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# Canine hypoadrenocorticism: A retrospective study of 32 cases from 2011 to 2018

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**Abstract:** Primary hypoadrenocorticism is characterized by insufficient adrenocortical hormonal secretion of glucocorticoids and mineralocorticoids, which causes unspecific signs and laboratory alterations such as hyponatremia and hyperkalemia, resulting in a low relation between these two electrolytes. The aim of this work was to carry out a retrospective study with data obtained from the medical records of 32 dogs with a proven diagnosis of hypoadrenocorticism between the years 2011 and 2018. The parameters weight, sex, reproductive condition, breed, and age were analyzed, as well as the results of laboratory tests of dogs with confirmed hypoadrenocorticism. There was no breed or sex predisposition. There was no association of the categories with the cortisol value after adrenocorticotropic hormone (ACTH), through the Chi-square tests and univariate logistic regression. There was no correlation between the numerical variables and cortisol value after ACTH, except for chlorine and ALT. The predictive values for the baseline serum cortisol concentrations of 0.8 µg/dL, 1 µg/dL, and 2 µg/dL were evaluated. Although a serum basal cortisol concentration equal to or less than 1 µg/dL has high sensitivity and specificity for a diagnosis of the disease, basal cortisol concentration alone cannot be used to diagnose the disease.

**Key words:** Hypoadrenocorticism, Addison's disease, dogs, canine, electrolytes

## 1. Introduction

Hypoadrenocorticism is characterized by inadequate secretion of hormones by the adrenal gland [1, 2, 3] and can cause a deficiency in glucocorticoids and mineralocorticoids, or only glucocorticoids [4]. According to the etiology, it is classified as primary or secondary; the primary pathogenicity is centered on the gland itself and occurs when there is atrophy or destruction of the adrenal cortex, mainly by immune-mediated reactions [5, 6], and secondary hypoadrenocorticism occurs when there is an injury to the hypothalamus or pituitary gland [7, 8], with a consequent decrease in secretion of the adrenocorticotropic hormone (ACTH) [4]. Hypoadrenocorticism is a rare hormonal disease [6, 9, 10], and affects 0.09 to 0.32% of dogs [6], from 1 month to 16 years of age [11]. According to some studies, there is a predilection for females [12, 13]. Dogs with a defined breed represent 58% [14] to 86.7% of dogs affected [10].

Clinical findings are nonspecific and depending on the severity of the disease may be acute or chronic, such as gastrointestinal signs [8, 15]. Laboratory alterations include anemia, eosinophilia, lymphocytosis, hyperkalemia, a sodium (Na): potassium (K) ratio below 27, azotemia, increased alanine aminotransferase (ALT), hypocholesterolemia, hypocalcemia, hypochloremia, hypoglycemia, and acidosis [4, 8, 11, 16].

The definitive diagnosis is made by the ACTH stimulation test [17, 18]. However, some authors have reported that this diagnosis can be excluded using only the measurement of basal cortisol with a sensitivity of 100% if the value is greater than 2 µg/dL as the chance of the dog not having the disease is high [19, 20]. However, the diagnosis cannot be confirmed if the baseline cortisol value is less than or equal to 2 µg/dL, since the specificity is low, among 20% [15], 63.3% [20], 67% [2], and 78.2% [19] although the sensitivity to disease is high, from 94% [2] to 100% [15, 19, 20].

Not enough studies have been performed to support the claim that baseline cortisol measurement can be used as the only diagnostic tool [2, 8, 15, 20]. However, it has been reported that a baseline serum cortisol concentration less than or equal to 0.8 µg/dL would characterize a better predictive value for hypoadrenocorticism, with a sensitivity of 96.9% and specificity of 95.7% [2], and for the basal cortisol value lower or equal to 1 µg/dL, the sensitivity was 85.7% [20] to 100% [19] and specificity

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from 91.8% [20] to 98.2% [19]. Therefore, further studies should be carried out to assess the diagnostic value of baseline cortisol [8, 15, 19].

The objective of the current article was to carry out the first retrospective study of laboratory and clinical alterations in canine hypoadrenocorticism in Brazil, showing the importance of the inclusion of the disease in the differential diagnosis in veterinary medical clinics as it deals with an underdiagnosed disease, and there are only isolated case reports about the disease in the country [21, 22]. The specific objectives were to identify the occurrence of the disease in the population studied and the frequency of clinical and laboratory alterations, to correlate the parameters with cortisol levels after ACTH stimulation, to analyze whether basal cortisol concentration can be used as the only diagnostic tool for hypoadrenocorticism, to have a less costly and more accessible diagnostic test, and to gather evidence on the sensitivity and specificity for three cut-off points of the basal cortisol value in the population studied.

## 2. Materials and methods

Data were obtained such as weight, reproductive condition, time of disease evolution, clinical signs, and results of laboratory tests of dogs with a confirmed hypoadrenocorticism diagnosis attended at the Veterinary Hospital and at the veterinary clinic, in the years from 2011 to 2018. The exclusion criteria were dogs that did not have a definitive diagnosis of hypoadrenocorticism, as well as patients stabilized with glucocorticoids before performing the ACTH stimulation test, and patients with no electrolyte alterations and a positive test compatible with hypoadrenocorticism.

The laboratory tests analyzed were hemogram, urea, creatinine, blood glucose, albumin, total protein, triglycerides, cholesterol, blood gasometry, and electrolytes (sodium, potassium, chlorine, phosphorus, total and ionized calcium). All tests were collected at the first appointment of the animals after they had begun to demonstrate the clinical signs. The hemogram, biochemical, and blood gasometry exams were performed in the clinical pathology laboratory of the veterinary hospital, using an automatic analyzer (poCH-100 iV Diff-Sysmex), a chemistry analyzer (Dimension X Pand Plus-Siemens), and a blood gas analyzer (RAPIDPoint 500-System Siemens), respectively. At the private clinic, the hemogram, biochemical, and blood gasometry exams were performed with the help of machines (IDEXX Laboratories, Inc., Westbrook, Maine, USA), using a hematological analyzer (ProCyte Dx), biochemical analyzer (Catalyst One), and blood gas and electrolyte analyzer (VetStat ), respectively.

The ACTH stimulation test was performed after the suspected diagnosis according to the literature [18] with an intravenous injection of 5 µg/Kg of ACTH (Synacthem). Blood samples were collected in two dry tubes, without anticoagulant, which were centrifuged after collection to separate the serum to be sent to the laboratory. The first sample to measure basal cortisol was obtained before the application of ACTH, and the second sample was obtained 1 h after application, to measure cortisol after ACTH.

Basal cortisol and post ACTH cortisol measurements were performed in private laboratories (IDEXX Laboratories, Inc.) (*Immulite*, chemiluminescence), Provet (Wizard 2, radioimmunoassay-RIA), and BetLab (*Wizard* 2, radioimmunoassay).

The statistical analysis of the data was performed in the programs R (R 3.6.3, The R Foundation, Vienna, Austria) and Statistica 13.1 (TIBCO Software, Inc., Palo Alto, California, USA) The mean, median, and range of variation were used to describe the nonparametric data and the categorical variables are described as absolute and relative frequencies (percentages) and proportions. The level of the confidence interval used was 95% and a P-value less than 0.05 was considered significant.

The Shapiro–Wilk test was performed for all variables, and the Wilcoxon signed rank nonparametric test was chosen to evaluate whether the baseline cortisol and post-ACTH tests differed. The correlations of all numerical variables with the cortisol value after ACTH were evaluated using the Spearman rank test, while the Pearson test was used to verify the correlation between parametric variables. In parallel, univariate logistic regression was also used to evaluate whether there was an association between cortisol levels after ACTH and nonnumeric variables.

The proportion of cases with hypocortisolemia (cortisol after ACTH less than 2 µg/dL) between each category was compared using the univariate Chi-square test with Yates correction. This test was also used to evaluate the accuracy of the diagnosis of hypoadrenocorticism by means of serum basal cortisol levels, comparing the sensitivity and specificity of three reference standards (£2 µg/dL, £1 µg/dL, and £0.8 µg/dL), using a healthy control population with nonadrenal diseases, with a total of 53 dogs.

## 3. Results

The occurrence of the disease was 0.0009%, as 32 dogs were identified with a confirmed diagnosis of hypoadrenocorticism, out of a total of 36685 dogs attended at the period from 2011 to 2018. The mean weight of the mixed breed dogs (NDB) was 10.2 kg with a range from 3.7 to 15.1 kg, and most dogs were castrated (59.4%, 19/32). The most affected breeds and sex are in Figure 1.

Regarding age, the youngest dog was one year of age when the diagnosis was confirmed, and the oldest dog was 14 years of age with a mean age at the time of diagnosis

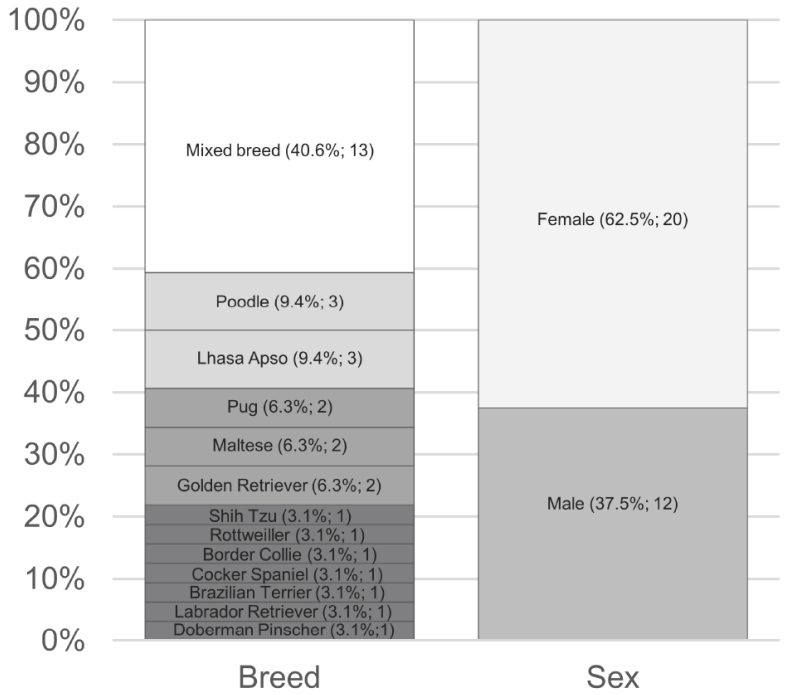


**Figure 1.** Relative and absolute frequency of breed and sex of 32 dogs with hypoadrenocorticism*. *Patients attended during the period from 2011 to 2018. Source: Author's own, 2020.

of 5.3 years. The mean age of the females was 4.6 years, ranging from 1 to 14 years, and males 6.3 years, ranging from 2 to 11 years.

The clinical signs found were apathy in 84.4% (27/32) of the dogs, emesis in 84.4% (27/32), diarrhea in 72% (23/32), weakness in 65.6% (21/32), anorexia in 62.5% (20/32), tremor in 37.5% (12/32), syncope in 6.2% (2/32), and epileptic seizures in 3.1% (1/32). The alterations observed in the physical examination were bradycardia in 62.5% (20/32) and dehydration, classified as mild in 18.7% (6/32) and moderate to severe in 81.3% (26/32) of the dogs.

With respect to the hemogram, eosinophilia 31.2% (10/32), lymphocytosis 56.2% (18/32), and anemia 50% (16/32) were observed as the main hematological findings. The anemia was classified as regenerative in 93.8% of anemic dogs (15/16), and 28.1% (9/32) of the dogs presented mild anemia (hematocrit of 30% to 36%) and 21.9% (7/32) presented moderate anemia (hematocrit of 23% to 27%).

The main biochemical and gasometry alterations (Table 1) were hypoglycemia, increased creatinine, increased urea, hypocholesterolemia, hypotriglyceridemia, acidosis, hyponatremia, hyperkalemia, hypocalcemia, and hypochloremia.

Basal cortisol was evaluated in 28 of the 32 dogs, that is, in 12.5% of the dogs the basal cortisol value was not obtained. The serum concentration of basal cortisol was less than 2 µg/dL in 84.4% (27/28) of the dogs. Cortisol after ACTH was evaluated in all 32 dogs and was less than 2 µg/dL in 93.7% (30/32).

The two dogs with elevated cortisol post ACTH presented compatible clinical signs and both had laboratory abnormalities common to hypoadrenocorticism, such as azotemia, hyponatremia, hyperkalemia, an Na:K ratio of 22, and hypochloremia, in addition to anemia in one dog and acidosis in the other. Figure 2 presents the medians, quartiles, and minimum-maximum values for Potassium (K), Sodium (Na), Sodium/Potassium ratio (Na:K), Phosphorus (P), ionized calcium (Ca+), Chlorine (Cl), basal cortisol, and cortisol post ACTH from the dogs.

The hypothesis of the diagnosis of hypoadrenocorticism being made only with the basal cortisol value was nullified, as there was a statistical difference between the basal cortisol values and post ACTH values ($P = 3.97^{-6}$, Wilcoxon signed rank test). There were no correlations between post ACTH cortisol with the parameters of time of evolution, weight, dehydration, glycemia, creatinine, urea, total protein, albumin, cholesterol, triglycerides, phosphorus, ionized calcium, sodium, potassium, the Na:K ratio, and hematocrit. There was a weak negative correlation between post ACTH cortisol and chlorine ($r = –0.40$) and ALT ($r = –0.45$).

A uniform distribution of hypocortisolemia was observed among all categories, according to the univariate Chi-square test with Yates correction. Hypoadrenocorticism

**Table 1.** Biochemical alterations in 32 dogs with hypoadrenocorticism from 2011 to 2018.

| Laboratory alteration | % | Mean | Median | Variation |
|---|---|---|---|---|
| Hypoglycemia | 40.6 | 79.6 mg/dL | 78 mg/dL | 43 to 162 mg/dL |
| Normoglycemia | 56.3 | | | |
| Hyperglycemia | 3.1 | | | |
| Creatinine- Increased | 71.9 | 2.6 mg/dL | 2.2 mg/dL | 0.7 to 10.3 mg/dL |
| - Normal | 28.1 | | | |
| Urea- Increased | 81.2 | 120.5 mg/dL | 84 mg/dL | 34.1 to 397 mg/dL |
| - Normal | 18.8 | | | |
| ALT- Increased | 18.7 | 63.3 U/L | 45 U/L | 20 to 232 U/L |
| - Normal | 81.2 | | | |
| Total protein - Normal | 71.9 | 7.3 g/dL | 7.1 g/dL | 5.6 to 9.5 g/dL |
| - Hypoproteinemia | 12.5 | | | |
| - Hyperproteinemia | 15.6 | | | |
| Albumin- Normal | 71.4 | 2.7 g/dL | 2.9 g/dL | 1.1 to 3.9 g/dL |
| - Hypoalbuminemia | 28.6 | | | |
| Triglycerides- Normal | 33.3 | 59.9 mg/dL | 43.5 mg/dL | 8 to 151 mg/dL |
| - Hypotriglyceridemia | 66.7 | | | |
| Cholesterol- Normal | 29.4 | 130.3 mg/dL | 112 mg/dL | 56 to 371 mg/dL |
| - Hypocholesterolemia | 70.6 | | | |

Source: Author's own, 2020.

in dogs was shown to have no predilection for sex or breed, and the disease most commonly affects young animals, but can occur in dogs of any age ($x^2 = 0.08$; P= 0.77).

Univariate logistic regression was used and the serum levels of blood cortisol after ACTH were not associated with the clinical and laboratory categories studied. There was no association between the hypoglycemia variables and the time of evolution (P = 0.12; OR = 1.02; CI = 0.99 ł 1.07), nor between glucose levels and the presence of azotemia (P = 0.95; OR = 1.00; CI = 0.93 ł 1.08).

Likewise, the Chi-square test ($x^2 = 0.55$, P = 0.46) showed that the prevalence of hypoglycemia was uniform among dogs with (11/23 or 48%) and without azotemia (3/9 or 33%). There was also no association between azotemia and the time of evolution of the disease ($x^2 = 17.24$, P = 0.31). No association was observed between K levels and the presence of anemia (P = 0.36; OR = 0.75; CI = 0.39 ł 1.45) according to univariate regression, and the Chi-square test ($x^2 = 1.14$, P = 0.29) showed that the prevalence of hyperkalemia was uniform among dogs with (15/16 or 94%) and without anemia (13/16 or 81%). The absolute frequencies and comparative sensitivity and specificity of the three reference standards used in the diagnosis of hypoadrenocorticism are shown in Table 2.

## 4. Discussion

The occurrence of hypoadrenocorticism in the studied population was significantly lower than the values reported in the literature [6], which could provide evidence that the disease is underdiagnosed in our country, mainly because it is not considered in the differential diagnosis of diseases with nonspecific clinical signs and due to the scarcity of electrolyte measurement and calculation of the Na:K ratio as routine exams. The occurrence of hypoadrenocorticism according to the distribution of breeds and NDB dogs [1, 5, 6, 10, 14, 23, 24], ages [5, 10, 11, 12, 25], reproductive condition [5, 10, 12], and sex [5, 12] was similar to that described in the literature.

The hemogram showed higher percentages of eosinophilia and lymphocytosis than those described in the literature [5, 10, 11, 17, 25], probably due to the greater involvement of the adrenal glands of the dogs in this study, since the occurrence of lymphocytosis and eosinophilia are explained by the deficiency of glucocorticoids, which regulate the peripheral leukocytes released [7, 14].

In many cases, anemia was masked by hemoconcentration, caused by dehydration, since the majority of these dogs had moderate to severe dehydration. The decrease in the reticulocyte count in the presence of

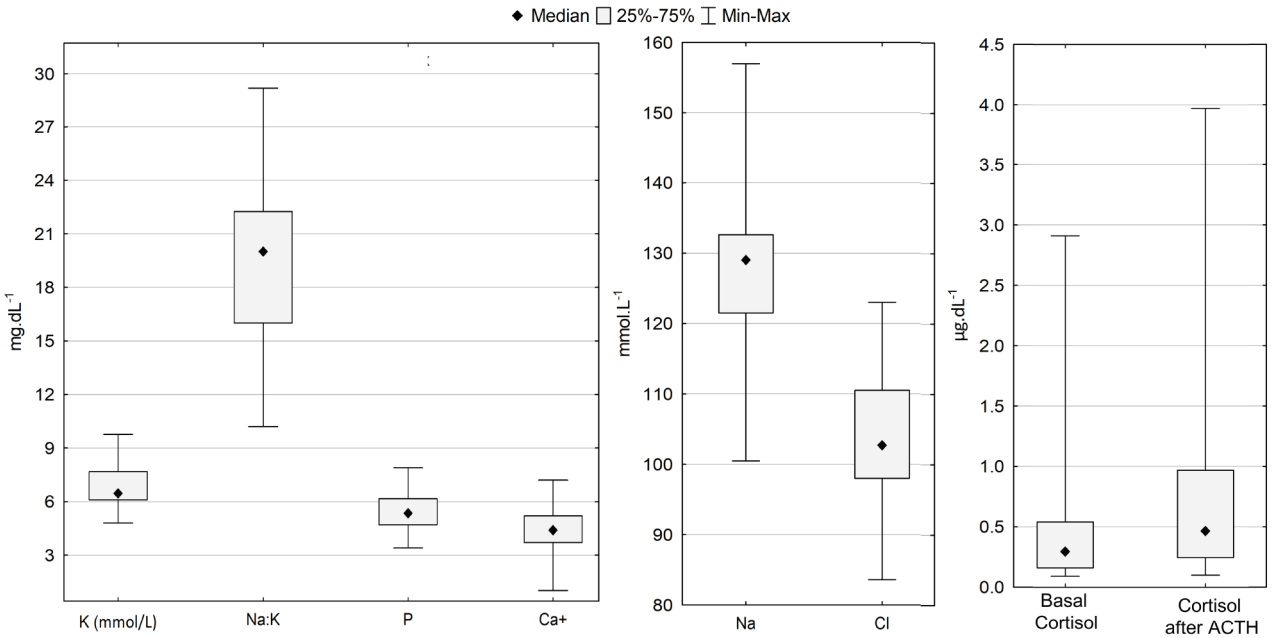


**Figure 2.** Median, quartiles, and minimum-maximum values of electrolytes, basal cortisol, and cortisol after ACTH of the dogs. Source: Author's own, 2020.

**Table 2.** Absolute frequencies, sensitivity, and specificity of three baseline cortisol values in 53 dogs attended in the period from 2011 to 2018.

| Basal cortisol value | Hypoadrenocorticism | | Sensitivity | Specificity |
|---|---|---|---|---|
| | Yes | No | | |
| Cortisol £ 2 µg/dL | 27 | 3 | 96.4% | 88% |
| Cortisol > 2 µg/dL | 1 | 22 | | |
| Cortisol £ 1 µg/dL | 25 | 0 | 89.3% | 100% |
| Cortisol > 1 µg/dL | 3 | 25 | | |
| Cortisol £ 0.8 µg/dL | 22 | 0 | 79% | 100% |
| Cortisol > 0.8 µg/dL | 6 | 25 | | |

**Source:** Author's own, 2020.

anemia reinforces this possibility. Another hypothesis is that cortisol deficiency in some cases could be progressing and, therefore, would not yet have altered erythropoiesis [4]. Anemia was mostly regenerative because it is a chronic disease and occurs due to a cortisol deficiency, which stimulates erythropoiesis, in addition to chronic loss due to gastrointestinal hemorrhage [7, 11, 16].

In biochemical tests, azotemia [5, 10, 11, 16, 25], hypocholesterolemia [17], and hypoalbuminemia [5, 11] were observed in percentages close to those reported in the literature. In the hemogasometry analysis, the occurrences of acidosis [25], hyperkalemia [12], hyponatremia [10, 11, 12, 25], and Na:K ratio lower than the reference [5, 7, 12, 26] were similar to those observed in the literature. Cases with serum creatinine, urea, and ALT values within the normal range may be due to the absence of significant alterations in renal perfusion and dehydration [11, 12, 26], and/or significant liver alterations, respectively [7, 8, 11, 16].

The occurrences of hypernatremia, normonatremia, and normocalcemia are due to loss of hypotonic fluids such as emesis and diarrhea [27], and may also be due to preserved renal tissue perfusion, with renal sodium reabsorption and potassium excretion not yet impaired, as in many cases the destruction of the adrenal gland zone is progressive [4]. The sodium value can also be

altered according to the aldosterone concentration, diet composition [27, 28], insufficient water intake, or administration of an excessive amount of physiological solution before exams [7, 8, 11], which probably did not occur in the dogs in the current study.

The occurrence of hypotriglyceridemia in more than half of the dogs, although not reported in the veterinary and human literature, can possibly be explained by the decrease in fat absorption or by anorexia and the consequent use of the body lipid reserve [4].

It was observed that the mean and median of serum basal cortisol values and post ACTH stimulation were compatible with the diagnosis of hypoadrenocorticism, as described by different authors [2, 19, 20]. According to the literature, serum cortisol concentrations between 2 and 8 µg/dL after ACTH may be suggestive of the diagnosis of hypoadrenocorticism, as the degree of injury to the adrenal cortex may be lower in these cases, but may also occur in dogs without the disease [4].

There was not association of cortisol value after ACTH with the studied parameters because these parameters are also affected by factors other than cortisol [8, 15], for example, due to secondary mechanisms as a result of aldosterone deficiency, such as dehydration and bradycardia [11, 12, 26].

The serum concentration of basal cortisol greater than 2 µg/dL in one patient, possibly occurred due to the progressive destruction of the adrenal gland [4] or due to episodic variations of cortisol in the body [2, 29]. Contrary to what was demonstrated by Lennon et al. [19] and Bovens et al. [20], who reported that baseline cortisol could be used to exclude the diagnosis of hypoadrenocorticism when the serum concentration is high, and therefore, in these cases, the ACTH stimulation test would not be necessary [19, 20]. If this premise had been followed in the current study, one dog would have been excluded from the study; however, this patient presented clinical signs and laboratory findings compatible with the disease, moreover, it is known that the value of basal cortisol depends on the degree of involvement of the adrenal gland cortex and stage of the disease, which could only be proven with the histopathology of the adrenal glands [4].

The hypothesis that basal cortisol can be used alone for the diagnosis of hypoadrenocorticism was invalidated, since basal cortisol values and post ACTH values were statistically different from each other, presumably due to the lower specificity and low positive predictive value of serum basal cortisol less than or equal to 2 µg/dL, and because it is necessary to perform the ACTH stimulation test for the definitive diagnosis, which allows better assessment of the function of the hypothalamic-pituitary-adrenal axis [2, 8]. In addition, studies have shown that there may be a basal serum cortisol concentration below 2 µg/dL in healthy dogs [15] and those that present diseases with clinical signs similar to hypoadrenocorticism [15, 30].

The sensitivities and specificities for the cut-off values of the basal cortisol concentration were close to those reported in the literature [2, 19, 20], with the exception of the sensitivity for the 0.8 µg/dL value which was slightly lower, and therefore, the cut-off points of 2 µg/dL and 0.8 µg/dL would not characterize good predictive values for the disease, since they could lead to a false positive diagnosis, in addition to the nondetection of some dogs with hypoadrenocorticism [15, 19, 20]. There was high specificity and sensitivity for the value of 1 µg/dL, in agreement with Lennon et al. [19] and Bovens et al. [20], which would characterize a better predictive value for the exam. However, further studies with a larger sample of dogs with hypoadrenocorticism and evaluation of the predictive value of this test are still needed, so that baseline cortisol can be used as the only diagnostic tool [8, 15, 19].

This work presents some limitations as it is a retrospective study, depending on the integrity of the information written in the files by different veterinarians, as well as the lack of certain data in the medical records and the hormonal tests that were carried out in different laboratories. In addition, the dosage of aldosterone or endogenous ACTH was not performed due to hormonal instability and the high cost of exams. However, the current work contributes epidemiological data on the disease.

It is concluded that basal cortisol cannot be used in isolation to diagnose the disease, even if the basal serum cortisol concentration is equal to or less than 1 µg/dL, and should also not be used to exclude the diagnosis of hypoadrenocorticism, even if the serum concentration of basal cortisol is greater than 2 µg/dL, up to 2.91 µg/dL.

**Acknowledgments/disclaimers/conflict of interest**
The authors declare that they have no conflict of interests.

**Ethics approval**
We certify that the project was evaluated by the ethics committee on the use of animals at the State University of Londrina, in November 2018, protocol CEUA number 20518.2018.68, and involves the production, maintenance, and/or use of animals belonging to the phylum *Chordata*, subphylum *Vertebrata* (except humans) for scientific research purposes, is in accordance with the precepts of Law number 11,794, of October 8, 2008, of decree number 6,899, of July 15, 2009, and with the rules issued by the National Council for the Control of Animal Experimentation (CONCEA), and was approved by the Ethics Committee on the Use of Animals of the State University of Londrina (CEUA/UEL) at a meeting held on 06/11/2018. The project aimed to perform a retrospective study of laboratory and clinical alterations in hypoadrenocorticism in dogs. Degree of invasiveness: 1.

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