VETERINARY QUARTERLY
2023, VOL. 43, NO. 1, 1–8
https://doi.org/10.1080/01652176.2023.2233584

Taylor & Francis
Taylor & Francis Group

Assessment of misdiagnosis in small animal intensive care patients using the Modified Goldman criteria

Sanne Hugen[a], Nynke Ankringa[b], Joris Henricus Robben[a] and Chiara Valtolina[a]

[a]Department of Clinical Sciences of Companion Animals, Utrecht University, Utrecht, The Netherlands; [b]Department of Biomolecular Health Sciences, Utrecht University, Utrecht, The Netherlands

ABSTRACT

The postmortem examination can be used as a means of quality control for clinical diagnoses. A retrospective study on 300 dogs and cats that had been admitted to a small animal intensive care unit was performed comparing the clinical and postmortem findings, using the Modified Goldman criteria. All patient files were reevaluated for clinical diagnoses and all postmortem material was reevaluated for pathological diagnoses. After this, the Modified Goldman criteria were applied to score the discrepancies between them, and factors associated with the occurrence of an undiagnosed major unexpected finding were analyzed. The postmortem examination revealed additional findings in 65% of the cases. Major discrepancies, defined as those affecting treatment and possibly outcome of the patient, were present in 21.3% of the cases. The most frequently missed diagnoses detected at necropsy were pneumonia of various etiologies, meningitis/meningoencephalitis, myocarditis and generalized vasculitis. A shorter ICU stay was associated with increased odds of a major discrepancy. Conditions affecting the urinary or gastrointestinal system were negatively associated with major discrepancy.

ARTICLE HISTORY
Received 7 February 2023
Accepted 1 July 2023

KEYWORDS
Postmortem; Goldman criteria; ICU; misdiagnoses; discrepancy; necropsy

Introduction

Postmortem examination is considered one of the most reliable methods to validate clinical diagnoses and can contribute to medical education, patient care, and improve quality of care in human and veterinary medicine (Schertenleib et al. 2017; Burton and Underwood 2007). In the critically ill human population, despite all the available diagnostics and supportive measures available, the difficulty in obtaining an adequate medical history and the speed at which their critical condition progresses can prevent the physician from making a definitive diagnosis that, if established, would probably prevent the death of these patients. Previous studies in human adult intensive care units (ICUs) have reported that between 7.8% and 22% of patients have a major misdiagnosis antemortem, i.e. conditions that, if diagnosed before death would have been likely to alter the outcome (Fröhlich et al. 2014; Winters et al. 2012; Fernandez-Segoviano et al. 1988).

In human medicine, autopsy-detected misdiagnoses are typically classified by the Goldman criteria. They can be used to stratify misdiagnosis as major (class I and II misdiagnosis) and minor errors (class III and IV misdiagnosis) (Fröhlich et al. 2014; Fernandez-Segoviano et al. 1988; Goldman et al. 1983; Tejerina et al. 2012). The most frequent class I discrepancies in human ICU patients are pulmonary embolism, invasive aspergillosis, myocardial infarction, gastrointestinal perforation, undiagnosed infection and aortic dissection (Fröhlich et al. 2014; Winters et al. 2012; Rusu et al. 2021; Tejerina et al. 2018).

In veterinary medicine too, postmortem examination is considered to be a crucial part of quality monitoring and education (Schertenleib et al. 2017; Vos et al. 2005). Literature comparing antemortem, i.e. clinical, and pathological diagnoses in veterinary medicine is limited and focusses on agreement versus disagreement, without taking patient's treatment and survival into account. An ICU population has also not been studied specifically (Vos et al. 2005; Dank et al. 2012).

The objective of the present study is to evaluate discrepancies between clinical diagnoses and postmortem findings by applying the Modified Goldman criteria to a population of cats and dogs admitted to a small animal ICU. A secondary objective is to assess the factors associated with these discrepancies.

CONTACT Sanne Hugen s.hugen@uu.nl Department of Clinical Sciences of Companion Animals, Utrecht University, Utrecht, The Netherlands.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/01652176.2023.2233584.

Materials and methods

We conducted a retrospective study on postmortem and clinical examinations of patients that died or were euthanized while being admitted to the small animal intensive care unit (SAICU) of the Utrecht University Faculty of Veterinary Medicine. Necropsies were performed at the Veterinary Pathological Diagnostic Laboratory (VPDC) of the Utrecht University by a veterinary pathologist or a resident supervised by a veterinary pathologist.

All pathology reports on small animal autopsies performed at the Utrecht University Veterinary Pathological Diagnostic Laboratory (VPDC) requested by an UU clinician between January 2010 and December 2020 were evaluated. Reports requested by clinicians working on the Emergency service or small animal ICU during that time period were selected for further evaluation.

Inclusion and exclusion criteria

Electronic patient files from all cases were reviewed and cases were included if they were admitted to the SAICU and a provisional or final clinical diagnosis was made. Transfer to a veterinary specialist in Emergency and Critical Care during normal opening hours was not a requirement. Exclusion criteria were death upon arrival or before the patient was admitted to ICU, absence of provisional or final clinical diagnosis in the patient record, missing pathology reports or slides and insufficient quality of pathology slides for reliable re-evaluation.

Ante-mortem data

Patient files were all reviewed by one single author (SH), blinded to the pathological diagnosis. All laboratory reports, imaging reports, clinical notes, clinical pathology and microbiology reports and communication logs and letters to the owner and referring veterinarian were reviewed to identify the diagnoses established by the responsible clinicians. The clinical cause of death, and other contributory causes or additional diagnoses were recorded. In cases where the animal was euthanized, the clinical diagnosis stated as reason for euthanasia was considered the cause of death.

Furthermore, age, sex, neuter status, breed, length of hospitalization, admitting department, presentation in or out of regular hospital hours, treatment, and manner the patient died (i.e. natural death versus euthanasia) were collected.

Postmortem data

Slides and reports from the VPDC archive were re-evaluated by a single pathologist (NA), blinded to the clinical diagnoses.

Postmortem diagnosis was defined as the syndrome, injury or disease representing the cause of death or clinical condition leading to euthanasia. This was classified according to the general pathological reaction patterns of cells and tissues into: inflammatory, neoplastic, degenerative, hematologic and other (disease category). And according to major organ system into: gastrointestinal (including liver and pancreas), respiratory, cardiovascular, neurological, urinary (including renal and reproductive tract), endocrine, hematopoietic, multisystemic and other (organ system) (Zachary 2022). As the endocrine subgroup and hematopoietic subgroup proved relatively small ($n=7$ and $n=10$) respectively, these groups were reclassified as "other" before analysis.

All additional postmortem diagnoses, both incidental findings and contributory causes of death, were classified using the same categories. A patient may thus have multiple diagnoses, but only one is considered the primary cause of death.

Comparison of clinical and pathological diagnoses

Clinical and pathological diagnoses were compared using the Modified Goldman criteria, as previously described by Frohlich, substituting 'patient wishes' by 'owner wishes' in criterium f (Fröhlich et al. 2014). A class I discrepancy is defined as an undiagnosed major unexpected finding before death that probably would have changed therapy, improved survival, or significantly altered treatment of a terminally ill patient. To satisfy a class I diagnosis, the following conditions must have been met: (a) possibility to diagnose the condition premortem, (b) unlikeliness for the condition to have occurred while the patient was moribund, (c) availability of effective therapy, (d) absence of contraindication to the use of the available therapy, (e) sufficient time to introduce the therapy to make a meaningful difference, (f) no refusal by owner of further diagnostics or therapy. Additionally, (g) if the major missed diagnosis was likely to have altered the patient treatment goals from curative to palliative for a period > 24h the missed diagnosis was a class I diagnosis, and (h) If the patient was empirically receiving treatment for the major undiagnosed condition, the diagnosis was categorized as class II.

If additional conditions were not met, the major missed diagnosis was categorized as class II. Class II discrepancy was also defined as: an undiagnosed major unexpected finding before death that would not have changed the treatment or the patient's survival.

A class III discrepancy was defined as unexpected findings that were not immediate or primary causes of death but could, if known, have altered treatment decisions or prognosis. A class IV discrepancy as: Other unexpected clinically relevant findings unrelated to the cause of death or findings that are of possible epidemiological or genetic interest. Class V was scored when complete agreement between premortem clinical diagnosis and autopsy findings was found.

Classification of I or II was considered a major discrepancy. Classification of III or IV was considered a minor discrepancy. In case of uncertainty on class I or II or III condition, the case was checked by a specialist in veterinary Emergency and Critical Care (ECC). When doubt about the primary cause of death existed, reevaluation of clinical and pathological case details with pathology and ECC specialist was performed until consensus was reached.

Statistical analyses

Statistical analysis was performed using RStudio version 4.1.2. All continuous data was converted to categorical data based on clinically relevant categories. Weight was converted into three categories small animals weighing < 5 kg, medium sized animals of 5–25 kg and large animals, weighing > 25 kg. Age was converted into young, adult and senior. And duration of hospitalization into short (up to 2 days) and long (3 days or longer). Chi square test or Fisher exact test were used to compare categorical values. A univariate analysis using logistic regression and Pearson χ^2 was performed to investigate the relationship between specific variables and a major discrepancy. Odds ratios and 95% confidence intervals are reported. As reference category for the disease category and organ system involved, the group with a distribution in discrepancy rate closest to the entire group of cases, provided it included > 20% of the study population, was chosen. All variables with a $p < 0.1$ in univariate analysis were entered into a binary multivariable logistic regression model. The model was optimized based on Akaike information criterion and goodness-of-fit was checked by qq-plotting the residuals. Statistical analysis was performed on the whole data set and separately for dogs and cats. Because the dataset of cats only was smaller, Firth's correction was used to calculate odds ratios. A significance of 0.05 was used for each hypothesis.

Results

Postmortem results were available from 390 patients from the Emergency and Critical Care department from 2010–2020. Of these records 78 were excluded, because patients were not admitted to the ICU. Another 11 records were excluded due to insufficient quality of the postmortem material due to autolysis (Figure 1). Records from 300 cases were included in the final analysis. These concerned 229 dogs and 71 cats. Most common dog breeds were Labrador retriever ($n=31$), mixed breed ($n=22$), Bernese mountain dog ($n=11$), German shepherd ($n=11$), Labrador mixed breed ($n=10$), golden retriever ($n=10$), staby-houn ($n=6$) and rottweiler ($n=5$). Most common cat breeds were domestic shorthair ($n=33$), Maine coon ($n=9$), British shorthair ($n=5$), Siamese ($n=3$) and Siberian ($n=3$). Median age at presentation of the overall population was 4.8 year (0.2–14.7). Median weight of dogs was 22.7 kg (1.6–80.0 kg). Median weight of cats was 3.8 (0.9–7.4 kg). Admitting department was Emergency medicine in 275 cases, Internal medicine in 16, Neurology in 4, Surgery in 3 and Cardiology in 2 cases. Median ICU length of stay was 1 day (range 0 – 14 days). Weight was the only variable that was significantly different between dogs and cats.

Postmortem findings

The most common pathological causes of death were inflammatory in nature in both dogs and cats. In dogs, the organ system affected by this

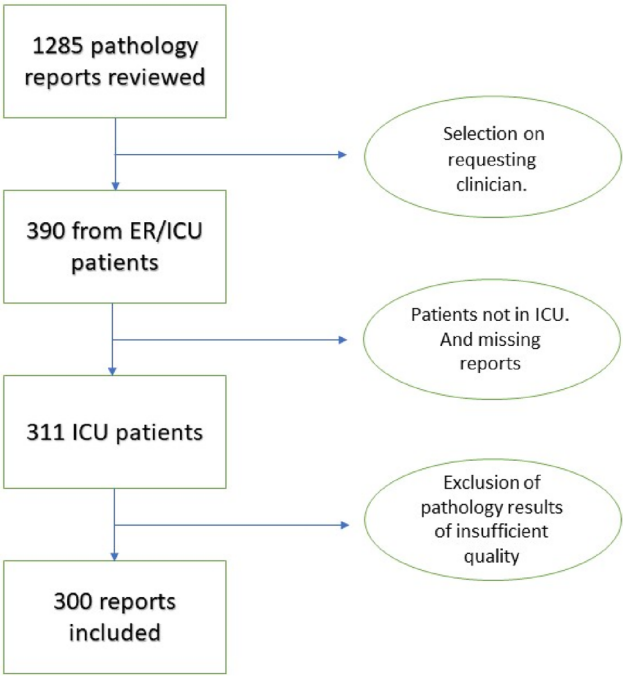

Figure 1. Overview of cases included.

inflammatory condition was most often the gastrointestinal tract ($n=54$), the respiratory tract ($n=39$), the urinary tract ($n=18$) or the cardiovascular system ($n=16$). Neoplasm of the respiratory tract was the most common non-inflammatory cause of death in dogs ($n=12$). In cats an inflammatory condition of the respiratory tract was most common ($n=14$), followed by the gastrointestinal tract ($n=11$), the urinary tract ($n=8$), and multisystemic ($n=6$ cats). All 6 cats with the classification multisystemic inflammatory cause of death had a pathological diagnosis of Feline Infectious Peritonitis (FIP).

Discrepancy classification

Major or minor discrepancies between pathological and clinical diagnosis were present in 65% of all cases. These were classified as class I in 5 cases (1.7%), class II in 59 cases (19.7%), class III in 67 cases (22.3%) and class IV in 65 cases (21.7%). Major discrepancies between clinical and postmortem diagnosis were present in 64 cases (16 cats, 48 dogs). The specific pathological diagnoses of the Goldman class I and II cases are displayed in Table 1. The most prevalently missed causes of death were pneumonia of various etiologies ($n=10$), encephalitis or meningoencephalitis ($n=6$), myocarditis ($n=4$) and generalized vasculitis ($n=4$). The generalized vasculitis cases were accompanied by edema, bleeding and thrombosis contributing to the patient's death. In the major discrepancy group, myocarditis was present in 12.5% of the cases. In the four cases where myocarditis was the major missed diagnosis, the patient's clinical signs were attributed to other concurrent disease processes and a possible problem with the heart was not suspected nor mentioned in the presumptive clinical diagnosis. Myocarditis was also documented in an additional 20 cases (6.7% of total cases). In these cases myocarditis was either a contributory cause of death or diagnosed ante-mortem. Of the total 24 myocarditis cases, 6 were cats and 18 dogs.

Five cases were judged to have a major discrepancy with a Goldman score of I. These cases are presented in Table 2. In two cases laboratory testing for

Table 1. Major discrepancies.

Disease category	Missed diagnosis	Dog Cat
Inflammatory		
Cardiovascular	Myocarditis	3 D, 1 C
	Pericarditis	1 D
	Generalized vasculitis	4 D
Respiratory	Angiostrongylus pneumonia	2 D
	Toxoplasmosis pneumonia	1 C
	Y. pseudotuberculosis pneumonia	1 C
	Bacterial pneumonia with lung lobe torsion	1 D
	Uremic pneumonitis/ ARDS related to kidney failure	1 D, 1 C
	Chronic eosinophilic bronchopneumopathy	1 C
	Pulmonary fibrosis	1 D
	Other pneumonia/ pleuropneumonia	5 D
Gastrointestinal	Hepatitis acute/ chronic	3 D
	Necrotizing/ ulcerative enteritis	1 D, 1 C
	Pancreatitis	2 D
	Perforative necrotizing esophagitis	1 D
Urinary	Ureteritis with steatitis and peritonitis	1 D
Neurological	(Meningo)encephalitis	4 D, 2 C
	Polyradiculoneuritis	1 C
Other	Sphenoid bone osteomyelitis with secondary meningitis	1 C
Neoplastic		
Cardiovascular	Chemodectoma	1 D
Respiratory	Histiocytic sarcoma	1 D
	Lymphoma	1 D
	Mediastinal carcinoma	1 D
	Diffuse metastatic carcinoma	1 D
Neurological	Lymphoma	1 D
	Round cell neoplasm in brain, spinal cord and brachial plexus	1 D
Endocrine	Neuroendocrine adrenal tumor, suspect pheochromocytoma	1 D
Multisystemic	Disseminated sarcoma	1 D
Degenerative		
Cardiovascular	Congestive heart failure	2 D
Gastrointestinal	Acute liver necrosis	2 C
Urinary	Extensive ureterolithiasis with hydronephrosis and necrosis. Contributory: Pulmonary thromboembolism, chronic myocardial infarction	1 C
Neurological	Hippocampal necrosis	1 C
Other	Degenerative myopathy	1 D
Hematologic		
Respiratory	Mediastinal bleeding due to aortic aneurysm rupture	1 D
	Pulmonary hemorrhage, likely traumatic	1 D
Neurological	Focal acute cerebellar hemorrhage and infarction	1 D
	Multifocal acute hemorrhage in brainstem, cerebellum and cervical spinal cord	1 D
Multisystemic	Hemothorax and hemoabdomen	1 D
Other		
Cardiovascular	Pericardial effusion with ectopic cystic thymus tissue	1 D

Disease category: general histopathological reaction pattern and organ system involved. Missed diagnosis: primary cause of death, including contributory cause of death if relevant. D: Dog, C: cat.

Table 2. Goldman class I discrepancies.

Disease category	Signalment	Missed diagnosis	Dog/Cat
Degenerative -Cardiovascular	Labrador retriever, 6 y, FC	DCM and mild MMVD with secondary congestive right and left sided congestive heart failure.	D
Inflammatory -Respiratory	Domestic shorthair, 3 y, FC	Toxoplasmosis leading to interstitial pneumonia, myocarditis and hepatitis.	C
	Weimaraner, 1 y, FC	Angiostrongylus vasorum pneumonia and arteritis	D
Inflammatory - Gastrointestinal	Rhodesian ridgeback, 7 y, MC	Pancreatitis, peritonitis, enteritis	D
Hematologic-Multisystemic	German pointer, 8 y, FC	Hemothorax and kidney laceration resulting in hemoabdomen. Laceration missed during surgery. Contributory: Pulmonary contusion, hemorrhage in liver, colon, bladder and adrenals	D

Disease category: general histopathological reaction pattern and organ system involved. Missed diagnosis: primary cause of death, including contributory cause of death if relevant. Signalment: breed and age of the animal with age rounded to full years. D: Dog, C: cat.

the underlying infectious disease was not performed and adequate therapy not started. Both these animals died of cardiopulmonary arrest during treatment. In the case of the German pointer, a major organ laceration was missed during after hours surgery after major trauma. The cause of ongoing abdominal bleeding was missed in ICU and medical management of the patient was unsuccessful.

A cardiac condition was missed on a dyspneic 6.5 year old Labrador presenting after hours. It was suspected of neoplasia based on thoracic radiographs. Cardiac ultrasound was not performed and the dog received IV fluids, further deteriorating his condition.

The fifth case was a Rhodesian Ridgeback presenting after hours, suspected of a septic peritonitis due to small bowel perforation based on point of care ultrasound and abdominal fluid cytology by an emergency clinician. The owners decided to euthanize the dog based on perceived poor prognosis and cost estimate for surgical and follow-up care. Further diagnostics were not offered. However, on postmortem examination no major gastrointestinal disease and no perforation was found, only mild enteritis in combination with pancreatitis and steatitis.

Factors influencing discrepancy rate

In univariate analysis of all cases, we did not find a statistically significant association between the finding of a major discrepancy and presenting in or out of office hours, sex, weight, age and dog vs cat. The results of univariate analyses are summarized in Table 3. Cardiopulmonary arrest (CPA) compared to euthanasia was significantly associated with major discrepancy. Shorter ICU stay was also associated with major discrepancy in univariate analysis. When looking at organ system involved, odds of a major

Table 3. Study population characteristics and univariate analysis results.

Variables	Categories	No major discrepancy ($n=236$) n (%)	Major discrepancy ($n=64$) n (%)	OR	95% CI	*P*-value
Dog vs Cat	Dog	181 (79.0%)	48 (21.0%)	1.0	Ref	0.78
	Cat	55 (77.5%)	16 (22.5%)	1.1	0.56–2.05	
Sex	Male intact	69 (81.1%)	16 (18.6%)	1.0	Ref	0.30
	Female intact	48 (81.4%)	11 (18.6%)	0.99	0.41–2.3	
	Male neutered	66 (81.5%)	15 (18.5%)	0.98	0.45–2.15	
	Female neutered	53 (70.7%)	22 (29.3%)	1.79	0.86–3.79	
Age	Young (<1 year)	58 (79.5%)	15 (20.5%)	1.0	Ref	0.83
	Adult(1–8 years)	124 (79.5%)	32 (20.5%	1.0	0.51–2.03	
	Senior (>8 year)	54 (76.1%)	17 (23.9%)	1.22	0.55–2.70	
Weight (kg)	0–5 kg	54 (79.4%)	14 (20.6%)	1.0	Ref	0.57
	5–25 kg	100 (80.6%)	24 (19.4%)	0.93	0.45–1.97	
	> 25 kg	68 (74.7%)	23 (25.3)	1.3	0.62–2.82	
Duration of hospitalization	Short (≤ 2 days)	154 (74.4%)	53 (25.6%)	1.0	Ref	0.005
	Long (≥ 3 days)	82 (88.2%)	11 (11.8%)	0.39	0.18–0.76	
Out of hours admission	No	111 (78.2%)	31 (21.8%)	1.0	Ref	0.84
	Yes	125 (79.1%)	33 (20.9%)	0.95	0.54–1.65	
Euthanasia	Euthanasia	191 (81.6%)	43 (18.4%)	1.0	Ref	0.023
	CPA	45 (68.2%)	21 (31.8%)	2.07	1.11–3.81	
Disease category	Inflammatory	151 (78.6%)	41 (25.8%)	1.0	Ref	0.90
	Neoplastic	38 (80.9%)	9 (19.1%)	0.87	0.37–1.88	
	Degenerative	23 (74.2%)	8 (25.8%)	1.28	0.51–2.97	
	Hematologic	15 (75.0%)	5 (25.0%)	1.23	0.38–3.38	
	Other	7 (87.5%)	1 (12.5%)	0.53	0.03–3.08	
Organ system	Respiratory	55 (73.3%)	20 (26.7%)	1.0	Ref	0.002
	Urinary	31 (93.9%)	2 (6.1%)	0.18	0.03–0.66	
	Gastrointestinal	73 (88.0%)	10 (12.0%)	0.38	0.16–0.85	
	Other	17 (85.0%)	3 (15.0%)	0.49	0.11–1.64	
	Multisystemic	12 (80.0%)	3 (20.0%)	0.69	0.15–2.44	
	Cardiovascular	24 (64.9%)	13 (35.1%)	1.49	0.63–3.47	
	Neurologic	21 (62.9%)	14 (37.1%)	1.63	0.68–3.82	

Disease category: general histopathological reaction pattern of primary cause of death. Organ system: organ system of primary cause of death. CPA: cardiopulmonary arrest, Out of hours admission: presentation outside of regular opening hours, OR: odd ratio.

discrepancy were 68% lower for gastrointestinal tract conditions and 82% lower for urinary tract conditions, compared to respiratory conditions.

In multivariable analysis, gastrointestinal tract conditions (adjusted OR 0.37 (0.15–0.85), $p = 0.002$), urinary conditions (adjusted OR 0.16 (0.02–0.62) $p = 0.002$) and prolonged hospitalization (adjusted OR 0.53 (0.28–0.77), $p = 0.01$) remained significantly associated with major discrepancy. The final multivariable logistic regression model included disease organ system, length of stay and euthanasia vs CPA.

In the analysis of the canine subgroup (supplementary material Table 3) duration of hospitalization (OR 0.52, 95% CI 0.23–1.07) and euthanasia vs cardiopulmonary arrest (OR 1.97, 95% CI 0.94–3.98) did not reach significance levels in univariate analysis and organ system involved remained significant ($p = 0.003$). The multivariable logistic regression model was not different for dogs only, compared to the group with dogs and cats

In the analysis of the feline subgroup (supplementary material Table 2), disease category was significantly associated with major discrepancy, with degenerative disease significantly more prevalent in the major discrepancy group (OR 4.47, 95% CI 1.14–17.44), as was and being age 1–8 years compared to < 1 years (OR 8.67, 1.03–72.9). Longer ICU stay (OR 0.11, 0.01–0.59) was negatively associated with major discrepancy. Organ system involved and euthanasia vs CPA did not reach significance in cats. Odds ratios were in the same direction as described in the complete dataset. Multivariable analysis was not reliably possible to perform due to small sample size.

Discussion

To the authors' knowledge, this is the first report of the application of the Modified Goldman criteria to analyze discrepancies between clinical and postmortem diagnoses in a population of dogs and cats admitted to an intensive care setting. Major or minor discrepancies were present in 65% of ICU postmortem examinations in our study, highlighting the important added value of postmortem macroscopical and histological evaluation. This total discrepancy rate is higher than what is described in human ICU pathology studies, where it is reported to be 23%–45% (Fröhlich et al. 2014,Fernandez-Segoviano et al. 1988; Goldman et al. 1983; Tejerina et al. 2012; Rusu et al. 2021). As the total discrepancy rate incorporates incidental findings and contributary causes of death, this could reflect the difference in diagnostics performed to pursue all full diagnoses in veterinary medicine due to costs and perceived risks when anesthesia is needed for diagnostics, and the option of euthanasia when prognosis is poor. The frequency of major discrepancy in this study was 21.3%, where in human ICU pathology studies it is between 7.8% and 23% (Fröhlich et al. 2014,Winters et al. 2012 ,Tejerina et al. 2012 ,Tejerina et al. 2018 ,Podbregar et al. 2011). Both for total and major discrepancy rate it is however difficult to compare veterinary ICU patients with human ICU patients given the more advanced character of human ICU care and often different nature of conditions being treated. The discrepancy rate is also higher than in two relatively recent reports on veterinary hospital patients, where only 14.9%,16% and 17.9% disagreement between clinical and postmortem diagnoses were found (Schertenleib et al. 2017,Dank et al. 2012). In a study comparing clinical and postmortem diagnoses in first opinion clinical practice, Vos et al. found no agreement in 26% and partial agreement in 22.7% of cases (Vos et al. 2005). However, the analytic method used and patient population studied was different and not standardized in these veterinary studies.

In our study, class II errors occurred almost 12 times more often than class I errors, compared to 1.1–3.4 times more often in human ICU Goldman classification studies (Fröhlich et al. 2014,Winters et al. 2012 ,Rusu et al. 2021 ,Tejerina et al. 2018). This is likely due to the application of the Modified Goldman criteria, which are very strict for classifying a discrepancy as a class I error. In veterinary critical care medicine, diagnostic and therapeutic capabilities are more limited than in human critical care patients. And many patients are in an advanced stage of disease at presentation. Another factor that may potentially cause class I errors to become class II errors, is the willingness of the owners to continue the diagnostic process in their pet that may already have a guarded to poor prognosis. As we analyzed class I and II errors together in this study, the impact of these factors on the results are minimalized.

The vast majority of postmortem diagnoses were categorized as inflammatory, both in the major discrepancy and non-major discrepancy cases. In only 16% of cases, neoplasia was considered the primary cause of death and when including neoplasia as contributory cause or incidental finding, another 11 cases (3.6%) are included. This is much lower than the incidence of neoplasia that was found for a veterinary general hospital population (38%) or first opinion clinical practice patient population (34%) (Vos et al. 2005,Dank et al. 2012). This is likely related to neoplasia being less prevalent in the veterinary ICU population and if present, it is more likely advanced in stage and thus less often misdiagnosed. The major discrepancies in the inflammatory category mainly were related to the respiratory and cardiovascular system. The majority of neoplastic cases in the major discrepancy group were also concerning the respiratory system, indicating the difficulty in making an appropriate diagnosis in patients with dyspnea. A prevalent underdiagnosed inflammatory condition in this study was myocarditis, consistent with a recent report by Lakhdir (Lakhdhir et al. 2020). The underlying cause of myocarditis was unknown in the majority of cases and it is known to be difficult to diagnose these even with molecular testing (Molesan et al. 2019). However, not all appropriate diagnostics were performed in the majority of cases in which myocarditis was undiagnosed. The prevalence of undiagnosed myocarditis may prompt ICU

clinicians to consider more elaborate diagnostic testing more often.

In this study there is an association between organ system involved and major discrepancy between postmortem and clinical diagnosis. Urinary system and gastrointestinal system involvement were associated with lower odds of a major discrepancy. This could be due to relative stability of these patients compared to cardiovascular or respiratory patients. In cats only, degenerative conditions were associated with higher odds of a major discrepancy. Conditions in this category were often acute and necrotic in nature, with suspected toxic etiology in the majority of cases (for example amanitin toxicosis (Tokarz et al. 2012)). Possibly, this is underdiagnosed in cats clinically compared to dogs because owner awareness of ingestion or exposure to environmental toxicants is limited. Organ system affected and type of disease entity were influential factors in concurrence of clinical and pathological diagnosis in a veterinary hospital population as well, however due to different methodology, the results are difficult to compare (Schertenleib et al. 2017).

Duration of hospitalization was significant in univariate and multivariable analysis, with shorter hospitalization more likely leading to a misdiagnosis. This could be related to less diagnostics being performed in the time period available, leading to higher chances of an inaccurate clinical diagnoses. In a recent study on discrepancies between pathological and clinical diagnosis in human hospitalized patients in Germany, duration of hospitalization and cardiovascular system disease were significantly associated with discrepancy (Kurz et al. 2021). And in a study on discrepancies in ICU patients, major discrepancies were also significantly more common in patients with a shorter (<10 days) duration of hospitalization (Rusu et al. 2021).

Cardiopulmonary arrest was associated with major discrepancy in univariate analysis in this study, but not in in the subgroup analyses of cats and dogs. It was retained in the multivariable regression model, but the confidence interval of the adjusted OR includes the chance that there is no association with major discrepancy. Cardiopulmonary arrest could be seen as a strong indicator of an inaccurate clinical diagnosis, because euthanasia is the preferred option for patients with a known condition with grave prognosis to prevent patient suffering. Lack of statistical significance may be due to underpowering of this study. However, Dank et al. also found no significant difference in discrepancies of dogs that died naturally or were euthanized (Dank et al. 2012). More research is needed to assess if euthanasia influences the odds of misdiagnosis in the ICU and veterinary hospitals in general.

Due to the retrospective nature of this study, there is the risk of selection bias and the sample tested not being representative of the total ICU population. Postmortem examination was offered without charge to all owners of patients that died or were euthanized in the ICU if there was uncertainty about the clinical diagnosis. This bias has likely contributed to the high total discrepancy rate. From studies in human medicine, it is known that lower autopsy rate results in higher diagnostic error frequency, by selecting the most complex cases to undergo autopsy (Shojania et al. 2003). Future studies on discrepancies between postmortem and clinical diagnoses in a random selection of ICU patients would be needed to assess the influence of this bias and could provide a more representative indication of misdiagnosis in the ICU and serve as a quality control measure.

Another limitation is that diagnosis is not always made as complete as possible, for example due to not having additional infectious disease testing, immunohistochemistry or PCR testing done. Another important consideration is that acute functional disorders may not be visible on postmortem as they may not induce histological visible changes. Thirdly, the presence of autolysis may influence the postmortem examination results. Even though cases were eliminated when pathology samples were deemed of insufficient quality upon reevaluation by the pathologist, a certain measure of autolysis is often present in the samples since postmortem examinations are not routinely performed after hours at our institution.

The analysis of the primary cause of death and not all additional findings and contributory causes could also be considered a limitation of the study. In veterinary critical care, conditions can often be complicated by multiple organ involvement and co-morbidities. Establishing what is the primary cause of death can be challenging in such cases. We aimed to minimize the chances of bias in determining the primary cause of death by judging all aspects off the case by a critical care resident and using extensive interdisciplinary consultation with the pathologist and ECC specialist to reach consensus.

This study demonstrates that postmortem examination remains a valuable tool for assessment of potential missed diagnoses in the clinic. By regularly evaluating postmortem reports and systematic analysis of postmortem data, patient care can be improved by determining potential 'blind spots' in clinical diagnostic workup. This study demonstrates that in a small animal ICU population, application of the Modified Goldman criteria can be a useful tool for analysis of clinical and postmortem data. Urinary system and gastrointestinal system conditions were negatively associated with the odds of a major discrepancy and shorter ICU stay was associated with greater odds of a major discrepancy.

Acknowledgements

We would like to thank dr J.C.M Vernooij for his valuable help with the statistical analyses.

Disclosure statement

The authors report there are no competing interests to declare.

Ethical statement

As this is a retrospective study involving post mortem samples, ethics approval is not applicable.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

References

Burton JL, Underwood J. 2007. Clinical, educational, and epidemiological value of autopsy. Lancet. 369(9571):1471–1480. doi:10.1016/S0140-6736(07)60376-6.

Dank G, Segev G, Moshe D, Kent MS. 2012. Follow-up study comparing necropsy rates and discrepancies between clinical and pathologic diagnoses at a veterinary teaching hospital: 2009 versus 1989 and 1999. J Small Anim Pract. 53(12):679–683. https://api.istex.fr/ark:/67375/WNG-MR2RRFT0-C/fulltext.pdf. doi:10.1111/j.1748-5827.2012.01296.x.

Fernandez-Segoviano P, Lazaro A, Esteban A, Rubio JM, Iruretagoyena JR. 1988. Autopsy as quality assurance in the intensive care unit. Crit Care Med. 16(7):683–685. doi:10.1097/00003246-198807000-00007.

Fröhlich S, Ryan O, Murphy N, McCauley N, Crotty T, Ryan D. 2014. Are autopsy findings still relevant to the management of critically ill patients in the modern era? Crit Care Med. 42(2):336–343. https://www.ncbi.nlm.nih.gov/pubmed/23989180. doi:10.1097/CCM.0b013e3182a275b1.

Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. 1983. The value of the autopsy in three medical eras. N Engl J Med. 308(17):1000–1005. doi:10.1056/NEJM198304283081704.

Kurz SD, Sido V, Herbst H, Ulm B, Salkic E, Ruschinski TM, Buschmann CT, Tsokos M. 2021. Discrepancies between clinical diagnosis and hospital autopsy: a comparative retrospective analysis of 1,112 cases. PLoS One. 16(8):e0255490. https://search.proquest.com/docview/2561074631. doi:10.1371/journal.pone.0255490.

Lakhdhir S, Viall A, Alloway E, Keene B, Baumgartner K, Ward J. 2020. Clinical presentation, cardiovascular findings, etiology, and outcome of myocarditis in dogs: 64 cases with presumptive antemortem diagnosis (26 confirmed postmortem) and 137 cases with postmortem diagnosis only (2004–2017). J Vet Cardiol. 30:44–56. https://www.sciencedirect.com/science/article/pii/S1760273420300473. doi:10.1016/j.jvc.2020.05.003.

Molesan A, Goodman L, Ford J, Lovering SJ, Kelly K. 2019. The causes of canine myocarditis and myocardial fibrosis are elusive by targeted molecular testing: retrospective analysis and literature review. Vet Pathol. 56(5):761–777. doi:10.1177/0300985819839241.

Podbregar M, Kralj E, Čičak R, Pavlinjek A. 2011. A triad algorithm for analysing individual ante- and post-mortem findings to improve the quality of intensive care. Anaesth Intensive Care. 39(6):1086–1092. doi:10.1177/0310057X1103900617.

Rusu S, Lavis P, Domingues Salgado V, Van Craynest M-P, Creteur J, Salmon I, Brasseur A, Remmelink M. 2021. Comparison of antemortem clinical diagnosis and post-mortem findings in intensive care unit patients. Virchows Arch. 479(2):385–392. https://link.springer.com/article/10.1007/s00428-020-03016-y. doi:10.1007/s00428-020-03016-y.

Schertenleib TI, Pospischil A, Hässig M, Kircher PR, Hilbe M. 2017. Comparison of clinical and pathological diagnoses in cats and dogs. J Comp Pathol. 156(2–3):217–234. doi:10.1016/j.jcpa.2017.01.004.

Shojania KG, Burton EC, McDonald KM, Goldman L. 2003. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. JAMA. 289(21):2849–2856. doi:10.1001/jama.289.21.2849.

Tejerina E, Esteban A, Fernández-Segoviano P, María Rodríguez-Barbero J, Gordo F, Frutos-Vivar F, Aramburu J, Algaba Á, Gonzalo Salcedo García Ó, Lorente JA, et al. 2012. Clinical diagnoses and autopsy findings: discrepancies in critically ill patients. Crit Care Med. 40(3):842–846. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00003246-201203000-00019. doi:10.1097/CCM.0b013e318236f64f.

Tejerina EE, Padilla R, Abril E, Frutos-Vivar F, Ballen A, Rodríguez-Barbero JM, Lorente JÁ, Esteban A. 2018. Autopsy-detected diagnostic errors over time in the intensive care unit. Hum Pathol. 76:85–90. doi:10.1016/j.humpath.2018.02.025.

Tokarz D, Poppenga R, Kaae J, Filigenzi M, Lowenstine LJ, Pesavento P. 2012. Amanitin toxicosis in two cats with acute hepatic and renal failure. Vet Pathol. 49(6):1032–1035. doi:10.1177/0300985811429307.

Vos JH, Borst GHA, Visser IJR, Soethout KCJ, de Haan L, Haffmans F, Hovius MPJ, Goedendorp P, de Groot MAMH, Prud'homme van Reine FH, et al. 2005. Comparison of clinical and pathological diagnoses in dogs. Vet Q. 27(1):2–10. https://agris.fao.org/agris-search/search.do?recordID=US201300997512. doi:10.1080/01652176.2005.9695181.

Winters B, Custer J, Galvagno SM, Colantuoni E, Kapoor SG, Lee H, Goode V, Robinson K, Nakhasi A, Pronovost P, et al. 2012. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. BMJ Qual Saf. 21(11):894–902. doi:10.1136/bmjqs-2012-000803.

Zachary JF. 2022. Cellular and molecular mechanisms of disease. In Pathologic basis of veterinary disease. 7th ed. St Louis, MO: Elsevier; p. 16–395.