Factors associated with anesthetic-related death in dogs and cats in primary care veterinary hospitals

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OBJECTIVE
To identify risk factors for anesthetic-related death in pet dogs and cats.

DESIGN
Matched case-control study.

ANIMALS
237 dogs and 181 cats.

PROCEDURES
Electronic medical records from 822 hospitals were examined to identify dogs and cats that underwent general anesthesia (including sedation) or sedation alone and had death attributable to the anesthetic episode ≤ 7 days later (case animals; 115 dogs and 89 cats) or survived > 7 days afterward (control animals [matched by species and hospital]; 122 dogs and 92 cats). Information on patient characteristics and data related to the anesthesia session were extracted. Conditional multivariable logistic regression was performed to identify factors associated with anesthetic-related death for each species.

RESULTS
The anesthetic-related death rate was higher for cats (11/10,000 anesthetic episodes [0.11%]) than for dogs (5/10,000 anesthetic episodes [0.05%]). Increasing age was associated with increased odds of death for both species, as was undergoing nonelective (vs elective) procedures. Odds of death for dogs were significantly greater when preanesthetic physical examination results were not recorded (vs recorded) or when preanesthetic Hct was outside (vs within) the reference range. Odds of death for cats were greater when intra-anesthesia records for oxygen saturation as measured by pulse oximetry were absent. Underweight dogs had almost 15 times the odds of death as nonunderweight dogs; for cats, odds of death increased with increasing body weight (but not with overweight body condition).

CONCLUSIONS AND CLINICAL RELEVANCE
Several factors were associated with anesthetic-related death in cats and dogs. This information may be useful for development of strategies to reduce anesthetic-related risks when possible and for education of pet owners about anesthetic risks. (*J Am Vet Med Assoc* 2017;250:655–665)

Anesthetic-related death rates and associated risk factors have been evaluated and reported for people[1] as well as for dogs and cats.[2–9] Such rates have steadily declined in human patients, and larger studies of dogs and cats have shown similar decreases, compared with anesthetic-related death rates reported in the early 1980s.[10] These decreases are perhaps not surprising given that anesthetic agents and monitoring techniques have changed substantially over the last 30 years.

Identification of risk factors for anesthetic-related death would support the development of appropriate preventive measures. The largest set of studies[4,5,9] involving companion animals to date was performed by Brodbelt et al and involved 98,036 dogs and 79,178 cats, yielding an anesthetic-related death rate of 0.17% for dogs and 0.24% for cats. Those investigators also found through case-control studies[5,9] that, controlling for certain other factors, the odds of anesthetic-related death (including animals that received SA or GA) increased in both species with increasing ASA status or greater procedure severity (major vs minor procedure). In those studies,[5,9] the odds of anesthetic-related death were greater for cats that weighed < 2 kg (4.4 lb) or ≥ 6 kg (13.2 lb) than for cats that weighed 2 to < 6 kg and were greater for dogs that weighed < 5 kg (11.0 lb) than for those that weighed 5 to < 15 kg (33 lb). Endotracheal intubation and IV fluid administration (vs none) were also associated with greater odds of anesthetic-related death among cats, whereas among dogs, these odds were greater for those ≥ 12 years than for those < 12 years of age.[5,9] The odds

ABBREVIATIONS

ASA	American Society of Anesthesiologists
CI	Confidence interval
GA	General anesthesia
SA	Sedation alone
SpO_2	Oxygen saturation as measured by pulse oximetry

of anesthetic-related death for cats were lower when heart rate was monitored (vs not monitored), when pulse oximetry was used (vs not used), or when both types of monitoring were performed.[9] Forty-seven percent of deaths in dogs and 61% of deaths in cats occurred in the postoperative period.[4] The results of these studies[4,5,9] in the United Kingdom also revealed a lack of relationship between anesthetic-related death and various drugs used for sedation and induction of anesthesia (primarily propofol).

A study[8] involving 2,252 dogs and 1,294 cats in France revealed that healthy animals had an anesthetic death rate of 0.12%, whereas sick animals (ASA status ≥ 3) had a death rate of 4.77%. The only specific risk factors identified in that study, after certain other factors were controlled for, were poor health (ASA status of 4 or 5 vs 3) and use of an anesthetic regimen other than one involving premedication, administration of isoflurane, and administration of thiopental, ketamine, or propofol. A prospective cohort study[11] conducted in Spain that involved 2,012 dogs revealed that, after certain other factors were controlled for, ASA status ≥ 4 (vs 1) was associated with an increase in the odds of intraoperative and postoperative anesthetic-related death, whereas opioid administration with or without an NSAID was associated with a decrease in these odds.

At Banfield Pet Hospital, a national primary care practice network, > 300,000 cats and dogs are anesthetized each year. Staff at Banfield facilities use the same well-defined anesthetic protocols[12] and anesthetic equipment, which makes the patient population different from those included in other multihospital studies where protocols and equipment can vary among locations. The purpose of the study reported here was to identify factors associated with anesthetic-related death in dogs and cats evaluated at these hospitals over a specific period.

Materials and Methods

Animals

The source population of this study was all dogs and cats undergoing a procedure requiring anesthesia or chemical restraint (sedation) from January 1, 2010, through March 31, 2013, at any Banfield Pet Hospital in the United States. At the time, the hospital network included 822 primary care veterinary hospitals in 43 states with a mean of approximately 125,000 dog and cat office visits/wk. All hospitals were equipped with standard proprietary practice management software, which was used to create electronic health records that were uploaded nightly to a central database. The original sample size calculation[a] for a case-control study and post hoc calculation for a matched case-control study revealed that to detect a difference between cases and controls given a 2-sided test for binomial proportions ($\alpha = 0.05$; $\beta = 0.20$), with a hypothetical prevalence of any given factor set at 25% in the case group and 10% in the control group, 100 animals and 97 animals, respectively, would be needed per group. The target sample size was set at 100 animals/group.

Study design

The study was designed as a matched case-control study, with dogs and cats evaluated separately. All dogs and cats that underwent SA or GA (including sedation) for a medical, surgical, or diagnostic procedure at a Banfield hospital were eligible for inclusion. General anesthesia was considered to have been provided when an animal had been chemically restrained to the point of permitting endotracheal intubation and inhalation anesthetic had been administered. This included uncommon situations in which anesthetic gas was delivered and anesthesia was maintained via face mask, without use of an endotracheal tube, when tube placement was difficult or impractical. Sedation alone was considered to have been provided when the chemical restraint used was insufficient to allow endotracheal intubation. Chemical restraint in this regard included administration of benzodiazepines, phenothiazines, butorphanol, propofol, or other drugs without subsequent or concurrent use of inhalant anesthetics. The degree of sedation ranged from mild tranquilization to heavy sedation during which no response could be elicited with minor or moderate stimuli. Staff at all hospitals used the same anesthetic agents and were encouraged to follow species-specific protocols.[12] These protocols were intended to provide a standardized approach to patient care that also included preanesthetic hematologic tests, pre- and postsurgical patient preparation and care (eg, guidelines for endotracheal intubation and extubation), IV fluid administration, and use of particular drugs (eg, acepromazine, butorphanol, or midazolam for premedication or chemical restraint; propofol for anesthetic induction; and sevoflurane for maintenance of anesthesia), with choice of dosages and additional considerations (eg, particular analgesics or antimicrobials) made on the basis of patient status and the procedure performed.

Case groups were created to comprise all dogs or cats that were reported to have died in relation to an anesthetic or sedation episode (herein referred to as the anesthetic episode, with any death referred to as an anesthetic-related death) as part of a surgical, medical, or diagnostic procedure. Candidate cats and dogs for the case groups were preselected electronically through a search of the medical records to identify patients that had a death or euthanasia date recorded in the patient status field within 7 days after an anesthetic episode. The 7-day period was chosen because, in the authors' experience, a delay often existed between the time an anesthetic-related death occurred and was recorded in the narrative of the medical record and the time that death was recorded electronically through the closing of the electronic medical record, thereby resulting in a recorded death date that was later than the actual death date when the records were searched electronically.

The preselection process was followed by manual review of each medical record by one of the authors (TJM), who independently assessed potential causes of death. Only patients for which anesthesia or sedation could not be reasonably ruled out as contributing to death were included in the case group. Animals with surgical complications that likely resulted in death (eg, animals with a death attributed to uncontrollable hemorrhage or euthanasia because of underlying disease while anesthetized but not animals that simply failed to recover from anesthesia) were excluded before records were further reviewed.

For each case animal, 1 control animal of the same species from the same hospital that underwent surgery within the same week was identified in the patient database by specification of the exclusion and inclusion criteria in the data extraction code and inclusion of a random selection command. After computer identification of potential candidates, the suitability of each was confirmed by manual review of the patient records. Once selected, a given control animal was no longer eligible to be included as a control for another case animal. All control animals were required to have undergone SA or GA ≤ 7 days before or after the date on which a case animal underwent the anesthetic episode and to have survived ≥ 7 days after the qualifying anesthetic episode. Dogs and cats were excluded from either study group when their medical records lacked information on age, sex, breed, reproductive status, or hematologic testing ≤ 2 weeks prior to the qualifying anesthetic episode (in situations where hematologic testing was not recorded, the reason [eg, owner declined, tests were not performed, or test results were not recorded] could not be distinguished).

Data extracted from the medical records of each qualifying case and control animal as of the date of the anesthetic episode included age, body condition score (on a 3-point scale [1 = underweight, 2 = ideal, and 3 = overweight] or a 5-point scale [1 = very thin, 2 = thin, 3 = ideal, 4 = overweight, and 5 = obese], depending on the year of the visit), reproductive status before anesthesia (ie, prior to gonadectomy for patients that underwent gonadectomy), and type of procedure performed (elective [eg, dental cleaning, routine gonadectomy, or diagnostic imaging] vs nonelective [eg, foreign body removal or other medically necessary procedure, including ovariohysterectomy performed because of pyometra]). Because computer options for body condition scoring changed during the study period, scores assigned on a 5-point basis were reassigned so they could be combined with those of the 3-point scale as underweight (very thin and thin), ideal, and overweight (overweight and obese).

For each cat or dog, all recorded hematologic data, physical examination findings, anesthetic monitoring data, and other information pertinent to the anesthetic episode were extracted. Data pertaining to the preanesthetic period included hematologic findings, rectal temperature, heart rate, respiratory rate, and whether an anesthetic equipment check had been performed. Hematologic testing comprised a standard CBC and serum biochemical analysis, which included the following analytes: albumin, alanine aminotransferase, alkaline phosphatase, BUN, calcium, cholesterol, creatinine, glucose, phosphorus, total bilirubin, potassium, sodium, and chloride. Other data related to the anesthetic episode included whether an endotracheal tube and IV catheter were used (yes or no for each), whether sevoflurane and oxygen were administered according to the standard protocol (yes or no for each), and whether anesthetic flow rate and percentage of anesthetic gas in the mixture had been used in accordance with the hospital's anesthetic protocol[12] (yes or no for each). Whether (yes or no) the following variables had been recorded was also annotated: Spo_2, ECG tracings, arterial blood pressure as measured by oscillometry, rectal temperature, heart rate, and respiratory rate.

An ASA status score reflecting preoperative health status was also assigned to each animal by the same veterinarian (TJM), who used information in the medical record to determine the animal's condition at the time of evaluation in addition to its disease history. Scores were assigned as follows: 1 = clinically normal, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe systemic disease that is a constant threat to life, and 5 = moribund and not expected to survive > 24 hours without surgery.[13] Diseases included in the assessment and assignment of ASA score included previously diagnosed chronic ailments, such as periodontal disease, osteoarthritis, diabetes mellitus, chronic kidney disease, hypothyroidism, hyperadrenocorticism, and cardiomyopathy as well as other ailments, such as otitis externa, ectoparasite infestation (fleas and ticks), gastrointestinal parasitism (roundworms, hookworms, whipworms, and tapeworms), pyometra, urinary tract obstruction, and trauma.

Statistical analysis

All statistical analyses were performed with the aid of computer software.[b] Initially, the data were explored through calculation of summary statistics, including tests to determine whether values of the continuous variables age and body weight were normally distributed (Shapiro-Wilk and Kolmogorov-Smirnov tests). Because those values were not normally distributed, they are reported as median and interquartile range. For further analyses, age and body weight were transformed by calculation of the square root (which yielded a normal distribution).

Anesthetic death rates and their 95% CIs for cats and dogs during the study period were calculated by use of data from animals confirmed to have had an anesthetic-related death, prior to application of exclusion criteria to remove those lacking certain information in their medical records. Proportions of all cats and dogs that underwent an anesthetic session during the study period and had a confirmed anesthetic-related death (prior to application of exclusion criteria) were compared by use of the z test for independent proportions.

Conditional univariable logistic regression was performed to identify variables associated with the outcome (anesthetic-related death), controlling for hospital. Factors hypothesized to be associated with anesthetic-related death as well as potential confounders such as those that would simply increase the likelihood of any type of death (eg, ASA score) were evaluated in this manner. Variables identified as having liberal associations (ie, $P < 0.20$) with anesthetic-related death through univariable regression were included in conditional multivariable logistic regression modeling (controlling for hospital), as were 2-way interaction terms that were deemed biologically plausible (eg, the interaction between sex and reproductive status or between age and body condition). Correlations among all variables were examined via calculation of the Pearson correlation coefficient (r), and for variables that were moderately correlated (ie, $r > 0.60$), the variable with the greatest OR was selected for modeling purposes.

Two conditional multivariable models were constructed for each species (dogs and cats). One included all case and control animals (GA-SA dataset), and the other included only animals that underwent GA, excluding animals that received SA (GA dataset). The purpose of the subgroup approach was to yield results that could be compared with results of other studies involving the same definition of anesthesia[4,5] while providing additional findings specific to GA (in which an inhalant anesthetic was used). Physiologic variables, such as Spo_2, arterial blood pressure, rectal temperature, heart rate, and respiratory rate, were classified as recorded versus not recorded because it was unclear whether missing values meant those data had not been measured or that they had been measured but not recorded. A manual approach to model building was used initially, with values of $P < 0.05$ considered significant and the effect of adding or subtracting each term examined for evidence of confounding (ie, change in other variable coefficients by > 20%). Values of the Akaike information criterion were used to select final models from among all candidate models. Final model goodness-of-fit was assessed with the Hosmer-Lemeshow test. Data were examined to identify observations that lacked fit or had undue influence on final models. After final models had been identified, the model for the GA-SA dataset for cats was run again, with a variable added to control for whether cats received SA or GA for post hoc investigation of whether that variable had an influence on the association of body weight with anesthetic-related death.

Results of conditional logistic regression analysis are reported as ORs and 95% CIs. Odds ratios (the odds of disease in one group vs another) can be used to quantify the magnitude of association between a factor and a disease. An OR of 1 indicates no association; a significant OR > 1 indicates that the factor, when present, is associated with increased odds of the outcome; and a significant OR < 1 indicates that the factor is associated with decreased odds of the outcome. For example, in the present study, an OR of 3 would indicate that a patient with a particular factor had 3 times the odds of having an anesthetic-related death as a patient without that factor. Significant ORs indicate only an association (ie, the factor is more common [or less common] in the group with disease than the group without disease); they do not imply a causal relationship between a factor and the outcome.

Results

Animal characteristics

Over the study period, 1,006,736 cats and 4,143,795 dogs were brought to Banfield hospitals in the United States. Patients undergoing anesthesia or sedation during this period included 273,684 (27%) cats with 377,565 anesthetic episodes and 1,269,582 (31%) dogs with 1,817,193 episodes. Of these animals, 424 cats and 982 dogs were identified by the search parameters used as having had an anesthetic-related death during the study period, yielding an anesthetic-related death rate for cats of 11 deaths/10,000 anesthetic episodes (0.11%; 95% CI, 0.10% to 0.12%) and for dogs of 5 deaths/10,000 anesthetic episodes (0.05%; 95% CI, 0.05% to 0.06%). Comparison of these death rates revealed that cats were significantly ($P < 0.001$) more likely to have an anesthetic-related death than were dogs.

Eighty-nine of 424 (21%) cats and 115 of 982 (12%) dogs met the inclusion criteria for the case group (ie, had age, sex, breed, reproductive status, and hematologic test result data available). These case animals were matched to 92 control cats and 122 control dogs. The cats originated from 85 hospitals, and the dogs originated from 109 hospitals.

General characteristics of case and control cats and dogs were summarized for each species as a whole (ie, GA-SA datasets) and for those that underwent GA (ie, excluding patients in the SA group; **Table 1**). Regression analyses controlling for hospital revealed that animals in each of the 4 case groups (in the 2 GA-SA and 2 GA datasets) were significantly older and weighed significantly more than those in the corresponding control groups. The proportion of neutered cats in the GA case group was significantly ($P = 0.001$) less than the proportion in the GA control group. With respect to body condition, none of the case-control group pairs differed significantly in proportions of cats or dogs assessed as overweight. However, for dogs (but not for cats), both case groups contained a significantly ($P < 0.001$) greater proportion of underweight animals than did the corresponding control groups.

For dogs and cats alike, the distribution of ASA status (as assigned by a single investigator on the basis of medical record review [not by the attending clinicians]) differed significantly ($P < 0.001$) between all corresponding case and control groups, with greater proportions of individuals in the case groups having high ASA statuses (Table 1). Examples of animals assigned the various ASA statuses were as follows: 1, a clinically normal patient; 2, a patient with well-controlled, uncomplicated diabetes mellitus; 3, a patient with uncontrolled or complicated diabetes mellitus or early heart failure; 4, a patient with life-threatening metastatic neoplasia, fulminant heart failure, or hypoadrenocortical crisis; and 5, a moribund patient or one with fatal systemic disease.

Timing of death for patients in the GA-SA datasets was as follows: at anesthetic induction, 13 of 115 (11%) dogs and 22 of 89 (25%) cats; during anesthesia, 21 of 115 (18%) dogs and 21 of 89 (24%) cats; after anesthesia but before hospital discharge, 12 of 115 (10%) dogs and 13 of 89 (15%) cats; and after discharge, 69 of 115 (60%) dogs and 33 of 89 (37%) cats. These proportions were similar for patients in the GA datasets: at anesthetic induction, 9 of 98 (9%) dogs and 10 of 63 (16%) cats; during anesthesia, 16 of 98 (16%) dogs and 16 of 63 (25%) cats; after anesthesia but before hospital discharge, 11 of 98 (11%) dogs and 12 of 63 (19%) cats; and after discharge, 62 of 98 (63%) dogs and 25 of 63 (40%) cats.

Of the 69 case dogs in the GA-SA dataset that died after hospital discharge, 17 (25%) had death or euthanasia recorded in the patient status field on the date of the anesthetic episode, 28 (41%) had death recorded between 1 and 2 days after anesthesia, and the remainder (24 [35%]) had death recorded between 3 and 7 days after anesthesia. Of the 33 cats in the GA-SA dataset that died after hospital discharge, 8 (24%) had death or euthanasia recorded in the patient status field on the date of the anesthetic episode, 8 (24%) had death recorded between 1 and 2 days after anesthesia, and the remainder (17 [52%]) had death recorded between 3 and 7 days after anesthesia. Anesthesia could not be excluded as a cause of death for any of these patients.

Procedure characteristics

Proportions of cats and dogs that underwent GA or SA to facilitate various procedures were summarized **(Table 2)**. Dental cleaning was the most com-

Table 1—Characteristics of 237 dogs and 181 cats in a retrospective study to identify risk factors for anesthetic-related death.

	GA-SA dogs		GA dogs		GA-SA cats		GA cats	
Variable	**Case group (n = 115)**	**Control group (n = 122)**	**Case group (n = 98)**	**Control group (n = 119)**	**Case group (n = 89)**	**Control group (n = 92)**	**Case group (n = 63)**	**Control group (n = 87)**
Male (vs female)	59 (51)	69 (57)	50 (51)	69 (58)	57 (64)	47 (51)	38 (60)	43 (49)
Neutered (vs sexually intact)	73 (63)	76 (62)	61 (62)	73 (61)	69 (78)	63 (68)	50 (79)*	60 (69)
Age (y)	6.0* (2.6–9.5)	3.8 (0.7–8.0)	6.1* (2.6–9.7)	3.7 (0.6–7.8)	5.0* (2.1–10.7)	2.7 (0.5–6.8)	5.3* (1.0–10.7)	1.8 (0.5–6.8)
Body weight (kg)	5.2* (1.9–11.9)	3.7 (2.0–7.6)	5.2* (2.1–11.6)	3.8 (1.9–7.9)	2.1* (1.6–2.6)	1.7 (1.3–2.4)	2.0* (1.4–2.4)	1.7 (1.3–2.4)
Underweight body condition (vs not underweight)	22 (19)*	5 (4)	21 (21)*	5 (4)	18 (20)	9 (10)	13 (21)	9 (10)
Overweight body condition (vs not overweight)	33 (29)	42 (34)	31 (32)	41 (34)	23 (26)	26 (28)	15 (24)	23 (26)
ASA status								
1	38 (33)*	107 (88)	34 (35)*	106 (89)	32 (36)*	79 (86)	30 (48)*	78 (90)
2	22 (19)*	13 (11)	16 (16)	12 (10)	11 (12)	7 (8)	10 (16)	5 (6)
3	23 (20)*	1 (1)	19 (19)*	0 (0)	25 (28)*	5 (5)	13 (21)*	4 (5)
4	23 (20)*	1 (1)	22 (22)*	1 (1)	18 (20)*	1 (1)	10 (16)*	0
5	9 (8)	0	7 (7)	0 (0)	3 (3)	0	0	0

Values are reported as median (interquartile range) for age and body weight and number (percentage of group total) for all other variables.

*Value differs significantly ($P < 0.05$) from that for the respective control group in a model controlled for matching of cases to controls on the basis of hospital.

All patients were admitted to primary care hospitals for procedures requiring SA or GA; those with death plausibly related to the anesthetic episode ≤ 7 days after the procedure and those that survived > 7 days after the procedure were classified as case and control animals, respectively. For purposes of analysis, 2 categories were created for each species. One included all case and control animals (GA-SA dataset), and the other included only those that underwent GA, excluding animals that received SA (GA dataset). The ASA statuses used for study purposes were assigned retrospectively by 1 investigator according to criteria described elsewhere.[13]

Table 2—Number (%) of case and control dogs and cats in Table 1 that underwent various procedures requiring GA or SA.

Procedure	Case dogs (n = 115)	Control dogs (n = 122)	Case cats (n = 89)	Control cats (n = 92)
Dental cleaning or treatment	34 (30)	75 (61)	25 (28)	45 (49)
Ovariohysterectomy	10 (9)	18 (15)	5 (6)	11 (12)
Orchidectomy	6 (5)	23 (19)	6 (7)	14 (15)
Gastrointestinal surgery	38 (33)	2 (2)	9 (10)	0 (0)
Craniofacial surgery	0 (0)	1 (1)	0 (0)	0 (0)
Orthopedic surgery	2 (2)	1 (1)	7 (8)	14 (15)
Thoracic surgery	0 (0)	0 (0)	2 (2)	0 (0)
Urological surgery	1 (1)	0 (0)	0 (0)	0 (0)
Diagnostic imaging	11 (10)	0 (0)	3 (3)	0 (0)
Other minor procedures*	13 (11)	2 (2)	32 (36)	8 (9)

*Other minor procedures ranged from facilitation of physical examination to minor surgical procedures such as laceration repair or superficial mass removal.

See Table 1 for remainder of key.

mon surgical procedure performed in case and control cats and control dogs; it was the second most common surgical procedure for case dogs (in which gastrointestinal surgery was most frequent) and was also among the most common procedures requiring GA that were performed at Banfield hospitals during the study period (data not shown). Sedation alone had been provided only for cats and dogs undergoing diagnostic imaging or for other minor procedures. For all cats, other minor procedures (n = 40) included urinary catheter placement (10/40 [25%]; 7 cases and 3 controls), physical examination (of cats with fractious behavior; 6/40 [15%]; 5 cases and 1 control), esophagostomy tube placement (5/40 [13%]; cases only), fight-wound treatment (5/40 [13%]; 4 cases and 1 control), IV catheter placement (4/40 [10%]; 3 cases and 1 control), enema administration (4/40 [10%]; case cats only), superficial mass removal (3/40 [8%]; 2 cases and 1 control), ocular debridement (1/40 [3%]; 1 control), and oral abscess treatment and nasal flushing (each, 1/40 [2%]; both case cats). For all dogs, other minor procedures (n = 15) included superficial mass removal (3 cases and 2 controls), fight-wound treatment (5 cases), laceration repair (2 cases), and physical examination after being hit by a car, thorough rectal examination, and grooming (1 case each).

Univariable regression analyses

Six of 115 (5%) dogs with an anesthetic-related death underwent ≥ 2 unrelated surgical, treatment, or diagnostic procedures (eg, treatment of impacted anal glands or skin biopsy in addition to the main procedure for which the dog was anesthetized) during the same anesthetic episode, compared with 1 of 122 (1%) control dogs in the GA-SA dataset (*P* = 0.08). Only 1 of 89 (1%) case cats underwent 2 or more procedures, compared with 6 of 92 (7%) control cats in the GA-SA dataset (*P* = 0.06). Odds ratios and 95% CIs for variables recorded before and during the preanesthetic and anesthetic periods and that had a liberal association (ie, *P* < 0.20) with anesthetic-related death were summarized **(Table 3)**.

An ASA status ≥ 3 (vs ≤ 2) was associated with a significant (*P* < 0.001) increase in the odds of anesthetic-related death with a magnitude of 3- and 4-fold for all datasets in univariable models controlling for hospital. Abnormalities in several hematologic variables were also identified as associated with an increase in the odds of anesthetic-related death in cats and dogs, regardless of dataset, including abnormal results (values outside the respective reference ranges) for RBC count; Hct; platelet count; serum concentrations of albumin, creatinine, phosphorus, urea nitrogen, globulin, and chloride; and serum activity of alkaline phosphatase (data not shown).

Multivariable regression analysis

During the modeling process to identify factors associated with anesthetic-related death, it was discovered that ASA status was moderately correlated

Table 3—Odds ratios (95% CIs) derived from conditional univariable regression analysis (controlled for hospital) for variables that were recorded before or during anesthetic episodes and were subsequently included in a multivariable modeling process to identify risk factors for anesthetic-related death for the same dogs and cats as in Table 1.

	GA-SA dogs		GA dogs		GA-SA cats		GA cats	
Time point and variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Before premedication								
Age (square root)	1.39 (1.07–1.82)	0.015	1.47 (1.10–1.97)	0.009	1.70 (1.24–2.33)	0.001	1.94 (1.30–2.90)	0.001
Body weight (square root)	1.20 (1.00–1.42)	0.045	1.19 (0.99–1.14)	0.064	3.85 (1.63–9.10)	0.002	2.95 (1.11–7.81)	0.030
Male sex	—	—	0.66 (0.36–1.24)	0.197	1.95 (1.00–3.79)	0.050	—	—
Neutered	—	—	0.14 (0.05–0.43)	0.001	1.92 (0.95–3.87)	0.070	2.94 (1.12–7.75)	0.029
Physical examination recorded	0.17 (0.02–1.51)	0.113	0.17 (0.02–1.51)	0.113	—	—	—	—
Rectal temperature recorded	0.56 (0.25–1.26)	0.163	0.55 (0.23–1.31)	0.117	2.18 (0.85–5.60)	0.106	3.07 (0.89–10.61)	0.076
Patient noted as fractious	—	—	—	—	0.32 (0.12–0.87)	0.026	0.49 (0.27–1.42)	0.188
After premedication, before anesthetic induction								
Physical examination recorded	0.06 (0.01–0.43)	0.006	0.09 (0.01–0.72)	0.023	—	—	—	—
Anesthetic equipment test performed	0.14 (0.04–0.49)	0.002	0.14 (0.02–1.16)	0.069	0.04 (0.01–0.31)	0.002	—	—
Endotracheal tube used	0.28 (0.11–0.69)	0.006	0.38 (0.10–1.41)	0.147	0.22 (0.08–0.57)	0.002	—	—
IV catheter used*	0.14 (0.03–0.60)	0.008	—	—	0.08 (0.01–0.60)	0.014	—	—
SA used	5.56 (1.58–19.60)	0.008	—		12.14 (2.85–51.61)	0.001	—	—
During anesthesia								
Appropriate anesthetic protocol used†	0.33 (0.13–0.86)	0.024	0.45 (0.17–1.21)	0.113	0.12 (0.04–0.43)	0.001	—	—
Spo_2 recorded	0.20 (0.08–0.54)	0.001	0.27 (0.08–0.98)	0.046	0.10 (0.03–0.32)	< 0.001	0.10 (0.01–0.81)	0.031
Hypoxia recorded	4.61 (1.99–10.67)	< 0.001	4.16 (1.78–9.73)	0.001	9.04 (1.05–77.58)	0.045	7.95 (0.90–70.50)	0.063
Hypotension recorded	—	—	—	—	2.63 (0.92–7.51)	0.071	2.63 (0.92–7.51)	0.071
Heart rate recorded	0.09 (0.02–0.37)	0.001	—	—	0.11 (0.03–0.36)	< 0.001	0.13 (0.01–1.00)	0.050
Elective procedure	0.01 (0.00–0.10)	< 0.001	0.02 (0.00–0.14)	< 0.001	0.18 (0.08–0.40)	< 0.001	0.29 (0.10–0.80)	0.017

Correlations among all pairs of variables did not exceed 0.50. The referent group in all dichotomous comparisons was the one lacking the particular variable; for age and body weight, ORs reflect the change in odds of anesthetic-related death for each 1-unit increase in the square root of a given value (years and kilograms, respectively).

*All patients that underwent GA had an IV catheter placed. †Appropriateness of anesthetic protocols was judged by comparison with published protocols.[12]

— = Not applicable.

See Table 1 for remainder of key.

with type of procedure (elective vs nonelective) and that either variable could be used in the final models with similar results (with ORs for other variables slightly smaller but still significant when ASA rather than type of procedure was used). However, the 2 variables could not be used in the models together without rendering each other nonsignificant and, in some circumstances, dramatically changing the coefficients of other variables. For these reasons, because values of the Akaike information criterion suggested the models including type of procedure (and not ASA status) explained the data better; because ASA status was also influenced by or reflected in other variables evaluated in the study, such as body condition or physiologic variables (and the aim was to identify specific characteristics associated with anesthetic-related death); and most importantly because ASA status was assigned retrospectively by an investigator who was aware of patient case or control status (potentially biasing the assessment), the type of procedure and not ASA status was included in final multivariable models.

All 4 multivariable models controlling for hospital and designed to identify factors associated with anesthetic-related death fit the data reasonably well (results of goodness-of-fit tests, $P > 0.18$ for all). A few observations were identified as influencing the models or their fit; however, because no justification could be found to remove them from the analyses, they were retained.

The same risk factors were identified for dogs in the GA-SA dataset as for dogs in the GA dataset, with the same degree of significance **(Table 4)**. Odds of anesthetic-related death increased with increasing age such that for each 1-unit increase in the square root of age (years), the odds increased approximately 2-fold. In other words, the odds of death for a 9-year-old cat (square root = 3) in that dataset were approximately twice those for a 4-year-old cat (square root = 2). Dogs that underwent a nonelective procedure had between 85 and 91 times the odds of an anesthetic-related death as did dogs that underwent an elective procedure, depending on the dataset. Dogs with no record of a preanesthetic physical examination had ≥ 267 times the odds of death as had dogs with such a record. Dogs with an underweight body condition had 15 times the odds of death, compared with that for dogs that were not underweight. Finally, the odds of death for dogs with an Hct outside the reference range (37% to 55%) were 5.5 times as high as those for dogs with values within the reference range. In the multivariable models, controlling for identified confounders, results outside the respective reference ranges for the following hematologic parameters were not significantly associated with outcome: RBC count; platelet count; serum concentrations of albumin, creatinine, phosphorus, urea nitrogen, globulin, and chloride; and serum activities of alkaline phosphatase.

For cats in both datasets, increasing age was associated with increased odds of anesthetic-related death **(Table 5)**; this association was similar to findings for dogs. The odds of death for cats that underwent nonelective procedures were between 5 and

Table 4—Results of conditional multivariable regression analysis of associations between various factors and the odds of anesthetic-related death for the dogs in Table 1.

	GA-SA (n = 219)		GA (n = 187)	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Nonelective (vs elective) procedure	90.76 (8.95–920.55)	< 0.001	85.29 (8.29–877.07)	< 0.001
Age (square root)	2.24 (1.30–3.85)	0.004	2.23 (1.30–23.40)	0.004
Preanesthetic physical examination not recorded (vs recorded)	279.34 (2.28–34,161.25)	0.022	267.39 (2.31–30,930.44)	0.021
Underweight (vs not underweight) body condition	14.91 (1.32–168.25)	0.029	14.71 (1.32–163.85)	0.029
Abnormal* (vs normal) Hct	5.53 (1.29–23.73)	0.021	5.47 (1.28–23.40)	0.022

*Abnormal was defined as < 37% or > 55%.

Total numbers of patients included in the conditional multivariate models do not match the total numbers included in the study because in these models, hospitals (and associated patients) were automatically dropped from analysis when all patients in those hospitals had the same outcome.

See Tables 1 and 3 for remainder of key.

Table 5—Results of conditional multivariable regression analysis of associations between various factors and the odds of anesthetic-related death for the cats in Table 1.

	GA-SA (n = 164)		GA (n = 108)	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Nonelective (vs elective) procedure	5.06 (1.81–14.22)	0.002	5.66 (1.51–21.22)	0.010
Age (square root)	1.65 (1.04–2.60)	0.032	2.66 (1.52–4.70)	0.001
Body weight (square root)	7.57 (1.02–62.36)	0.049	—	—
Spo_2 not recorded (vs recorded) during anesthesia	5.09 (1.14–22.75)	0.033	34.63 (1.39–861.93)	0.031

— = Not evaluated.

See Tables 1, 3, and 4 for remainder of key.

6 times those for cats that underwent elective procedures. Lack of a record of preanesthetic physical examination was not a risk factor for death in cats, but lack of a record of intra-anesthesia Spo_2 measurement was associated with a 5-fold increase in the odds of death for cats in the GA-SA dataset and almost 35-fold increase for cats in the GA dataset. Also different from the findings for dogs, increasing body weight was associated with an increase in the odds of anesthetic-related death for cats in the GA-SA dataset such that for each 1-unit increase in the square root of body weight (kg), the odds increased almost 8-fold. Additional modeling of the GA-SA data to control for whether cats received SA or GA revealed that the effect of body weight remained significant (OR, 7.59; 95% CI, 1.03 to 61.33; $P = 0.047$).

Discussion

The present study was conducted to identify factors associated with anesthetic-related death in dogs and cats undergoing GA or SA at primary care hospitals. Selection of these patients for the study involved 2 steps. First, an electronic search of the general patient database was performed to identify patients that underwent GA or SA and had death or euthanasia recorded in the patient status field ≤ 7 days after the anesthetic episode. Second, those patient records were manually reviewed to eliminate those for which other plausible causes of death could not reasonably be ruled out. Anesthetic-related death rates for all cats and dogs identified through that process were 11 deaths/10,000 anesthetic episodes (0.11%) and 5 deaths/10,000 anesthetic episodes (0.05%), respectively.

Comparison between overall death rates for cats and dogs in the present study revealed that cats that underwent anesthesia were significantly ($P < 0.001$) more likely to die than dogs. Although statistical comparisons between cats and dogs were not performed in the study by Brodbelt et al,[4] the anesthetic death rate in cats (0.24% [95% CI, 0.20% to 0.27%]) appeared to be higher than that for dogs (0.17%; 95% CI, 0.14% to 0.19%) as well, as suggested by the non-overlapping CIs. In contrast, in a study by Bille et al[8] that had a smaller sample size than those evaluated by Brodbelt et al[4] or in the present study, statistical comparison revealed that the odds of anesthetic-associated death for cats (OR, 1.9; 95% CI, 0.9 to 3.9) did not differ significantly ($P = 0.11$) from those for dogs.

In the study reported here, the postoperative period was the most common time of death for dogs (81/115 [70%]) and cats (46/89 [52%]), with the largest proportions of all case animals dying after hospital discharge (69/115 [60%] dogs and 33/89 [37%] cats). The aforementioned proportions differed from those reported by Brodbelt et al[4] for deaths in the postoperative period (70/148 [47%] and 106/175 [61%] for dogs and cats, respectively). However, clinicians are cautioned against making direct comparisons between the 2 studies with respect to these proportions as well as death rates because of important differences in inclusion criteria for an anesthetic-related death (including the manner in which those deaths were identified), distributions of patients with an ASA status ≥ 3, and anesthetic protocols. In the present study, an anesthetic-related death was defined as a death recorded ≤ 7 days after sedatives or anesthetics were administered, whereas in the aforementioned study,[4] deaths were included only when they occurred ≤ 48 hours after the procedure. Despite these differences in study design, both sets of findings suggest that the postoperative period is an important risk period for anesthetic-related death and highlight the importance of monitoring patients after anesthesia.

Controlling for hospital but no other factors, conditional regression analysis of medical record data for patients that met the inclusion criteria in the present study revealed several factors associated with anesthetic-related death in cats and dogs. Among these factors were several hematologic and physiologic variables, none of which were strongly correlated with each other and most of which were no longer significant when other factors were controlled for. Unconditional analysis also indicated that dogs and cats that underwent SA were > 5 times and > 12 times as likely to have an anesthetic-related death, respectively, as were their counterparts that underwent GA. This significant association was not sustained during the multivariable modeling process in our study, nor was an association between SA (vs GA) and outcome identified in unconditional analyses for cats and dogs in the research by Brodbelt et al,[4] so the clinical importance of our finding remained unknown. The SA group in the present study did not include patients that were intended to undergo GA but that died during sedation, before anesthesia was induced. However, we believe further investigation of this association is warranted, given that it appeared to indicate that the odds of anesthetic-related death were higher when patients were sedated rather than when they were fully anesthetized.

Conditional multivariable analyses revealed several factors associated with anesthetic-related death. Some of these factors such as increasing age have been previously reported.[2–5] However, other findings are novel. First, lack of documentation of a physical examination prior to anesthesia appeared to increase the odds of an anesthetic-related death in dogs. With respect to physical examination, although an examination might appear to be an easy way to identify a patient at greater odds of an anesthetic-related death than others, some patients, particularly cats, can be difficult to handle, making examination difficult or impossible (although fractious temperament was not identified as a risk factor for anesthetic-related death, nor was it correlated with lack of a physical examination in cats [$r = 0.08$]). Perhaps the reasons for not performing a physical examination should be more closely assessed (presuming that the lack of documentation indicated that an examination had not been performed). Handling or housing strategies might improve the ability to perform examinations and possibly improve a patient's physiologic status by decreasing stress.

With respect to cats, failure to document Sp_{O_2} readings during anesthesia was also associated with an increase in the odds of anesthetic-related death. This failure might have been attributable to weak pulses, low blood pressures, or impending cardiac collapse, which might serve as an early-warning system when observed. Our findings regarding data for Sp_{O_2} were in agreement with those of Brodbelt et al,[9] who found that use of a pulse oximeter also had a protective association against anesthetic-related death in cats (OR, 0.2; 95% CI, 0.1 to 0.5). We believe both sets of findings underscore the importance of patient assessment before and during anesthesia.

Another interesting finding that was also identified in previous studies[5,9] was an association between body weight (and in our study, body condition) and anesthetic outcome in models controlling for other factors such as age. Results of the present study suggested that for dogs, overweight body condition was not associated with an increase in the odds of death but that underweight body condition was (OR, 14.91; $P = 0.029$). No effect of body weight was identified for dogs with the statistical approach used (square root transformation rather than categorization of body weights). On the other hand, the investigation by Brodbelt et al[5] that involved dogs revealed that those with a low body weight (0 to < 5 kg) were almost 8 times as likely to have an anesthetic-related death as were dogs that weighed 5 to < 15 kg; however, whether dogs with a low body weight also had an underweight body condition could not be discerned from the report. No association between anesthetic-related death and body weight was identified in the study[11] involving dogs from Spain. For cats, the odds of death increased with increasing body weight (OR, 7.57) in the present study, but only for cats in the GA-SA dataset (this variable was nonsignificant in the final multivariate model for the GA dataset). In the Brodbelt et al study[9] involving cats, body weights < 2 kg (OR, 15.7) or ≥ 6 kg (OR, 2.8) were associated with an increased odds of death, compared with the odds for cats weighing 2 to < 6 kg.

For the present study, 2 points are important to consider when interpreting body weight and body condition data for cats. First, it is possible that the cats with high body weights were overweight but were simply not recorded as such at the time of the anesthetic episode. Second, one may be tempted to interpret the finding that body weight was significant in the multivariate model for the GA-SA dataset but not for the GA dataset (which excluded cats that underwent SA) as suggesting that the association identified between body weight and anesthetic-related death for cats had something to do with SA and perhaps the sedation process (eg, that heavy cats were more difficult to safely chemically restrain than lighter cats). However, we identified no other evidence to support that interpretation. Overall for both cats and dogs, it is also important to consider that, during the analyses, no distinction was made between overweight and obese body condition because of changes in the manner in which body condition was electronically recorded over the study period, and it is possible that had obesity been able to be evaluated as a separate variable, outcomes would have been different for cats or dogs. Although range of body size in cats is less extreme than it is in dogs and one could argue that high body weight in adult cats suggests development of an overweight body condition, we were unable to confidently identify whether the body weight recorded for individual cats reflected a healthy value. Additional investigation would be needed to discern whether it is body condition, body weight, or both that truly influences the odds of anesthetic-related death in dogs and cats and to identify the mechanisms underlying that influence.

Cats and dogs undergoing nonelective procedures were at considerably greater odds of anesthetic-related death than those undergoing elective procedures in the present study. This result was expected, particularly given that results of previous research[5,9] also revealed that cats and dogs undergoing major intended procedures had greater odds of death than did those undergoing minor procedures (definitions not provided). The result was also expected because, in the authors' experience, most cats and dogs requiring nonelective procedures have serious ailments for which emergency surgery is required or that contribute to or complicate the reason for surgery.

A surprising finding was the lack of a significant association between most hematologic variables and anesthetic-related death once other factors were controlled for in the analysis. This result may have been attributable to limited sample sizes. The only hematologic or physiologic variable identified as significant through multivariable modeling was Hct outside the reference range in dogs, which was associated with a 5.5-fold increase in the odds of death, compared with results for dogs that had values within the reference range. It is possible that, with a larger sample size, other associations could have been identified. Another possibility is that significant associations simply did not exist, which would be consistent with the findings of another study,[14] the results of which suggested that preanesthetic screening was of little clinical importance, compared with the importance of information provided by patient history and physical examination. Before veterinarians reconsider the value of preanesthetic blood testing, we recommend that additional research be performed with larger numbers of cats and dogs.

None of the specific physiologic abnormalities identified such as hypothermia, tachycardia, or hypertension were associated with anesthetic-related death in the present study, although failure to record general physical examination findings was associated with greater odds of death in dogs. Presumably, most physiologic abnormalities would be corrected as soon as they were identified and would, therefore, not progress to death. However, whether abnormalities were corrected in the study patients was difficult to ascertain from historical records.

Other studies[8,15] have included investigation of differences between anesthetic induction regimens in the odds of an anesthetic-related death; however, we made no attempt to assess the association between various regimens and outcome. This was primarily because the protocols for the study hospitals primarily involve use of propofol for induction of anesthesia and sevoflurane for maintenance of anesthesia. One benefit to such a standardized approach was that the potential confounding influence of variations in anesthetics on overall study findings was avoided. Use of IV catheters, endotracheal tubes, and intraoperative fluids is also included in the protocols for GA at these hospitals, thereby limiting our ability to investigate associations between these variables and anesthetic-related death for patients undergoing GA in the present study.

The present study provided no support for the hypothesis that anesthetic-related death is associated with the number of surgical, treatment, or diagnostic procedures performed while the patient was anesthetized or chemically restrained (and, potentially, total anesthetic duration). Information on procedure and anesthetic duration was unavailable for this retrospective study but would be interesting to explore in prospective studies. Given that multiple planned procedures would have likely been aborted had a patient been unstable during anesthesia, the failure to identify an association between number of procedures and the odds of death in the study reported here was perhaps not surprising.

Although several significant associations were identified in the present study, analyses were limited by a fairly small sample size for the number of variables investigated, as reflected in the wide CIs of the ORs produced by multivariable modeling. Thus, factors with a small magnitude of effect would not reach significance. Although the target sample size was set at 100 patients/study group, the decision was made to proceed with 89 case cats because of the general lack of qualifying cats as the study period came to a close and the subsequent discovery that the sample size was adequate for identifying many differences. Fewer cats than dogs were available because, although cats were more likely to have an anesthetic-related death over the study period, their medical records were less likely to be complete than were the dogs' records. Another limitation was the retrospective nature of the study, which required reliance on data entered in the medical record, preventing interpretations or analyses when data were missing, further restricting our sample size and the scope of the investigation. A third limitation was the possibility that patient outcome influenced the recordings made by veterinary staff. Although it was possible that failure of documentation of physical examinations or other monitoring data may have occurred after a patient died (eg, by staff that recorded findings at the end of the day), we believe that was unlikely because other examination findings such as cardiovascular values recorded before and during anesthesia were included in the records. The fact that other data were recorded also led us to strongly suspect that absence of information from the record likely did reflect a lack of monitoring rather than simple failure of recording. As previously mentioned, a fourth limitation of the study was that the investigator who retrospectively assigned ASA scores had full knowledge of case or control status and was the same individual who had initially determined whether the death of a particular patient qualified as anesthetic related. Therefore, the interpretation of available data and assignment of those scores could have been influenced to some extent by this knowledge, and the variable was not used in the final models. We do not believe any of the aforementioned limitations invalidated the findings.

In the study reported here, several factors were identified to increase the odds of anesthetic-related death in dogs and cats. Results suggested important differences between cats and dogs in overall anesthetic-related death rates as well as other variables such as the relationship between body weight or body condition and the odds of death and the magnitude of association between nonelective procedures and outcome. All the aforementioned findings highlight the importance of preanesthetic physical examinations and physiologic monitoring during anesthesia as well as stabilization of cats and dogs prior to nonelective or emergency procedures. The high proportion of case patients that died after anesthetic recovery in the present study highlights the need for rigorous monitoring of patients beyond that period, both before and after hospital discharge. Opportunities exist to provide remote monitoring of newly discharged patients at home, particularly those with identified risk factors for anesthetic-related death. Development of checklists for all stages of anesthetic procedures including the postoperative period can ensure comprehensive quality of care; a checklist to specifically assess a patient's suitability for hospital discharge could be helpful for decreasing anesthetic deaths that occur after a cat or dog has left the hospital.

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Footnotes

a. Sampsize: sample size for a case-control study, Glaziou P. Available at: sampsize.sourceforge.net/iface/s3.html. Accessed May 2, 2013.

b. SAS, version 9.3, SAS Institute Inc, Cary, NC.

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From this month's *AJVR*

Effect of cold storage on immediate graft function in an experimental model of renal transplantation in cats

Rebecca A. Csomos et al

OBJECTIVE
To assess the effect of cold storage (CS) on immediate posttransplantation function of renal autografts in cats.

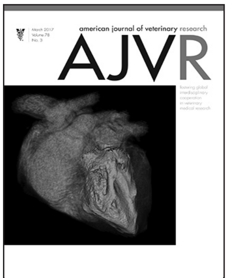
ANIMALS
15 healthy 1-year-old cats.

PROCEDURES
Cats were assigned to 2 groups and underwent autotransplantation of the left kidney followed by nephrectomy of the right kidney. The left kidney was autotransplanted either immediately (IT group; n = 6) or after being flushed with a cold sucrose phosphate solution and stored on ice while the implant site was prepared (CS group; 9). Serum creatinine and BUN concentrations were monitored daily and autografts were ultrasonographically examined intermittently for 14 days after surgery.

RESULTS
Mean duration of CS was 24 minutes for the CS group. Posttransplantation serum creatinine and BUN concentrations for the CS group had lower peak values, returned to the respective reference ranges quicker, and were generally significantly lower than those for the IT group. Mean posttransplantation autograft size for the CS group was smaller than that for the IT group.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that immediate posttransplantation function of renal autografts following a short period of CS was better than that of renal autografts that did not undergo CS, which suggested CS protected grafts from ischemic injury and may decrease perioperative complications, speed recovery, and improve the long-term outcome for cats with renal transplants.

IMPACT FOR HUMAN MEDICINE
Cats metabolize immunosuppressive drugs in a manner similar to humans; therefore, renal transplantation in cats may serve as a desirable model for investigating the effects of renal transplantation in human patients. (*Am J Vet Res* 2017;78:330–339)



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