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Evaluation of cardiac troponin I as a predictor of death in critically ill cats

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Abstract

Background: Abnormally high serum cardiac troponin I (cTnI) concentration, reflecting leakage from or necrosis of cardiomyocytes, is a negative prognosticator for death in dogs.

Objectives: To investigate in critically ill cats whether serum cTnI concentration is abnormally high, identify conditions associated with abnormally high cTnI concentrations, and evaluate cTnI as an independent prognosticator for death and a potential coprognosticator to the acute patient physiologic and laboratory evaluation (APPLE) score in cats.

Animals: One hundred nineteen cats admitted to intensive care units (ICU) and 13 healthy cats at 2 university teaching hospitals.

Methods: Prospective study. Clinical examinations were performed, APPLE scores calculated, and serum cTnI and serum amyloid A (SAA) measured within 24 hours after admission. Outcome was defined as death/euthanasia or survival to discharge, 28 and 90 days after ICU-admission. Prognostic capacity of cTnI, APPLE scores and models combining cTnI and scores were evaluated by receiver-operator-characteristic analyses.

Results: Median (IQR) serum cTnI concentration was higher in ill (0.63 [0.18-2.65] ng/mL) compared to healthy (0.015 [0.005-0.041] ng/mL) cats ($P < .001$) and higher in subgroups with structural cardiac disease (2.05 [0.54-16.59] ng/mL; $P < .001$) or SAA >5 mg/L (0.84 [0.23-2.81] ng/mL; $P = .009$) than in cats without these characteristics (0.45 [0.12-1.70] and 0.35 [0.015-0.96] ng/mL). The in-hospital case fatality rate was 29%. Neither serum cTnI concentration for all critically ill cats (area-under-the-curve 0.567 [95% CI 0.454-0.680], n = 119) or subgroups (0.625 [0.387-0.863], n = 27; 0.506 [0.360-0.652], n = 86), nor APPLE scores (fast 0.568 [0.453-0.682], full 0.585 [0.470-0.699], n = 100), were significant prognosticators for death.

Abbreviations: APPLE, acute patient physiologic and laboratory evaluation; AUC, area under the curve; BP, blood pressure; CHF, congestive heart failure; cTnI, cardiac troponin I; DSH, domestic shorthair; HCM, hypertrophic cardiomyopathy; HDO, high definition oscillometry; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure; ROC, receiver operating characteristic; SAA, serum amyloid A.

Conclusions and Clinical Importance: Abnormally high serum cTnI concentration was common in critically ill cats. Unlike in dogs, cTnI did not confer prognostic information regarding death.

KEYWORDS
cardiovascular dysfunction, feline, intensive care unit, myocardial injury, survival

1 | INTRODUCTION

Myocardial injury is common in critically ill people[1,2] and dogs.[3-5] Confirmation of cellular injury requires biomarkers reflective of content leakage from the cell. Cardiac troponin I (cTnI) is the most sensitive and specific biomarker of cardiomyocyte injury.[6,7] Such injury, even in the absence of myocardial infarction for which troponin was traditionally applied, has negative prognostic implications, both in people with structural cardiac disease[8,9] and in people with noncardiac disease that secondarily affects the heart.[10,11] Furthermore, for intensive care unit (ICU)-hospitalized people with noncardiac disease, myocardial injury contributes additional prognostic information to established human ICU severity scores.[12,13]

Abnormally high serum concentration of cTnI is also a negative prognostic indicator for death in critically ill dogs, independently of the underlying disease.[3,14] Similar to findings in human medicine, this biomarker increases the prognostic specificity of the acute patient physiologic and laboratory evaluation (APPLE) score for dogs with noncardiac disease, if incorporated into the score.[5]

In cats with primary cardiac disease, cTnI is considered a prognosticator for death on a population basis,[15,16] but, to the authors' knowledge, there are no published studies evaluating the prognostic value of cTnI in cats admitted for intensive care. In 1 study of cats with sepsis, presence of cardiovascular dysfunction (defined as hypotension in a volume-resuscitated cat requiring inotropic or vasopressor support) increased the risk of death,[17] but cTnI concentrations were not evaluated.

While the pathophysiology of myocardial injury (necrosis versus membraneous leakage) could vary depending on underlying disease, myocardial injury has prognostic relevance in dogs with both cardiac and noncardiac disease.[4,6,18,19] Abnormally high serum cTnI concentrations in dogs and cats with renal disease, previously suspected to be caused by decreased elimination, appears to represent true myocardial injury.[20,21] Hence, cTnI appears to be a reliable marker of myocardial injury independent of diagnosis, but has yet to be evaluated in critically ill cats.

The primary objectives of the present study were, therefore, to evaluate serum cTnI concentration in cats admitted to ICU care, independent of diagnosis, and to investigate serum cTnI concentration as an independent prognosticator for death and a potential co-prognosticator to the fast and full APPLE scores. A secondary objective was to identify conditions associated with abnormally high cTnI concentrations.

2 | MATERIALS AND METHODS

2.1 | Study cohorts

This prospective observational cohort study was performed at 2 university animal hospitals, the University Hospital for Companion Animals at the University of Copenhagen, Frederiksberg, Denmark and the University Animal Hospital at the Swedish University of Agricultural Sciences, Uppsala, Sweden. The study protocol was approved by the Ethical and Administrative Committee at the Department of Veterinary Clinical Sciences, University of Copenhagen (10th of February 2017, reference number 2017-5) and by Uppsala Regional Ethics Committee in Sweden (30th of June 2017, reference number 5.8.18-09724/2017).

Cats 1 year of age or older, admitted to the ICU of either animal hospital from June 2017 to September 2019 were eligible for prospective inclusion, irrespective of clinical diagnosis. Informed consent to participate in the study was obtained from owners of all included cats. Cats were excluded if they had a body weight <3 kg or if inclusion into the study was considered a risk for clinical deterioration. Study inclusion did not influence intensive care management of the cats.

Also, clinically healthy cats 1 year of age or older with a body weight ≥3 kg were included as a control group, recruited from cats undergoing breed cardiac screening for feline cardiomyopathy as well as through personal contacts. Cats were excluded from the control group if clinical investigation results (hematology, biochemistry, echocardiography, ECG or blood pressure [BP] measurements) were indicative of disease.

All critically ill cats were assigned 1 primary disease category based on investigator opinion: cardiovascular, endocrine, gastrointestinal, hematologic, neoplastic, neurologic, respiratory, urinary, trauma or other, dependent on the disease process that led to ICU hospitalization. Cats were also grouped according to presence/absence of structural cardiac disease (as determined by echocardiography) and presence/absence of abnormally high serum amyloid A (SAA) >5 mg/L within 24 hours after admission, as both primary cardiac disease and systemic inflammation can cause primary and secondary myocardial injury, respectively.[16,22-24]

2.2 | Study protocol

Blood was collected from the cephalic or jugular vein into EDTA, serum and heparin tubes within 24 hours of ICU admission for

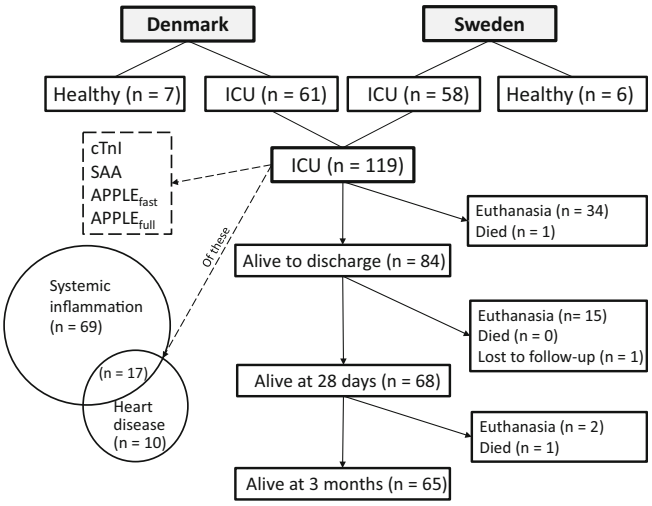

FIGURE 1 Flowchart of the study protocol and the distribution and outcome of the 119 critically ill and the 13 healthy control cats included in the study

analysis of CBC, biochemistry and lactate or complete venous blood gas analysis. Two aliquots of serum were frozen and stored at −70°C for batch analysis of serum SAA and cTnI concentration. Storage was considered acceptable based on human cTnI and equine SAA studies.[25-27] In case of sample collection out of hours, storage at −20°C was considered acceptable for a maximum of 48 hours until transfer to −70°C. A second blood sample was collected 12 to 24 hours later for cats still alive and handled similarly for batch analysis of SAA.

An echocardiographic examination and a 2-minute ECG were performed during hospitalization by 1 of the authors (J. Koch, J. Willesen, M. Bach, I. Ljungvall or J. Häggström). Echocardiography was performed to document potential presence of structural cardiac disease using color-flow Doppler, M-mode, and 2D echocardiographic modalities according to current recommendations.[28,29]

Systemic BP was measured as previously described using high definition oscillometry (HDO) within 24 hours after admission.[30] The cuff (c1) was placed on the tail and a minimum of 5 measurements were performed. The average mean arterial blood pressure (MAP) was calculated from a minimum of 5 measurements displaying systolic BP measurements that differed <20% from each other.

Based on clinical (mentation, body temperature, MAP, presence of free fluid in 1 or more body cavities), hematological (packed cell volume) and biochemical (urea, chloride and lactate concentrations) variables obtained during the first 24 hours of hospitalization, APPLE$_{full}$ and APPLE$_{fast}$ scores were calculated as previously described.[31] Mentation score was based on evaluation at admission, whereas, for all other variables, the most abnormal value detected within 24 hours after admission was used.

Outcome was defined as death/euthanasia or survival to discharge, 28 days and 3 months post ICU admission. Follow-up information about death (spontaneous/euthanasia and cause) or survival was obtained by personal communication with owners of cats that had been discharged. A flow chart of the protocol is provided in Figure 1.

2.3 | Clinical pathological analysis

In Denmark, CBC analysis was performed at the Veterinary Diagnostic Laboratory using ADVIA 2120 Hematology analyzer (Siemens Healthineers, Erlangen, Germany) or (out of hours) Procyte Rx hematology analyzer (IDEXX Laboratories, Inc, Westbrook, Maine). Biochemistry analyses were performed using ADVIA 1800 (Siemens Healthineers, Erlangen, Germany) or (out of hours) Catalyst Dx (IDEXX Laboratories, Inc, Westbrook, Maine). Lactate analyses were performed using a lactometer (Accutrend, Roche Diagnostics, Rotkreuz, Switzerland).

In Sweden, CBC analysis was performed at the Clinical Pathology Laboratory at the University Animal Hospital using ADVIA 2120 hematology analyzer (Siemens Healthineers, Erlangen, Germany) or (out of hours) Procyte Rx hematology analyzer (IDEXX Laboratories, Inc, Westbrook, Maine). Biochemistry analyses were performed using Architect c4000 (Abbott, Abbott Park, Illinois) or (out of hours) Catalyst Dx (IDEXX Laboratories, Inc, Westbrook, Maine). Analyses of lactate and chloride concentrations were performed using ABL 90 (Radiometer Medical Aps, Bronshoj, Denmark).

Batch analysis of serum SAA and cTnI concentrations were performed at the Veterinary Diagnostic Laboratory, University of Copenhagen, and at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark. For analysis of SAA, a human turbidimetric immunoassay (SAATIA; LZ-SAA, Eiken Chemical, Co, Tokyo, Japan) was validated for use in cats applying an automated analyzer (ADVIA 1800, Siemens Healthineers, Erlangen, Germany). Batch analysis of cTnI was performed using a high-sensitivity assay (ADVIA Centaur CP TnI-ultra, Siemens Healthcare Diagnostics, Inc, Tarrytown, New York), previously validated for use in cats.[23]

2.4 | Statistical analyses

Statistical analyses were performed using commercial statistical software Graph Pad Prism 8 (version 8.4.0, Graph Pad Software, San Diego, California) and R (R Core Team [2018]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Data were assessed for normality by visual inspection of graphs and by the Shapiro-Wilk test. Logarithmic transformation was applied where this resulted in a Gaussian distribution of otherwise nonparametric data. Normally distributed data were presented using mean and SD and nonnormally distributed data using median and interquartile range (IQR). A 2-tailed *t*-test was used for comparison of Gaussian data and the Mann-Whitney *U*-test for non-Gaussian data. When multiple groups were compared (disease categories), the Kruskal-Wallis test was applied followed by Dunn's multiple comparison test.

A binary logistic regression model including survival at discharge (Y/N) as the dependent variable was applied. The univariate prognostic value of cTnI, APPLE$_{full}$ and APPLE$_{fast}$ for the critically ill cats was evaluated using receiver operating characteristic (ROC) curve analysis. Similar univariate binary logistic regression models were constructed for cTnI for survival at day 28 and day 90, respectively. Additionally,

multivariable logistic regression models including cTnI combined with either $APPLE_{full}$ or $APPLE_{fast}$ were plotted using ROC curves to assess the prognostic value of these combinations at discharge. Cardiac troponin I concentrations were logarithmically transformed for the logistic regression analyses.

Because cats were included in 2 countries, case fatality rates between countries were compared with chi square testing, and, in case of a significant difference between countries, the logistic regression analyses were repeated for each country separately.

Analyses were also completed excluding the cats euthanized without a perceived poor prognosis (eg, for financial reasons). This was retrospectively determined based on medical record information and communication with the attending clinician.

The prognostic value of cTnI was similarly examined in the subgroups of cats with structural cardiac disease and with abnormally high SAA.

A *P*-value <.05 was considered significant. A significant prognosticator was defined as having a 95% confidence interval of the area under the curve (AUC) greater than 0.5. If univariate predictors were significant, cut-offs for predicting death were reported based on optimal combined sensitivity and specificity.

3 | RESULTS

3.1 | Study sample

In total, 132 cats (119 critically ill cats and 13 healthy controls) were included. The majority of the critically ill cats were domestic shorthair (DSH) cats (n = 77), 9 were Maine coons, 6 were Birmans and 5 were Ragdolls. Four critically ill cats were British shorthairs, Persian and Norwegian forest cats, respectively. The remaining cats in the critically ill group consisted of ≤3 individuals of 6 other breeds. In the group of healthy cats, there were 5 DSH cats, 3 Maine coons, 2 Ragdolls, 2 Persians and 1 Norwegian forest cat. Demographic data of included cats is presented in Table 1.

Of the critically ill cats, 27 cats were diagnosed with structural cardiac disease. Twelve of these presented to the hospital for a cardiac cause (7 with congestive heart failure [CHF]), and 15 were diagnosed as a consequence of study inclusion (echocardiography), but presented because of noncardiac illness. Eighty-six cats had SAA >5 mg/L within 24 hours after admission. Seventeen cats fell into both categories with structural cardiac as well as abnormally high SAA detected (see Figure 1). There was no difference in median age or median body weight between cats with and without structural cardiac disease ($P = .14$) or with and without abnormally high SAA ($P = .99$). Primary disease categories of all critically ill cats are shown in Figure 2.

Thirty-five of the 119 cats died or were euthanized before discharge, representing an in-hospital case fatality rate of 29%. One cat was lost to follow-up after discharge. The 28-day case fatality rate was 42% (50/119), and the 3-month case fatality rate was 45% (53/119; Figure 1).

The percentage of cats that did not survive to discharge was higher in Denmark (39%, 24/61) than in Sweden (19%, 11/58; $P = .02$), but there was no difference in case fatality rates between countries at 28 days (51%, 31/61 vs 33%, 19/58, $P = .08$) or 3 months (52%, 32/61 vs 37%, 21/58, $P = .13$).

3.2 | Cardiac troponin I

Median (IQR) serum concentration of cTnI in the critically ill cats at admission was 0.63 (0.18-2.65) ng/mL, which was higher than that of the healthy cats 0.015 (0.005-0.041) ng/mL ($P < .001$; Figure 3). In total, 88% (105/119) of critically ill cats had cTnI concentrations above the range of the healthy controls. Within the group of critically ill cats, serum concentrations of cTnI were higher in the subgroup of cats with structural cardiac disease (2.05 [0.54-16.59] ng/mL) than in cats without structural cardiac disease (0.45 [0.12-1.70] ng/mL; $P < .001$). Serum cTnI concentrations were also higher in cats with abnormally high SAA (0.84 [0.23-2.81] ng/mL) than in cats with SAA concentrations within the reference range (0.35 [0.015-0.96] ng/mL; $P = .009$). There was, however, considerable overlap between groups (Figure 4A,B).

An overall significant difference in serum cTnI concentrations was found among primary disease groups ($P = .002$). Post hoc analyses revealed that cats with cardiac disease (2.14 [0.68-33.03] ng/mL) or trauma (2.38 ng/mL [0.69-3.95] ng/mL) as their presenting illness had significantly higher serum concentrations of cTnI than cats with neurological disease (0.02 [0.01-0.22] ng/mL; $P = .004$ and $P = .002$). Apart from this finding, there was no difference in serum cTnI concentrations among cats in different primary disease categories.

There was no significant difference between admission serum cTnI concentrations of survivors and nonsurvivors (Figure 5A-C), and serum cTnI concentration was not a significant prognosticator for death before discharge, at 28 days or at 3 months (Table 2). Prognostic analyses were repeated including only cats that died spontaneously or were euthanized due to a perceived poor prognosis (Table S1) and, when relevant, separately for cats from each country (Table S2) with similar results. Finally, serum cTnI concentration was evaluated specifically for the subgroups of cats with structural cardiac disease or abnormally high SAA, again without prognostic significance (Table 2).

3.3 | APPLE scores

Median (IQR) $APPLE_{full}$ score (maximal score = 80; available for 100/119 cats) was 44 (36-50) and the $APPLE_{fast}$ score (maximum score = 50) was 26 (21-31). Neither $APPLE_{fast}$, nor $APPLE_{full}$ were significant prognosticators for death at discharge (Table 3). Similar findings were obtained when including only cats that died spontaneously or were euthanized due to a perceived poor prognosis (Table S1) or cats from each country separately (Table S2). As a combined model, $APPLE_{full}$ and cTnI significantly predicted death in the whole cohort of critically ill cats (Table 3), but with a low AUC. When including only

TABLE 1 Demographic data of 132 included cats

	All cats (n = 132)	Healthy (n = 13)	Critically ill (n = 119)	Survivors to discharge (n = 84)	Nonsurvivors (n = 35)
Age (years; median (IQR))	6.5 (2.0-10.0)	6.0 (1.0-6.5)	7.0 (2.0-10.0)	6.5 (1.0-10.0)	7 (5.0-10.0)
Sex (F/FN/M/MN)	14/39/11/68	6/4/2/1	8/35/9/67	3/22/8/51	5/13/1/16
Breed (purebred/DSH)	49/83	8/5	41/78	29/55	12/23

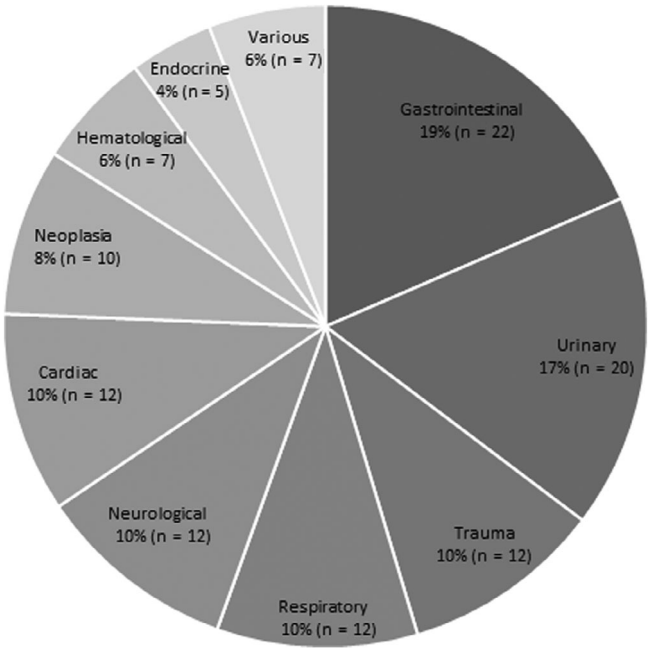

FIGURE 2 Disease categories of the included 119 critically ill cats dependent on the disease process leading to ICU hospitalization

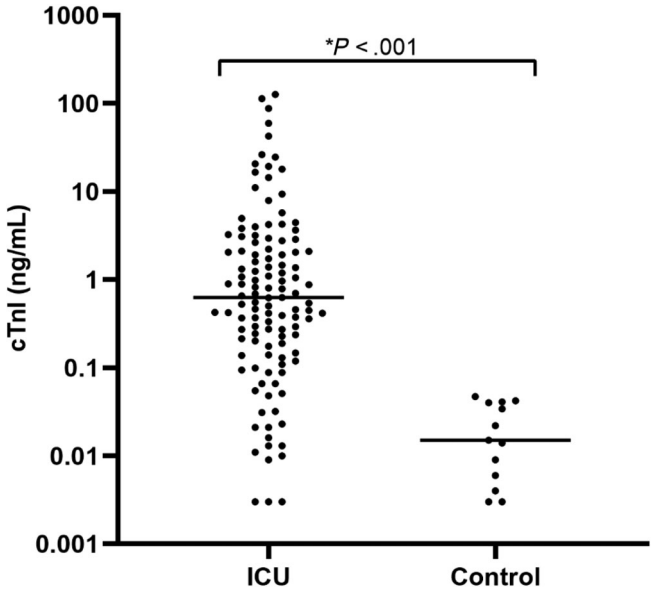

FIGURE 3 Serum cTnI concentrations of 119 critically ill cats at intensive care unit admission and 13 healthy control cats. Median concentrations are shown as horizontal lines. Significant difference between groups is symbolized with *

cats that died spontaneously or were euthanized due to a perceived poor prognosis, the prediction was not significant (Table S1).

4 | DISCUSSION

The primary objective of the present study was to investigate the presence and prognostic relevance of myocardial injury in critically ill cats. This study showed that myocardial injury is common in ICU-hospitalized cats, corresponding to that in dogs.[5] Interestingly, and unlike for dogs, cTnI was not predictive of death. In dogs, serum cTnI concentration provides prognostic information on survival in critically ill dogs beyond the immediate posthospitalization period.[4] Accordingly, the present study also included follow-up 3 months after ICU admission, but again without any detectable prognostic relevance concerning survival in cats. Interestingly, case fatality rate for the included cats was similar 1 and 3 months after ICU admission.

Structural cardiac disease was associated with considerably higher cTnI concentrations compared to previous studies of cats with hypertrophic cardiomyopathy (HCM). In studies applying the same cTnI assay, cats with HCM rarely (except in cases with arterial thromboembolism) exceed cTnI concentrations of 3 ng/mL,[16,32] whereas, in the present study, half of the cats with structural cardiac disease had concentrations above this level, with 2 cats exceeding 100 ng/mL. Of the 7 cats with CHF, only 1 had a cTnI concentration substantially above the level expected based on the above-mentioned studies (Figure 4A), and this cat presented with concurrent epistaxis and had severely abnormally high SAA, suggesting that a comorbidity was involved.

Comorbidities were common in the cardiac group. Of the 27 cats with structural cardiac disease, 15 were hospitalized because of non-cardiac disease, with the cardiac condition discovered only owing to the study protocol (echocardiography). Also, 17/27 cats with cardiac disease had a concurrently abnormally high SAA concentration, which is comparably uncommon in cats with HCM, and only described in 5/37 and 1/51 of cats in 2 previous studies.[33,34] Finally, the 2 cats in the cardiac group with the highest cTnI concentrations were not in CHF. Hence, comorbidities are a likely cause of the pronounced myocardial injury, (most likely because of hypoxia, cytokine-mediated cellular injury, or myocardial infarction), seen in the cats with structural cardiac disease in this study. It is also possible that the heart is more susceptible to secondary injury from noncardiac disease when already

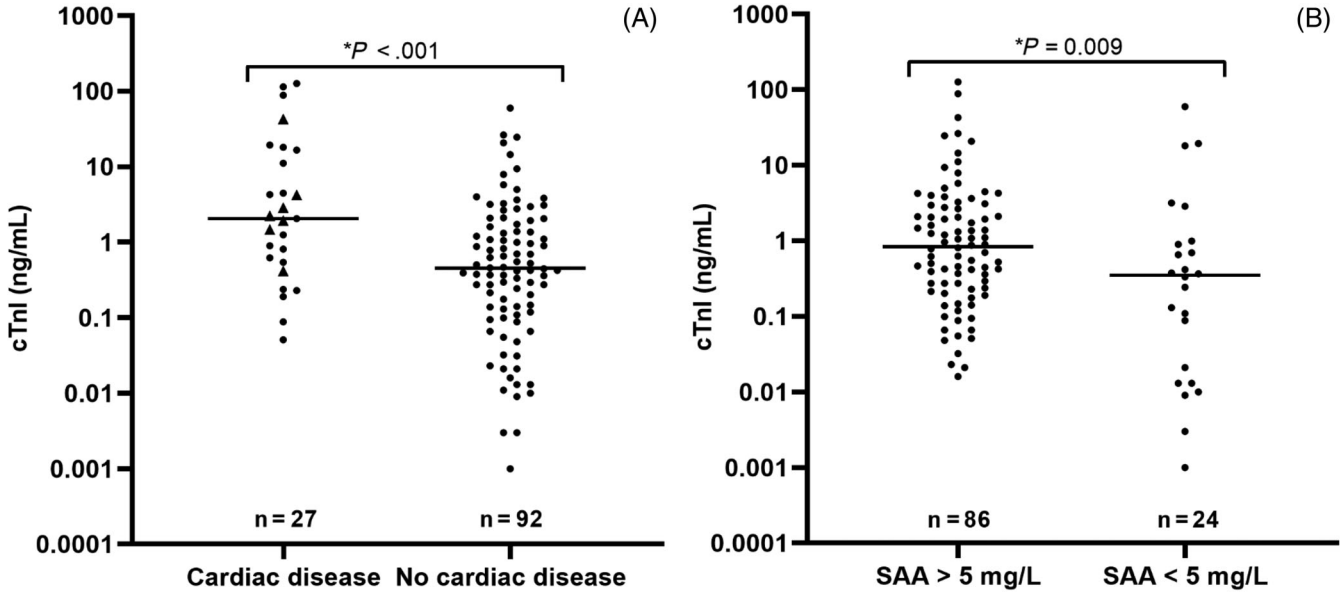

FIGURE 4 Serum cTnI concentrations in critically ill cats with and without structural cardiac disease as detected by echocardiography (A) and with and without serum amyloid A (SAA) >5 mg/L (B). Within the group of cats with structural cardiac disease, serum cTnI concentrations of cats with congestive heart failure are presented as triangles instead of circles. Median concentrations are shown as horizontal lines. Significant differences between groups are symbolized with *

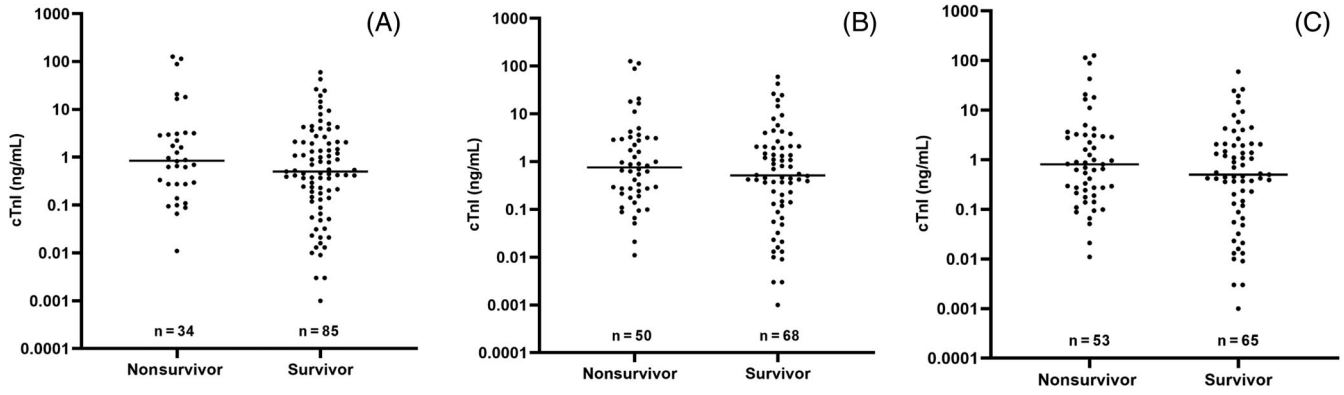

FIGURE 5 Serum cTnI concentrations of nonsurvivors and survivors to discharge (A), 28 days (B) and 3 months (C) after intensive care unit admission

affected by primary cardiac disease. Nevertheless, in cats with primary cardiac disease, cTnI is a significant prognosticator for death,[15,16] suggesting that the chronic low-grade myocardial injury typically detected in cats with cardiomyopathies might have stronger clinical relevance for the cat.

Cats with SAA >5 mg/L at admission or increasing to this level within 24 hours after admission had higher serum cTnI concentrations than cats without abnormally high SAA. These findings suggests that systemic inflammation might be involved in the disease processes leading to the cardiomyocyte injury seen in this study. However, unlike in critically ill dogs and people, for which myocardial injury is associated with a 2-4 times higher case fatality rate and especially well described in patients with systemic inflammation,[1,5,12] the cTnI concentration did not seem to offer prognostic information for death in critically ill cats. This was an unexpected finding based on the prognostic importance of the biomarker in people and dogs. Nevertheless, a previous, similar study in dogs required only a study cohort of 42 dogs to detect a prognostic significance of cTnI.[5] The present study included 3 times as many cats, which would suggest that the results are comparably reliable. As such, while myocardial injury is common in ICU-hospitalized cats, its presence might not be clinically relevant with regard to prognosis for case fatality. It might, however, be a cause of more severe morbidity.

The question remains as to why this difference between species exists. The lack of prognostic importance of cTnI in ICU-hospitalized cats could suggest a higher frequency of reversible myocardial injury in this species. Transient increases in cTnI concentrations, arising through membraneous leakage, is suggested to occur with severe

TABLE 2 Receiver operating characteristic analysis of cardiac troponin I (cTnI) as predictor of death in 119 critically ill cats

	Total	AUC	95% CI	Survival
All critically ill cats				
cTnI - Discharge	n = 119	0.567	0.454-0.680	84 (70.6%)
cTnI - Day 28	n = 118	0.554	0.449-0.659	68 (57.6%)
cTnI - Day 90	n = 118	0.561	0.456-0.665	65 (55.1%)
Cats with heart disease				
cTnI—Discharge	n = 27	0.625	0.387-0.863	16 (59.3%)
cTnI—Day 28	n = 27	0.494	0.268-0.720	10 (37%)
cTnI—Day 90	n = 27	0.526	0.296-0.756	8 (29.6%)
Cats with SAA >5 mg/L				
cTnI—Discharge	n = 86	0.506	0.360-0.652	65 (75.6%)
cTnI—Day 28	n = 86	0.502	0.368-0.637	55 (64%)
cTnI—Day 90	n = 86	0.509	0.377-0.640	52 (60.5%)

TABLE 3 Receiver operating characteristic analysis of the acute patient physiologic and laboratory evaluation (APPLE) score with or without inclusion of cardiac troponin I (cTnI) as predictor of death in 100 critically ill cats

	Total	AUC	95% CI	Survival
Survival at discharge				
APPLE score (fast)	n = 100	0.568	0.453-0.682	70 (70%)
APPLE score (full)	n = 100	0.585	0.470-0.699	70 (70%)
APPLE score (fast) + cTnI	n = 100	0.618	0.499-0.737	70 (70%)
APPLE score (full) + cTnI	n = 100	0.631	0.515-0.747	70 (70%)

systemic inflammation in people.[35,36] While reversible injury can be severe with serum cTnI concentrations rising to levels similar to what is seen with myocardial infarction, one might speculate that feline cardiomyocytes perhaps both leak and repair more easily than those of dogs and humans.

The APPLE score was included in this study mainly to evaluate if addition of cTnI improves its predictive performance on survival. However, neither the fast nor the full APPLE scores were independently predictive of survival in the present study. The reason for these discrepant results compared to the study that constructed and validated the scores[31] is not clear. Age distribution and death at discharge were similar in the 2 studies. Also, the most common primary disease categories (gastrointestinal, urinary and trauma) were similar, although severity of illness within disease categories could not be compared between studies. However, the construction and validation cohorts were based on data from a single center in North America, while the present study included cats from 2 centers in Scandinavia. Hence, a geographical difference, perhaps related to disease prevalence or insurance coverage, might be 1 factor at play. Another possible explanation for the lack of performance of the APPLE score in this study could be the variations in the decision to euthanize between countries. Therefore, the prognostic statistical analyses were repeated including only cats that had died spontaneously or had been euthanized due to a perceived poor prognosis, thus omitting cats that were euthanized for financial reasons. The results remained unchanged for both cTnI and APPLE scores individually. Additionally, while 1 study of cats with polytrauma found the scores to be significant prognosticators,[37] our findings of lack of prognostic value are in agreement with results from several other studies in cats that have applied the APPLE scores, suggesting a need for additional prognostic composite score development in cats.[17,38-41]

In contrast, several studies applying the APPLE scores in critically ill dogs have found the scores to be significant prognosticators for death.[3,5,42] Nevertheless, substantial overlap between survivors and nonsurvivors confirms that such scores are not useful (or intended) for prognostication of individual animals. The incorporation of cTnI into the APPLE score improved prognostic specificity of the model in 1 study of dogs,[5] but results of the present study suggests that this might not be the case in cats. While the combined model of $APPLE_{full}$ and cTnI was significant when including the entire cohort of critically ill cats in the present study, its area under the curve was low, and it was not significant when applied to only cats with spontaneous death or a poor prognosis.

4.1 | Limitations

This study was affected by a limitation common to veterinary survival studies, as it included cats that were euthanized as well as cats that died spontaneously. In order to restrict the effect of this limitation on the study, prognostic analyses were repeated for only cats euthanized because of a perceived poor prognosis. This did not change the results. Nevertheless, some nonsurviving cats might have survived, should treatment have been continued, but the course of treatment and possibility of euthanasia were decided upon at the discretion of the attending veterinarian and the owner and were not influenced by the study.

The prognostic analyses performed were chosen to allow for comparisons with similar studies in dogs.[3,4] Nevertheless, it is possible that performing time-to-event survival analysis by collecting data on the specific date of death/euthanasia of each animal rather than evaluating only their survival status at given time-points would have increased the power of the analyses.

Several different analyzers were used for CBC, biochemistry and acid-base analyses. The analyses were used for clinical characterization of included cats and for calculation of APPLE scores. However, because the scores are developed for use with different analyzers, and because the main results of this study were similar when the 2 study centers were considered separately, a major influence of the use of different analyzers at the 2 centers seems unlikely.

Cats were subgrouped based on presence/absence of structural cardiac disease and abnormally high SAA concentrations. This was done to evaluate whether these conditions influence the degree of myocardial injury and the prognostic value of cTnI in the cohort. However, because many cats had comorbidities, it must be emphasized that the cTnI concentrations presented in these subgroups cannot be directly compared to those of studies including cats with 1 specific disease and no comorbidities.

Finally, the majority of the healthy cats were recruited from cats undergoing breed cardiac screening for cardiomyopathy, which led to a higher proportion of purebred cats in the control group than in the critically ill group. However, while breed-specific reference intervals for cTnI have been suggested necessary for 1 dog breed,[43] this has not been shown in cats and is therefore not likely to have influenced the results of this study.

4.2 | Conclusion

Abnormally high cTnI concentration was common in cats admitted to intensive care in this study, but was not found to be an independent prognosticator for death. While there was an indication of an improved prognostic performance of the APPLE scores when adding cTnI, this was lost when evaluating only cats with spontaneous death or perceived poor prognosis.

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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

The study protocol was approved by the Ethical and Administrative Committee at the Department of Veterinary Clinical Sciences, University of Copenhagen (10th of February 2017, reference number 2017-5) and by Uppsala Regional Ethics Committee in Sweden (30th of June 2017, reference number 5.8.18-09724/2017).

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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