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Evaluation of a Hand-Held Point-of-Care Analyser for Measurement of Creatinine in Cats

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Abstract

Objectives: To evaluate whether a hand-held creatinine analyser (StatSensor® Xpress; SSXp), available for human patients, can be used to reliably measure creatinine in cats.

Methods: Analytical performance was evaluated by determining within-run and between-run coefficient of variation (CV, %), total error observed (TE_{obs}, %) and sigma metrics. 50 client-owned cats presenting for investigation of clinical disease had creatinine measured simultaneously, using SSXp (whole blood and plasma) and a reference instrument (Konelab, serum); 48 paired samples were included in the study. Creatinine correlation between methodologies (SSXp vs Konelab) and sample types (SSXp_{whole blood} vs SSXp_{plasma}) was assessed by Spearman's correlation coefficient and agreement was determined using Bland-Altman difference plots. Each creatinine value was assigned an IRIS stage (1-4); correlation and agreement between Konelab and SSXp IRIS stages was evaluated.

Results: Within-run CV (4.23-8.85%), between-run CV (8.95-11.72%), TE_{obs} (22.15-34.92%) and sigma metrics (≤ 3) did not meet desired analytical requirements. Correlation between sample types was high (SSXp_{whole blood} vs SSXp_{plasma}; $r = 0.89$) and between instruments was high (SSXp_{whole blood} vs Konelab_{serum}; $r = 0.85$) to very high (SSXp_{plasma} vs Konelab_{serum}; $r = 0.91$). Konelab and SSXp_{whole blood} IRIS scores exhibited high correlation ($r = 0.76$). PCV did not significantly affect SSXp determination of creatinine. Bland-Altman difference plots identified a positive bias for the SSXp (7.13 $\mu\text{mol/l}$ SSXp_{whole blood}; 20.23 $\mu\text{mol/l}$ SSXp_{plasma}) compared with the Konelab. Outliers (1/48 whole blood; 2/48 plasma) occurred exclusively at very high creatinine concentrations. The SSXp failed to identify 2/21 azotaemic cats.

Conclusions and relevance: Analytical performance of the SSXp in feline patients is not considered acceptable. The SSXp exhibited high to very-high correlation compared to reference methodology but the two instruments cannot be used interchangeably. Improvements in SSXp analytical performance are needed before its use can be recommended in feline clinical practice.

Introduction

Chronic kidney disease (CKD) is highly prevalent within the feline population, affecting up to 20% of clinic-attending cats, with increasing incidence with age.^{1,2} The disease is invariably progressive and remains an important cause of morbidity and mortality, particularly within the geriatric population.^{3,4,5} Recent literature has explored the incidence of occult, hospital acquired, acute kidney injury (HA-AKI) and identified a prevalence within the feline population of up to 21.2%.⁶ Despite a trend towards evaluating more sensitive serum and urine biomarkers of renal disease, creatinine remains an important diagnostic marker.^{7,8}

Point-of-care (PoC) creatinine testing has found utility in human medicine in both screening programmes for the prevalence of CKD and early identification of kidney injury in at-risk patients.^{9,10,11} PoC analyzers typically have small sample requirements and a rapid turnaround time, providing real-time clinical information.¹¹⁻¹⁵

A PoC creatinine analyzer is an attractive tool in feline clinical practice, given the high incidence of CKD in this species and their relative risk of kidney injury. Various publications have assessed the use of PoC creatinine analyzers in human medicine and a single abstract reports their use in dogs.¹⁶ To the authors' knowledge, such devices have not previously been evaluated in cats. We evaluated a hand-held analyser that is available for use in human patients; the 'StatSensor® Xpress-i™ Creatinine Hospital Meter' (SSXp; Nova Biomedical Corporation, Waltham, MA, USA). The aims of this study were (1) to perform imprecision studies using the SSXp to determine whether device performance was acceptable for the measurement of creatinine in cats and (2) to compare the results obtained from clinical samples using the SSXp to those generated from a commercial high-throughput wet

chemistry analyzer (Konelab PRIME 60, Thermo Scientific, Finland). Ethical approval was granted for the study by the University of Bristol Ethics Committee.

Materials and Methods

Clinical cases and samples

Privately owned cats presented to The Feline Centre at Langford between January 2013 and January 2014, for investigation of clinical disease, were eligible for inclusion. Blood (1.5-3ml, jugular venepuncture) was collected into an EDTA tube (TEKLAB, 0.5 ml) for routine haematology and a non-anticoagulant (plain) tube (BD Vacutainer, 1-2.5ml) for serum biochemical analysis, which included creatinine measurement using the Konelab analyser (Konelab_{serum}). The remaining blood was used for immediate creatinine measurement by the SSXp (1.2µl whole blood [SSXp_{whole blood}]) and then to fill a microhaematocrit tube (NRIS microhaematocrit tubes, Soda Lime Glass Na-Heparinized [80 iu/ml], Vitrex Medical) to enable centrifugation for determination of packed cell volume (PCV) and measurement of creatinine in the supernatant plasma using the SSXp (SSXp_{plasma}).

Icteric, haemolysed or lipaemic samples were excluded from analysis due to known interferences of bilirubin, haemoglobin and lipaemia with the creatinine methodology employed by the Konelab, and the lack of information regarding the effect of these interferences on the SSXp methodology.¹⁷

For the imprecision studies, a pooled serum sample was created using excess serum from clinical samples, stored in frozen aliquots; this sample was first analyzed in duplicate using the Konelab to confirm that the creatinine concentration was within the analytical range of the SSXp.

StatSensor Xpress

The SSXp is a small hand-held battery powered device that utilizes amperometric methodology, detecting H₂O₂ elimination from an immobilized three-enzyme membrane. Single-use Multi-Well™ technology reagent test strips are inserted into the device. Delivery of the clinical sample fills the test strip by capillary action. An audio sound confirms sample receipt and the creatinine concentration (µmol/l or mg/dl) is displayed after 30 seconds. The reported measurable creatinine range is 27-1056 µmol/l (0.31-11.95mg/dl); results outwith this are reported as 'Hi' or 'Lo'.

Three quality control solutions (StatSensor Creat Control C1, C2, C3; Nova Biomedical [QCM]) were provided which were run daily and each time a new canister of strips was opened.¹⁸ The purpose of this was to evaluate device performance prior to sample analysis. In the event of QCM results outside the provided reference interval, algorithms for device calibration were available from the manufacturer.

Konelab

Creatinine concentration was measured in serum samples using an enzymatic colorimetric methodology. Calibration procedure and sample analysis were performed according to the manufacturer's instructions.¹⁷ Control material (Biostat Diagnostic Systems) with low, normal and high values was included in every run of Konelab samples. Methodology accuracy was assessed by continuous bimonthly participation in an external quality assurance programme (RIQAS; Randox). The measuring range is 10-2500µmol/l (0.11-28mg/dl), extending to 10,000µmol/l (113mg/dl) following dilution. Imprecision is ≤4.5% total CV; within-run and between-day CV range from 0.4-1.4% and 0.3-0.5%, respectively. This laboratory's established reference interval for feline serum creatinine was 133-175µmol/l (0.37-1.98mg/dl).

Imprecision

Imprecision is the lack of repeatability of a result, during sequential analysis of a sample and is expressed as coefficient of variation (CV; %).¹⁹

SSXp imprecision was assessed by within- and between-run repeatability using the three QCM and the serum pool.

Within-run repeatability was determined by measuring creatinine in the same sample 20 times sequentially (QCM and feline serum pool).

Between-run repeatability was determined from the values generated over a 20 day period (QCM) and by measuring creatinine in duplicate daily for five consecutive days (feline serum pool).¹⁹

Sample type and method comparisons

On each day of testing, SSXp_{whole blood} was analysed immediately following sample collection and SSXp_{plasma} within 15-30 minutes afterwards. Plain tubes were transported to the Diagnostic Laboratories where Konelab_{serum} was run within 45-60 minutes post blood collection.

Data collection and statistical analysis

Data regarding the date of sample acquisition, cats' signalment, disease, creatinine results and PCV were recorded in a commercially available spreadsheet (Microsoft Excel, USA). All statistical analyses were performed using the 2D graphing and statistics software Prism® 4 GraphPad (GraphPad Software Inc., USA).

Imprecision, total error observed (TE_{obs}) and sigma (σ) metrics

Within- and between-run imprecision were determined by calculating the CV (%):

$$CV = 100 \times \text{standard deviation (SD)} / \text{mean}$$

Total error observed (TE_{obs} ; %) is the sum of random error (imprecision) and systematic error, with the former represented by CV and the latter represented by bias (inaccuracy of the generated result compared to the true value). TE_{obs} for creatinine was determined by the following formula:¹⁹

$$TE_{obs}(\%) = 2 \times CV + \text{bias}(\%)$$

Bias was calculated using the QCM according to the following formula:

$$\text{Bias}(\%) = (\text{target-measured})/\text{target}$$

Where 'target' is the mean creatinine value reported by the manufacturer and 'measured' is the mean creatinine value measured by the SSXp over the 20 day period.¹⁸

Since three different QCM (C1, C2, C3) were used daily, bias was determined from each of the three controls.

TE_{obs} was assessed in two ways: (1) $TE_{obs}(\%)$ values for each of the QCM [TE_{obs-C1} , TE_{obs-C2} , TE_{obs-C3}] were calculated using the specific between-run CV and bias for each QCM as determined above; (2) feline-specific $TE_{obs}(\%)$ was calculated using the between-run CV for the feline serum pool and each one of the three QCM bias as determined above. Since bias was determined for C1, C2 and C3, feline-specific $TE_{obs-C1}(\%)$, $TE_{obs-C2}(\%)$ and $TE_{obs-C3}(\%)$ were calculated for comparison. SSXp methodology was considered acceptable if $TE_{obs} < \text{total allowable error } (TE_A)$. Since published TE_A values vary throughout the literature, these were taken from the guidelines of the American Society for Veterinary Clinical Pathology (ASVCP) (TE_A : 20%) and published studies (TE_A : 17%).^{19,20}

Sigma metric values (σ), a universally-accepted objective measure of analytical methodologies, were calculated according to the following formula:^{19,20,21}

$$\sigma = (TE_A[\%] - \text{bias}[\%]) / CV$$

TE_A values were taken from published studies, bias was taken as the bias for the QCM C1 and CV as the between-run CV for the feline pool.^{19,20} As the TE_A values differed between the two sources (17% vs 20%), σ was calculated for both to generate one for the low (σ_{Low}) and one for the higher (σ_{High})

TE_A value. Interpretation of σ values was performed as follows: ≤ 3 : poor; >3 : marginal; >4 : good; >5 : excellent; >6 : world-class.^{22,23}

Sample type and method comparisons

Relationships between creatinine values for each collected set of data (Konelab_{serum} vs SSXp_{whole blood}, Konelab_{serum} vs SSXp_{plasma}, SSXp_{whole blood} vs SSXp_{plasma}) were evaluated for normality using the D'Agostino-Pearson omnibus normality test.

Using the same data sets, Spearman's correlation coefficient was calculated to measure the strength of relationship between (a) methodologies (SSXp vs Konelab), (b) SSXp values obtained from different sample types (whole blood vs plasma) and (c) PCV and SSXp_{whole blood} Creatinine results. To further explore the clinical applicability of the device, every creatinine value was also assigned an IRIS stage ($<140\mu\text{mol/l}$ [$<1.6\text{mg/dl}$] = IRIS stage 1; $140\text{-}250\mu\text{mol/l}$ [$1.6\text{-}2.8\text{mg/dl}$] = IRIS stage 2; $251\text{-}440\mu\text{mol/l}$ [$2.9\text{-}5.0\text{mg/dl}$] = IRIS stage 3; $>440\mu\text{mol/l}$ [$>5.0\text{mg/dl}$] = IRIS stage 4) and correlation of IRIS staging between methodologies (Konelab vs SSXp) was evaluated, with IRIS stage 1 considered non-azotemic and IRIS stages 2-4 considered azotemic.²⁴ Correlation coefficients were interpreted as proposed by Zady: 0.9-1 very high correlation, 0.70-0.89 high correlation, 0.50-0.69 moderate correlation, 0.30-0.49 low correlation and <0.30 little, if any, correlation.²⁵

Sensitivity and specificity for the SSXp's ability to determine non-azotemic vs azotemic samples (using a cut-off of $140\mu\text{mol/l}$, based upon IRIS staging) were calculated using the following formulae:

$$\text{Sensitivity} = \text{true positive results} / (\text{true positive results} + \text{false negative results})$$

$$\text{Specificity} = \text{true negative results} / (\text{true negative results} + \text{false positive results})$$

Deming regression analysis was used to determine the mathematical relationship and the constant (intercept) and proportional (slope) error of the SSXp relative to the Konelab and SSXp_{plasma} relative to the SSXp_{whole blood} values. Bland-Altman analysis was used to assess agreement between the two

instruments and between SSXp results obtained from the two different sample types.²⁶ Agreement was considered good when the 95% limits of agreement (LOA; mean of the differences $\pm 2SD$) were narrow and the bias was small.

Results

Clinical cases

50 samples from 44 cats were analysed for inclusion in the study. Two samples, both from the same cat on different occasions, were visibly icteric, thus excluded from analysis. No sample was visibly haemolysed or lipaemic. Of the 43 cats included in the study, ages ranged from 1 year 1 month to 16 years (median 9 years 11 months). There were 20 male neutered, one male entire and 22 female neutered cats of a variety of breeds; 33 Domestic Shorthair, two Domestic Longhair, two British Shorthair, two Persian and one each of Burmese, Norwegian Forest, Siamese and Somali. Thirty one of the 43 cats presented for a single clinical problem and 12 had multiple clinical problems, encompassing a variety of diseases; endocrine (20), urinary tract (15), respiratory (6), cardiac (6), hepatic (4), neurological (3), nutritional (2), gastro-intestinal (2), neoplastic (1) and haematological (1).

StatSensor

No technical problems occurred when using the device. The error code 'E-4', indicating insufficient sample, occurred three times during precision analysis and repeatability; repeat samples were successfully measured. No error codes occurred whilst measuring clinical samples.

Manufacturer provided target ranges for C1, C2 and C3 QCM were 44-124 μ mol/l, 133-239 μ mol/l and 398-663 μ mol/l (0.50-1.40mg/dl, 1.50-2.70mg/dl and 4.50-7.50mg/dl), respectively. No QCM failures were identified during the study; every result was within its designated range.

Imprecision, total error observed (TE_{obs}) and sigma (σ) metrics

The imprecision studies identified SSXp imprecision (CV, %) within- and between-run of 4.23-8.85% and 8.95-11.72% respectively (Table 1).

CV (%)	C1 Mean target: 84 μ mol/l (0.95mg/dl)	C2 Mean target: 186 μ mol/l (2.10mg/dl)	C3 Mean target: 530 μ mol/l (6.00mg/dl)	Serum pool
Within-run	6.32	8.85	5.07	4.23
Between-run	11.72	10.13	10.23	8.95

Table 1: Precision values (CV, %) for creatinine measurement by the SSXp, as determined by within-run and between-run CV for the three levels of QCM and the pooled feline serum sample

CV, coefficient of variation (%); QCM, quality control media; C1, C2 and C3, levels 1, 2 and 3 QCM, respectively

Quality requirements

Average (mean) TE_{obs} (between-run) for QCM was 29.36 (range 22.15-34.92) and for the feline serum pool was 25.87 (range 19.78-29.39) (Tables 2 and 3). No within-run QCs fell outside 20% of the mean target value. 5/20 C1, 1/20 C2 and 5/20 C3 between-run QCs fell outside 20%.

	QCM						TE_A (%)
	Bias	Bias	Bias	TE_{obs-C1}	TE_{obs-C2}	TE_{obs-C3}	

	C1	C2	C3				
Creatinine	-11.49	1.88	10.55	34.92	22.15	31.00	17, 20

Table 2: Calculated bias and TE_{obs} of the SSXp at all three level QCM (C1, 2 and 3)

QCM, quality control media; TE_A , total allowable error; TE_{obs} , total error observed; $TE_{obs-C1-3}$, total error observed for each of the three QCM

	Serum pool					TE_A (%)
	TE_{obs-C1}	TE_{obs-C2}	TE_{obs-C3}	Σ_{Low}	Σ_{High}	
Creatinine	29.39	19.78	28.45	0.616	0.951	17, 20

Table 3: Calculated total error observed and sigma metrics of creatinine measurement of the feline serum pool by the SSXp

TE_A , total allowable error; TE_{obs} , total error observed; Σ_{Low} , sigma metrics calculated for TE_A of 17%; Σ_{High} , sigma metrics calculated for TE_A of 20%

Creatinine

Analysis of the 48 clinical samples generated a wide range of Konelab creatinine values (range: 48-1299 μ mol/l [0.54-14.69mg/dl], median: 129.5 μ mol/l [1.46mg/dl]), reflecting all IRIS CKD stages (stage 1: 27 samples, stage 2: 17, stage 3: one, stage 4: three) thus enabling evaluation of SSXp performance across a wide range of creatinine concentrations.

The range of creatinine results generated by the SSXp on clinical samples was 63-682 μ mol/l (0.71-7.71mg/dl; median 141 μ mol/l [1.60mg/dl]) for SSXp_{whole blood} and 73-664 μ mol/l (0.83-7.51mg/dl; median 170.5 μ mol/l, [1.93mg/dl]) for SSXp_{plasma}. No 'Hi' or 'Lo' results were generated.

Comparison studies

Comparing SSXp and Konelab, very high correlation was demonstrated between SSXp_{plasma} and Konelab_{serum} ($r = 0.91, P < 0.0001$) and high correlation between SSXp_{whole blood} and Konelab_{serum} ($r = 0.85, P < 0.0001$). LOA were very wide (474.6 $\mu\text{mol/l}$ [5.37mg/dl] and 433.6 $\mu\text{mol/l}$ [4.90mg/dl] respectively). Similarly high correlation was demonstrated between SSXp_{whole blood} and SSXp_{plasma} ($r = 0.89, P < 0.0001$, although again, with relatively wide LOA; 206.78 $\mu\text{mol/l}$ [2.34mg/dl]). There was no statistically significant correlation between PCV and SSXp_{whole blood} creatinine values ($r = -0.28$), across the tested range (PCV 18-42%). These findings are shown in Tables 4 and 5.

SSXp_{whole blood} determination of azotemia (compared to Konelab_{serum}) as based on IRIS staging (creatinine $\geq 140\mu\text{mol/l}$ [$\geq 1.6\text{mg/dl}$]) had sensitivity of 90% and specificity of 82%.

	<i>r</i>	95% CI	<i>P</i> value
a) Konelab _{serum} vs SSXp _{whole blood} (n=48)	0.85	0.73 – 0.91	<0.0001
b) Konelab _{serum} vs SSXp _{plasma} (n=48)	0.91	0.85 – 0.95	<0.0001
c) SSXp _{whole blood} vs SSXp _{plasma} (n=48)	0.89	0.82 – 0.94	<0.0001
d) PCV vs SSXp _{whole blood} (n=46)	-0.28	-0.53 – 0.02	0.0609*
e) Konelab _{serum} vs SSXp _{whole blood} (IRIS stages) (n=48)	0.76	0.61-0.86	<0.0001

*Table 4. Comparison studies, as expressed by Spearman's correlation coefficient and 95% confidence intervals for creatinine measurement between different methodologies (Konelab vs SSXp) (a, b), creatinine measurement between different matrices (SSXp_{whole blood} vs SSXp_{plasma}) (c), creatinine measurement vs PCV (d) and IRIS stages between different methodologies (Konelab vs SSXp) (e) *r*, Spearman's correlation coefficient; CI, confidence interval; *, not statistically significant*

Constant error, proportional error and bias for the SSXp relative to the Konelab and SSXp_{plasma} relative to the SSXp_{whole blood} values are presented in Table 5 and Figures 1(a-d) and 2(a,b).

	Deming regression				Bland-Altman		
	Slope	95%CI	y-intercept	95% CI	Bias	95% LOA	% in LOA
Konelab _{serum} vs SSXp _{whole} blood	0.56± 0.04	0.47–0.65	85.72± 11.91	61.72– 109.7	7.13	-209.7– 223.9	98
Konelab _{serum} vs SSXp _{plasma}	0.48± 0.04	0.40–0.57	112.0± 10.87	90.6– 133.9	20.23	-217.1– 257.5	96
SSXp _{whole} blood vs SSXp _{plasma}	0.80± 0.05	0.70–0.91	49.23± 11.69	25.67– 72.79	-13.10	-116.5– 90.28	98

Table 5: Deming regression analysis results, depicting constant (intercept) and proportional (slope) error, with 95% confidence intervals. Bland-Altman data used to determine agreement between methodologies

CI, confidence interval; LOA, limits of agreement

Figure 1; Deming-regression plots between Konelab and (a) SSXp_{whole blood} and (b) SSXp_{plasma}. Bland-Altman difference plots between Konelab and (c) SSXp_{whole blood} and (d) SSXp_{plasma}

[Insert figure 1a]

[Insert figure 1b]

[Insert figure 1c]

[Insert figure 1d]

Figure 2; Deming-regression and Bland Altman difference plots demonstrating very high correlation (a) and agreement (b) respectively, between SSX_{p whole blood} and SSX_{p plasma} creatinine values

[Insert figure 2a]

[Insert figure 2b]

Discussion

To the authors' knowledge, this is the first study in which analytical and clinical performance of a hand-held PoC creatinine analyser has been evaluated for use in cats.

Imprecision guidelines are provided by Westgard, the governing standard for analytical quality requirements, with desired within-run and between-run imprecision for serum creatinine of 2.98% and 3.96% respectively; indicating inadequate precision of the SSXp (within-run and between-run CV of 4.23-8.85% and 8.95-11.72% respectively), compared to laboratory standard.²⁷ A recent study evaluating the SSXp in human patients (whole blood) reported comparable findings, with mean within-run imprecision of 2.3-5.9% and mean between-run imprecision (using three level QCM) of 4.2-9.0%; therefore similarly failing to meet desired specifications.¹¹ CV values for pooled feline serum (our study) and whole blood (previous human studies) were lower than for QCM.¹¹ This is unexpected; the uniform matrix of the latter would be expected to yield a more consistent result compared with the less homogenous matrix of whole blood, plasma or serum.¹¹

Average TE_{obs} (QCM: mean 29.36%, range 22.15-34.92%; feline serum pool: mean 25.87%, range 19.78-29.39%) also failed to meet desired TE_A (17, 20%).^{18,19,20} Possible explanations for this include machine, reagent strip, operator or environmental error; further work would be needed to identify which factors are most influential. Sigma metrics for the SSXp was consistent with very poor

performance ($\sigma \leq 3$) at both creatinine TE_A thresholds. A recent study evaluating the SSXp in human patients neither reported TE_{obs} nor sigma metric values, so a direct comparison cannot be made.¹¹ Whilst creatinine is reported to be among those biochemical analytes having the greatest imprecision, bench-top veterinary devices perform considerably more precisely; a recent study evaluating analytical performance of a dry chemistry analyser reported TE_{obs} and σ for feline creatinine of 10 and 5.7 respectively.^{28,29}

The population of cats in our study had a serum creatinine range, as determined by Konelab, of 48-1299 $\mu\text{mol/l}$ (0.54-14.69mg/dl). Despite being reported to measure creatinine over a range of 27-1056 $\mu\text{mol/l}$ (0.31-11.95mg/dl), the SSXp range for the same population was from 63-682 $\mu\text{mol/l}$ (0.71-7.71mg/dl) and 73-664 $\mu\text{mol/l}$ (0.83-7.51mg/dl) for SSXp_{whole blood} and SSXp_{plasma} respectively, indicating a failure of the SSXp to accurately quantify higher creatinine values. Further studies evaluating greater numbers of markedly azotemic samples are required to further elucidate the SSXp performance at high creatinine concentrations.

Although SSXp is intended for creatinine measurement in whole blood, we also measured creatinine in plasma as the similar matrix of plasma and serum rendered comparison between SSXp and reference methodology more representative. Indeed, SSXp_{plasma} exhibited greater correlation with Konelab_{serum} ($r = 0.91, P < 0.0001$) than did SSXp_{whole blood} with Konelab_{serum} ($r = 0.85, P < 0.0001$).

The Konelab_{serum} vs SSXp_{plasma} and Konelab_{serum} vs SSXp_{whole blood} regression plots revealed two (1299 $\mu\text{mol/l}$ vs 644 $\mu\text{mol/l}$ [14.69mg/dl vs 7.29mg/dl], 799 $\mu\text{mol/l}$ vs 408 $\mu\text{mol/l}$ [9.04mg/dl vs 4.62mg/dl]) and one (1299 $\mu\text{mol/l}$ vs 601 $\mu\text{mol/l}$ [14.69mg/dl vs 6.80mg/dl]) data points respectively, markedly deviating from the line of best fit. Whilst the trend at lower creatinine values

was for the SSXp (whole blood and plasma) to have a positive bias relative to the Konelab, this trended towards a considerable negative bias of SSXp compared with Konelab at higher creatinine values; with increased discordance associated with higher creatinine concentrations as indicated above. The reason for this switch from a positive to negative bias was not apparent and would require further investigation. Furthermore, this is of considerable importance when considering clinical applicability of the device; had a consistent positive or negative bias been identified, this may have enabled either generation of a device-specific reference range, or, application of a linear algorithm to SSXp results to yield greater correlation with reference methodology. However, the switch from a positive to negative bias makes exploring both of these options obsolete. The finding of a negative bias of the SSXp vs reference methodology at higher creatinine values was also identified in a recent human study; with demonstration of improved correlation if values $>600\mu\text{mol/l}$ ($>6.79\text{mg/dl}$) were excluded from analysis (r of 0.99 and 0.97 respectively).¹¹ The higher correlation in this previous study can be accounted for by excellent correlation at lower creatinine values, in comparison to the positive bias exhibited when SSXp is used to evaluate feline creatinine. Similarly, apparently higher correlation between reference methodology and SSXp evaluation of canine creatinine ($r=0.954$) in a previous study can be explained by a narrower range of creatinine values (maximum $610\mu\text{mol/l}$ [6.9mg/dl]).¹⁶ Discordance from laboratory methodology with increasing creatinine values has also been identified in earlier models of the SSXp.^{12,15} It is possible that unmeasured metabolites associated with azotemia cause interference with the methodology at higher creatinine values. These deviated data points also appeared as the only outliers on the Bland-Altman difference plots. If these outliers were excluded from analysis, this considerably narrowed the 95% limits of agreement, from $424.9\mu\text{mol/l}$ (4.81mg/dl) with outliers, to $150.1\mu\text{mol/l}$ (1.70mg/dl) without outliers for Konelab_{serum} vs SSXp_{whole blood} and from $464.8\mu\text{mol/l}$ (5.26mg/dl) with outliers to $114.1\mu\text{mol/l}$ (1.29mg/dl) without outliers for Konelab_{serum} vs SSXp_{plasma}.

Comparing Konelab_{serum} vs SSXp_{whole blood}, in 36/48 paired samples the same IRIS stage was established by both instruments. In the remaining 12 paired samples, the SSXp and Konelab IRIS stages differed by a single stage; in 6/12 the SSXp creatinine value would have resulted in a falsely diagnosed azotemia (SSXp stage 2 vs Konelab stage 1) and in 2/12 the SSXp failed to identify an azotemia (SSXp stage 1 vs Konelab stage 2 for both). These findings (36/48 correctly staged, 19/21 azotaemic patients identified) demonstrate reasonable sensitivity (90%) and specificity (82%) of the SSXp for identification of azotemia as based on IRIS staging (creatinine $\geq 140\mu\text{mol/l}$ [$\geq 1.6\text{mg/dl}$]).

Previous studies have considered variability between whole blood and plasma matrices and thus evaluated the impact of PCV on PoC testing, specifically regarding blood glucose and lactate concentrations.^{30,31} Regarding the former, previous studies have consistently identified an inverse correlation between HCT and blood glucose concentration; proposed mechanisms for this relationship include erythrocytes causing mechanical impedance of plasma diffusion into the reagent strip, blood viscosity affecting fluid permeability in the reagent layer and other matrix-associated complications (e.g. micro-clot formation, protein deposition, fibrin aggregation) or haemolysis.³¹ Conversely, PCV does not appear to influence lactate measurement; with a lack of correlation reported ($r = 0.04$; $P = 0.77$; PCV range 14-57.5%). Our findings of no significant correlation between PCV and SSXp_{whole blood} ($r = -0.28$) suggest that within the tested range (18-42%), PCV does not significantly affect SSXp measurement of creatinine. Further testing would be required to evaluate the effect of severe anaemia or erythrocytosis. The previous study evaluating the SSXp in human patients used whole blood but did not evaluate the impact of PCV on creatinine determination.¹¹

Conclusions

The SSXp was easy-to-use, providing rapid patient-side results. Precision studies identified poor repeatability and reproducibility, not meeting acceptable guidelines for a PoC device. Despite this, high to very-high correlation was exhibited, compared to the reference methodology for creatinine determination. The SSXp correctly classified the IRIS stage in 36/48 of patients, although 2/21 azotemic cats were not identified. Improved device precision and accuracy are required prior to recommending its' use in feline patients.

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Conflicts of interest

The authors do not have any potential conflicts of interest to declare.

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