHg before telmisartan was given as a treatment (Day 0). The blood pressure then reduced to 132 ± 2.0 mmHg on Day 14, 129.4 ± 15.9 mmHg on Day 30 and 128 ± 12.5 mmHg on Day 60 after administration of telmisartan. There was a significant decrease ($p<0.05$) in SBP especially Day 14 onwards where its median fell back within the normal range which is 120- 140 mmHg. (Refer figure 5)

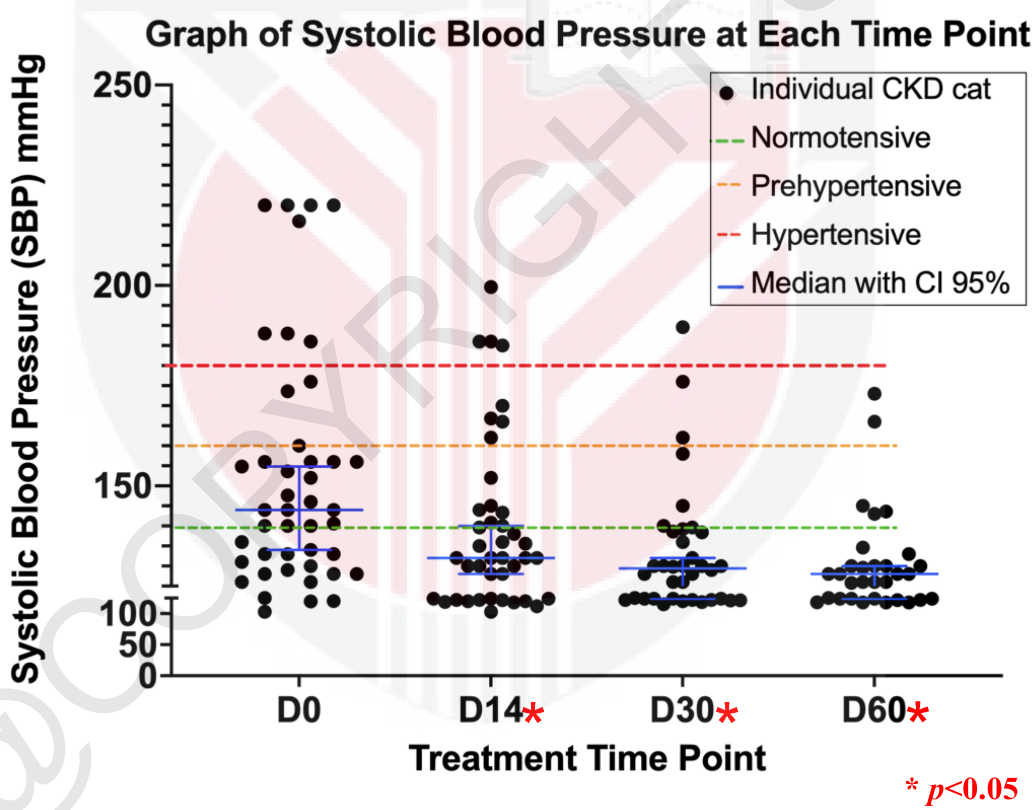

Figure 5: Graph of systolic blood pressure at each time point.

The body condition score (BCS) in the population increased slightly with statistical significance (*p*< 0.05) at the end of the study (Refer figure 6). The initial BCS median for the study population was 3 (Day 0) with most of them scored between 2-3 and it remained the same at the end of study (Day 60) however, with most of them scored between 3- 4. (Refer figure 6)

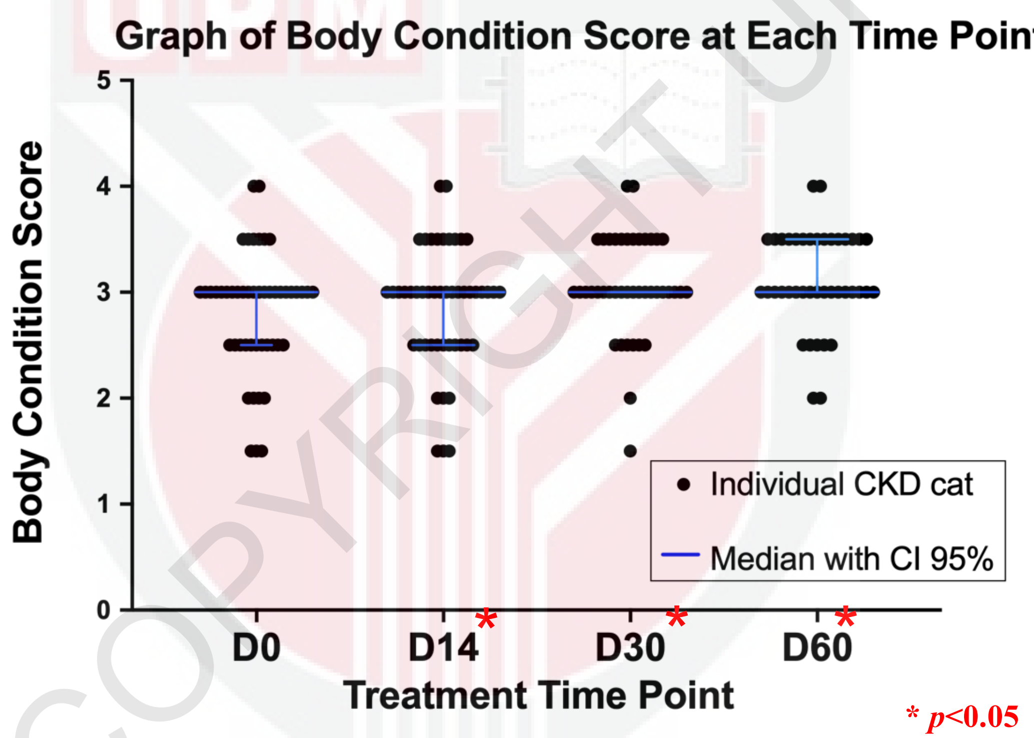

Figure 6: Graph of body condition score at each time point.

In comparison with the body weight, a slight increase was noted on the Day-60 although it was not proven to be statistically significant (p =0.92) when compared to Day-0 (Refer Figure 7).

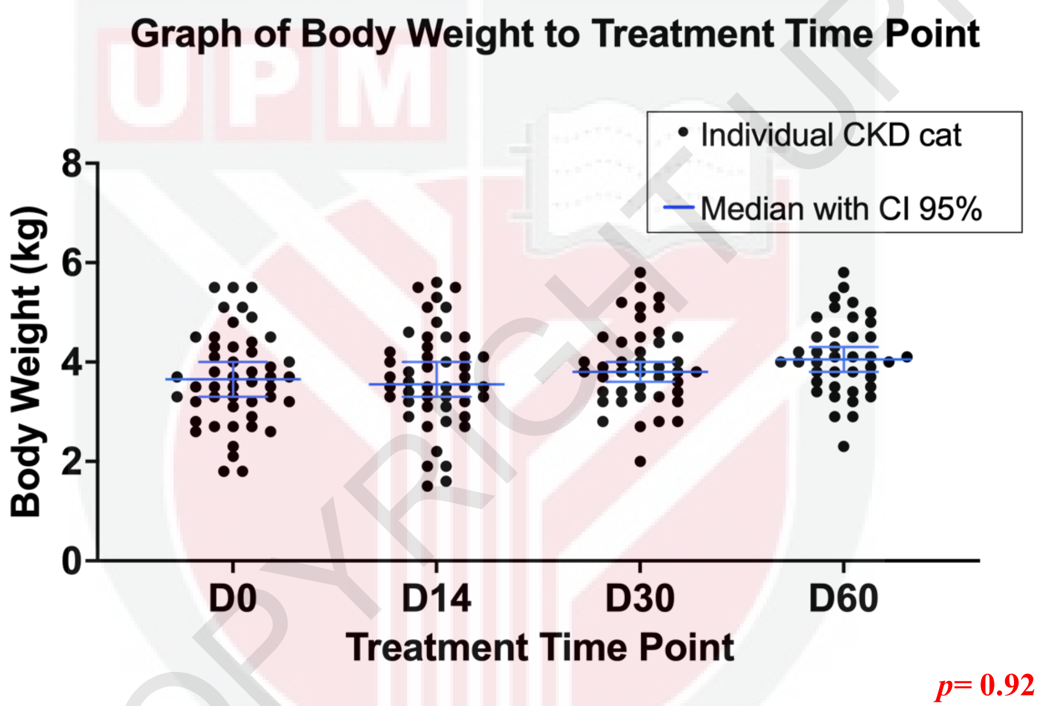

Figure 7: Graph of body weight to each time point

Spearman's Rho test was carried out to identify the correlation between UP/C ratio with body weight and BCS. There was a significant correlation between UP/C ratio with both body weight and BCS ($p< 0.001$) (Refer Table 3 and 4). UP/C was negatively correlated to body weight and BCS, indicating that a drop in UP/C ratio will increase the body weight and BCS. However, the correlation between the variables was weak (Refer Table 7 and 8).

Table 7: Correlation between UP/C ratio to body weight of CKD cats

			UP/C ratio	Body Weight
Spearman's rho	**UP/C ratio**	Correlation Coefficient	1.000	-.244**
		Sig. (2- tailed)	.	.000
		N	170	170
	Body Weight	Correlation Coefficient	-.244**	1.000
		Sig. (2- tailed)	.000	.
		N	170	184

**. Correlation is significant at the 0.01 level (2-tailed).

Table 8: Correlation between UP/C ratio to BCS of CKD cats.

			UP/C ratio	BCS
Spearman's rho	**UP/C ratio**	Correlation Coefficient	1.000	-.426**
		Sig. (2- tailed)	.	.000
		N	170	170
	BCS	Correlation Coefficient	-.426**	1.000
		Sig. (2- tailed)	.000	.
		N	170	179

**. Correlation is significant at the 0.01 level (2-tailed).

5.0 Discussion

CKD is a very common disease among geriatric cats (Brown *et al.*, 2016), usually presented at its senior life stage and was reported at the average age of 12 years old (Brown *et al.*, 2016). In this study, majority of the cats recruited were aged between 7 to 10 years old, the mature group (43.75%; n=21/48). This finding was compatible with a study that was carried out locally that stated the average age of cats diagnosed with CKD was 8 years old (Tiu *et al*., 2019).

This study recruited an equal number of cats, both male and female (n=48), and most of them were neutered. As to whether neuter status was a contributively factor in cats developing CKD could not be determined in the present study. Idiopathic membranous glomerulopathy has been reported as more common in male cats, and male neutered cats have been speculated may acquire CKD at a younger age than spayed females (Greene *et al*., 2014). In contrast, no sex-based risk of CKD has been documented in the general population according to IRIS guidelines (2019).

Persian, DLH, BSH and Maine Coon have been reported predisposed to CKD, and polycystic kidney disease was the most common diagnosis (Sato *et al.*, 2019). Among the 48 cats recruited, DSH (75%; n=36/48) was frequently diagnosed with CKD. It could be speculated that DSH is the favourite breed among cat lovers locally, and this causes it to be over-presented at the hospital compared with other breeds. Hence, DSH is more frequently diagnosed with CKD compared to other breeds of cats.

Detection of CKD at an early stage allows cat owners to decide on early intervention to delay CKD progression. SDMA, which is the methylated form of the amino acid arginine, was produced in the bloodstream during protein degradation and excreted by the kidneys (Braff *et al.,* 2014). In clinical practice, SDMA is a useful biomarker of the kidneys that indicates the glomerular filtration rate since it is virtually entirely removed by renal filtration (GFR) (Hall *et al.,* 2014). As the glomerular filtration rate declines, the concentration of the sensitive kidney biomarker symmetric dimethylarginine (SDMA) rises earlier than creatinine (Relford, 2016). Compared to creatinine, which does not rise until renal function has been reduced by 75%, SDMA increases on average when kidney function declines by 40% (Hall *et al.,* 2014). However, SDMA assays were not analysed in our study due to unavailability. Hence, only serum creatinine was used to stage the severity of kidney among the cats recruited. Out of 48 patients, only 1 CKD cat was staged as Stage 1 (2.1%; n=1/48).

The majority of the CKD cats recruited were in Stage 2 (58.3%; n=28/48), whereby an increase in the level of serum creatinine was detected, indicating mild renal azotaemia. Creatinine in the bloodstream typically being filtered out by the kidney at a constant rate. In CKD cats, GFR declines and creatinine failed to be filtered out of the bloodstream (Hall *et al.,* 2014). In Stage 2 CKD cats, the creatinine level is between 1.6 and 2.8 mg/dL, indicating that the kidneys have lost 66% to 75% of their function (King, 2022). In our study, most patients were detected in Stage 2 as serum creatinine levels do not increase unless renal function dropped by 75% (Hall *et al.,* 2014).

The diagnosis of CKD in dogs and cats is often made at the later course of the disease, typically after the animal has shown clinical symptoms (IRIS, 2019). Clinical symptoms may vary between different cats and dependent onthe stage of the disease. The common clinical signs of cats with CKD are lethargy, anorexia, poor body condition score (BCS) and polyuria/polydipsia (PU/PD) (Sent *et al.,* 2016). Before a better early CKD detection method was developed, the potential effect of treatment was often expected to delay progression rather than lead to the recovery of renal function, which makes it challenging to determine the underlying aetiology until today (IRIS, 2019).

CKD has been known to be the most common disease that causes secondary systemic hypertension in cats (Jepson, 2011). Systemic hypertension was associated with CKD and thought to be induced by activation RAAS (Williams *et al.,* 2013). Chronic RAAS activation results in persistent systemic hypertension (AT1 receptor), resulting in glomerular hypertension, leading to glomerular ischemia, proteinuria, activation of pro-inflammatory and profibrotic pathways (Sent *et al.,* 2015). The AT1 receptors are directly inhibited by ACE-independent angiotensin receptor blockers (ARBs) while leaving the angiotensin-II type 2 receptors (AT2 receptors) open to activation (Putnam *et al.,* 2012). This allows the renoprotective actions of the AT2 receptors to occur, namely vasodilation, natriuresis, suppression of renin secretion, anti-inflammatory, anti-ischemic, and anti-fibrotic actions (Sent *et al.,* 2015).

Creatinine is continuously produced throughout routine muscle breakdown, and as renal function declines, the kidneys become less capable of excreting creatinine, which causes its concentration to rise (Agrawal *et al.,* 2016). Observation from this study showed that telmisartan significantly reduced the serum creatinine level compared to pre-treatment (Day-0). Agrawal (2016) showed that telmisartan preserved the glomerular filtration rate and suppressed CKD progression (Agrawal *et al.,* 2016). Hence, our study further supports that telmisartan effectively enhanced kidney function to eliminate creatinine. However, there are contradictory findings regarding creatinine. While some studies claimed that the level did not significantly change upon treatment with telmisartan (Aranda *et al.,* 2005), others asserted that the level slightly decreased (Agrawal *et al.,* 2016). Perhaps majority of the CKD cats in this study were in Stage 2, and response to treatment would be more effective at this stage.

Our study showed that telmisartan has the ability to decrease proteinuria significantly, and this result was compatible with the findings by Sent (2015), which showed that telmisartan has the ability to decrease proteinuria significantly and was safe to be administered to cats with CKD. ARBs like telmisartan can effectively block the activity of RAAS because they selectively block the AT1 receptor while having no impact on the AT2 receptor that allows renoprotective properties (Sent *et al*., 2015). In contrast, the commercial drug, Benazepril (ACE inhibitor) inhibits the conversion of angiotensin I to angiotensin II, hence inhibiting the entire RAAS as well as preventing the renoprotective actions of the AT2 receptor. Therefore, our results explained the renoprotective properties in telmisartan and hence reduced proteinuria.

As hypertension has been known to be correlated with CKD and proteinuria in cats (Syme *et al.,* 2006). In cats with CKD, systemic arterial hypertension may hasten the loss of renal function, increases glomerulosclerosis, and worsen proteinuria; these are bad prognostic signs in feline CKD (Chakrabarti *et al.,* 2012). Without influencing other receptor systems that are involved in cardiovascular control, telmisartan as an ARB lowers the SBP by specifically inhibiting angiotensin II by blocking the AT1 receptor (Amrinder *et al.,* 2013). In this study population of CKD cats, a reduction in average SBP was observed in just 2 weeks after administration of telmisartan, with the median falling back within the normal range, which is 120- 140 mmHg as compared to Day-0 where the median of the SBP was 144 ± 30.4 mmHg. Our study finding was similar to a study that showed that telmisartan as an ARB reduces the SBP measurement (Coleman *et al*., 2018). Hence, our study supports the clinical use of telmisartan as an alternative for treatment in CKD cats with its antihypertensive properties.

With reference to BCS, the percentage of "thin" or "emaciated" cats with CKD ranges from 36.0 to 81.0% (Greene *et al.,* 2014), and it is one of the most common clinical signs in CKD cats that their owners will take note of (Freeman *et al*., 2016). In terms of BCS, telmisartan effectively improved the BCS of cats with CKD throughout the treatment period in contrast with pre-treatment BCS. There was a subtle gain in body weight, although it was not statistically significant. Due to the anti-proteinuric properties of telmisartan (Sent *et al*., 2015), protein loss in CKD cats can be lowered while their appetite may improve. The result might show a more significant effect of telmisartan in improving the BCS and body weight of the patients if the study was being carried out at a longer duration. Taking into account that telmisartan was prescribed to patients with existing hypertensive and proteinuria, the result of the study were considered satisfactory.

Multiple components, such as malabsorption, inflammation, increased energy needs, and anorexia, contribute to weight loss in CKD cats (Freeman *et al.,* 2016). UP/C ratio is the simplest way to quantify proteinuria, whereby an excessive amount of protein was found in the urine due to kidney dysfunction (Giraldi *et al.,* 2018). In this study, body weight and BCS were negatively correlated with UP/C, suggesting that a decrease in the UP/C ratio will lead to increased body weight and improved BCS. However, the association between the UP/C ratio to body weight and BCS were weak. A longer study duration may result in a stronger association in terms of the effectiveness of telmisartan in lowering proteinuria, reducing inflammation and improving the appetite across the treatment period.

6.0 Conclusion

Telmisartan is effective in the treatment in cats with CKD indicated reduction in serum creatinine level, reducing proteinuria (indicated by a drop in UP/C ratio), normalizing the systolic blood pressure, improving the BCS and maintenance of body weight. Our study also showed that a decrease in the UP/C ratio will result in an increase in body weight and BCS, as a result to the negative correlation between UP/C ratio to BW and BCS of CKD cats. Hence, incorporating telmisartan in the treatment of CKD cats will improve the quality of life. Overall, our study showed that CKD cats treated with telmisartan had a noticeable and gradual drop in serum creatinine level, SBP and UP/C ratio in cats with CKD together with its positive effect of improving BCS as well as maintaining body weight.

7.0 Recommendations

At the end of study, a prospective study on the effect of telmisartan for different stages of CKD in cats and dogs can be carried out. CKD cats treated with Telmisartan should be monitored at a longer duration to allow telmisartan to exert its full potential. Last but not least, the survivability of CKD cats treated with telmisartan in comparison with other anti-proteriuric drug can be done.

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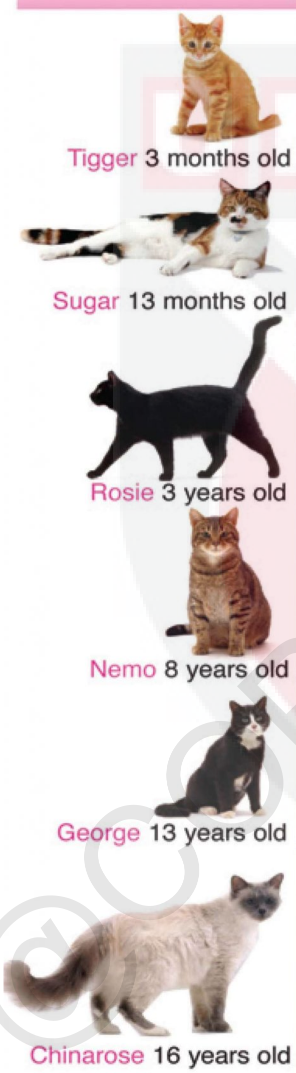
9.0 Appendices

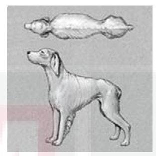
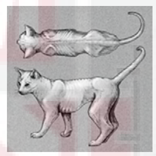
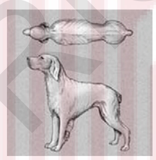
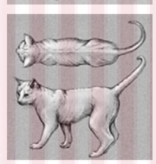
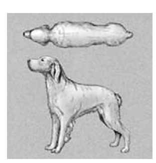
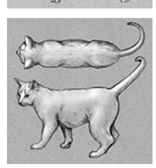
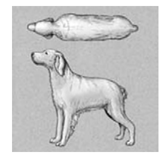
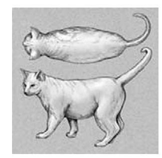
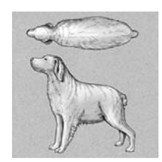
9.1 Life stage guidelines by the American Association of Feline Practitioners (AAFP) and American Animal Hospital Association (AAHA) (2010)



Life stage	Age of cat	Human equivalent
Kitten birth to 6 months	0 – 1 month	0 – 1 year
	2 – 3 months	2 – 4 years
	4 months	6 – 8 years
	6 months	10 years
Junior 7 months to 2 years	7 months	12 years
	12 months	15 years
	18 months	21 years
	2 years	24 years
Prime 3 years to 6 years	3	28
	4	32
	5	36
	6	40
Mature 7 years to 10 years	7	44
	8	48
	9	52
	10	56
Senior 11 years to 14 years	11	60
	12	64
	13	68
	14	72
Geriatric 15 years+	15	76
	16	80
	17	84
	18	88
	19	92
	20	96
	21	100
	22	104
	23	108
	24	112
	25	116

9.2 American Animal Hospital Association (AAHA) BCS System (2010)

Body Condition Scoring (BCS) Systems

5 Point	9 Point	Description
1/5	1/9	**Dogs:** Ribs, lumbar vertebrae, pelvic bones and all bony prominences evident from a distance. No discernible body fat. Obvious loss of muscle mass.  **Cats:** Ribs visible on short-haired cats; no palpable fat; severe abdominal tuck; lumbar vertebrae and wings of ilia obvious and easily palpable. 
1.5/5	2/9	**Dogs:** Ribs, lumbar vertebrae and pelvic bones easily visible. No palpable fat. Some evidence of other bony prominence. Minimal loss of muscle mass. **Cats:** Shared characteristics of BCS 1 and 3.
2/5	3/9	**Dogs:** Ribs easily palpated and may be visible with no palpable fat. Tops of lumbar vertebrae visible. Pelvic bones becoming prominent. Obvious waist.  **Cats:** Ribs easily palpable with minimal fat covering; lumbar vertebrae obvious; obvious waist behind ribs; minimal abdominal fat. 
2.5/5	4/9	**Dogs:** Ribs easily palpable, with minimal fat covering. Waist easily noted, viewed from above. Abdominal tuck evident. **Cats:** Shared characteristics of BCS 3 and 5.
3/5	5/9	**Dogs:** Ribs palpable without excess fat covering. Waist observed behind ribs when viewed from above. Abdomen tucked up when viewed.  **Cats:** Well proportioned; waist observed behind ribs; ribs palpable with slight fat covering; abdominal fat pad minimal. 
3.5/5	6/9	**Dogs:** Ribs palpable with slight excess fat covering. Waist is discernible viewed from above but is not prominent. Abdominal tuck apparent. **Cats:** Shared characteristics of BCS 5 and 7.
4/5	7/9	**Dogs:** Ribs palpable with difficulty; heavy fat cover. Noticeable fat deposits over lumbar area and base of tail. Waist absent or barely visible. Abdominal tuck may be present.  **Cats:** Ribs not easily palpable with moderate fat covering; waist poorly distensible; obvious rounding of abdomen; moderate abdominal fat pad. 
4.5/5	8/9	**Dogs:** Ribs not palpable under very heavy fat cover, or palpable only with significant pressure. Heavy fat deposits over lumbar area and base of tail. Waist absent. No abdominal tuck. Obvious abdominal distension may be present. **Cats:** Shared characteristics of BCS 7 and 9.
5/5	9/9	**Dogs:** Massive fat deposits over thorax, spine and base of tail. Waist and abdominal tuck absent. Fat deposits on neck and limbs. Obvious abdominal distention.  **Cats:** Ribs not palpable under heavy fat cover; heavy fat deposits over lumbar area, face and limbs; distention of abdomen with no waist; extensive abdominal fat pad.