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White Blood Cell Count and the Sodium to Potassium Ratio to Screen for Hypoadrenocorticism in Dogs

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Background: Abnormal sodium to potassium (Na : K) ratios can raise suspicion for hypoadrenocorticism (HA). Although dogs with HA usually have normal leukograms, their white blood cell counts may be useful in screening for HA.

Objectives: To examine the utility of combining the Na : K ratio with white blood cell counts to screen for HA in hospitalized dogs requiring fluid treatment administered IV.

Animals: Fifty-three dogs with confirmed HA and 110 sick dogs confirmed not to have HA.

Methods: Retrospective, case-control study. Dogs were included if they were hospitalized and administered fluids IV, had a complete blood count and measurement of serum Na and K concentrations. HA was diagnosed using an ACTH stimulation test, or ruled out by measurement of basal serum cortisol concentration.

Results: The receiver operating characteristic (ROC) curve for the lymphocyte count was not significantly different from the ROC curve of the Na : K ratio ($P = .55$). The ROC curve for the model combining the Na : K ratio and lymphocyte count was superior for identifying dogs with HA compared to the Na : K ratio ($P = .02$) or lymphocyte count ($P = .005$) alone. At the 100% sensitivity cutoff, lymphocyte count was more specific for detection of HA than Na : K ($P < .001$).

Conclusions and Clinical Importance: A combination of the Na : K ratio and lymphocyte count provides a better screening test for HA compared to the Na : K ratio or lymphocyte count alone. At 100% sensitivity, the lymphocyte count is a more specific test for HA than the Na : K.

Key words: Addison; Electrolytes; Endocrine; Lymphocytes.

Hypoadrenocorticism (HA) in dogs is characterized by a lack of cortisol secretion with or without concurrent aldosterone deficiency. Dogs with HA can present with a range of nonspecific clinical signs and clinicopathologic abnormalities that can mimic other diseases.[1–7] Definitive diagnosis of HA is based on demonstration of inadequate serum cortisol concentration after administration of exogenous ACTH.[1,3,4,8–10] Such testing is not routinely performed unless there is a high index of suspicion for HA. Basal serum cortisol concentration can be used as a simpler, less costly screening test for HA with a high sensitivity, but low specificity.[10]

Dogs with aldosterone deficiency often have hyponatremia, hyperkalemia, or a low sodium to potassium (Na : K) ratio. A Na : K ratio of 27 or less has been used to generate suspicion of aldosterone deficiency, with lower values considered more specific.[1,4–6] However, only 76% of dogs presenting to a referral hospital with HA have Na or K abnormalities at the time of initial examination and as few as 17% of dogs with a low Na : K ratio have HA, indicating that this screening test is neither highly sensitive nor specific.[5,7]

Abbreviations:

AUC	area under the curve
CBC	complete blood count
HA	hypoadrenocorticism
Na : K	sodium to potassium
ROC	receiver operating characteristic
MJR-VHUP	Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania
WBC	white blood cells

Leukocyte parameters have previously been reported to be unremarkable in dogs with HA, and most frequently within the reference range.[3,6,7] Changes in eosinophil count and neutrophil:lymphocyte ratio in response to exogenous ACTH administration have been used to assess adrenal function in dogs.[2] It has been postulated that a normal neutrophil and lymphocyte count along with an increased eosinophil count in dogs with physiologic stress are suggestive of HA, but to the authors' knowledge this has not been confirmed.[3,11]

The aim of this study was to evaluate the utility of the Na : K ratio combined with leukocyte counts as a screening test for HA within a population of dogs with a clinical suspicion of HA. We hypothesized that eosinophil, lymphocyte, and neutrophil counts would be useful in discriminating dogs with and without HA within this population and that a combination of Na : K ratio and leukocyte counts would be superior to Na : K ratio alone for this purpose.

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Materials and Methods

Case Selection

Computer-based medical records were searched for all dogs admitted to the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) between January 2005 and November 2009. Search criteria used to identify study dogs with HA were an appropriate code in the database diagnosis field or the dispensing of fludrocortisone[a] or desoxycorticosterone pivalate[b] from the hospital pharmacy. Control dogs were defined as cases in which the primary clinician seeing the case had a clinical suspicion of HA that was subsequently refuted. These dogs were identified by searching for cases in which basal cortisol was measured. Control dogs were not identified by searching for cases in which an ACTH stimulation test was performed, as this would have resulted in inclusion of dogs being screened or treated for hyperadrenocorticism as well as dogs being screened for relative adrenal insufficiency. Limiting the search of control dogs to those in which a basal cortisol concentration was requested ensured that the test was performed because of a clinical suspicion of HA. Some of the dogs in the control group might have ultimately had a complete ACTH stimulation test performed, if after reviewing the results of the basal cortisol concentration the clinician determined that a full ACTH stimulation test was needed. However, the control selection criterion was a basal cortisol concentration and not an ACTH stimulation test.

Dogs were included in the HA or control group if, following review of the medical record by one researcher (M.S.), they were found to have a complete blood count (CBC) and sodium and potassium concentration measurements at the time of initial examination at MJR-VHUP, serum cortisol concentration measurements during that hospital visit, and if they were hospitalized for IV fluid treatment. Dogs were excluded from the study if, following review of the medical record by 1 researcher (M.S.), they were found to have a history of recent glucocorticoid administration, a previous diagnosis of hyperadrenocorticism, or if results of cortisol concentration measurements were inconclusive for HA.

Dogs were included in the group of dogs with HA if their serum cortisol concentration was $\leq$1.0 μg/dL 1 hour after ACTH administration. ACTH stimulation tests were performed by IV administration of synthetic ACTH,[c] initially at a dose of 125 μg for dogs <15 kg or 250 μg for dogs $\geq$15 kg and more recently at a dose of 5 μg/kg.[8,9] Serum cortisol concentration was measured before and 1 hour after ACTH administration.

Dogs were included in the control group if a clinical suspicion of HA existed, but was subsequently refuted; if basal serum cortisol concentration was >2.0 μg/dL; or if serum cortisol concentration following exogenous ACTH administration was >5.0 μg/dL.[3,4]

After computer identification and subsequent record review of all dogs with HA, a random number generator[d] was used to select 3 dogs from the control population seen in the same year as each dog with HA that was included.

Clinical and Clinicopathologic Data Acquisition

Signalment, presenting clinical signs, initial physical examination findings, clinicopathologic and endocrine findings, duration of hospitalization, survival to hospital discharge, and final diagnoses were recorded. Medical records were reviewed by 1 author (M.S.).

The Na and K concentrations were taken from the biochemistry profile[e] or venous blood gas analysis[f] performed before institution of any treatment at MJR-VHUP. The recorded CBC parameters were obtained using an automated hematology analyzer[g] to determine hematocrit and total white blood cell (WBC) count, and a blood smear evaluation to obtain differential WBC counts and morphology evaluation. An automated chemiluminescent enzyme immunoassay[h] that has previously been validated was used to measure serum cortisol concentrations.[12]

Statistical Analysis

Continuous variables were evaluated for normality by visual inspection of histograms. Because the majority of these variables were not normally distributed, median (range) is used to describe them. The Mann–Whitney *U*-test was used to compare these continuous variables between groups of dogs with confirmed presence or absence of HA. Categorical variables were described with percentages and Pearson's Chi-squared test was used to compare categorical variables unless an expected cell count in the contingency table was < 5, in which case Fisher's exact test was used. Receiver operating characteristic (ROC) curve analysis was used to investigate the sensitivity and specificity of continuous variables for detecting dogs with HA. Area under the curve (AUC) was calculated for each ROC curve and expressed with 95% confidence intervals.[d,i] ROC curves were compared using the method of DeLong et al.[13] Specificities at selected cutoffs were compared using McNemar's Chi-squared test.[14]

Binary logistic regression was used to investigate the utility of combining various WBC counts to the Na : K ratio to detect HA. Forward stepwise logistic regression was performed on the Na : K ratio and all WBC counts that were found to be significantly different between groups using $P < .05$ for inclusion into the model and then $P > .10$ for removal from the model. The predictive ability of each model was evaluated using the Hosmer–Lemeshow test and ROC curve analysis.[15] Variables were subsequently excluded from the produced model in a stepwise fashion with variables that altered the AUC by <0.05 being excluded to simplify the final model.

All statistical analyses were performed and figures produced using software packages.[d,i] A *P*-value <.05 was considered significant.

Results

Demographic Data

There were 108,169 dog visits to MJR-VHUP during the study period. Computer searches of these records identified 101 dogs with a diagnosis coding of HA or that had mineralocorticoids dispensed through the hospital pharmacy. Following record review, 53 dogs met the inclusion criteria for the group with HA. Forty-eight dogs were excluded because of prior treatment for hyperadrenocorticism (n = 23), prior treatment with glucocorticoids (n = 11), the lack of a CBC (n = 6), the patient not being hospitalized (n = 4), incorrect diagnosis coding (n = 2), or a missing medical record (n = 2).

A search of the clinical pathology database of 108,169 dog visits identified a further 706 dogs that had basal cortisol concentration measured during the study period, and 159 of these dogs were randomly selected. Following review of these records, 110 dogs without HA met the inclusion criteria for the control group. Forty-nine dogs were excluded because of the dog not being hospitalized (n = 16), the lack of a CBC (n = 14), the lack of Na and K measurements from

Table 1. Comparison of signalment, historical, and physical examination findings between dogs with and without hypoadrenocorticism (HA). Data are expressed as median (range) or number (frequency).

Variable	Dogs with HA (n = 53)	Dogs without HA (n = 110)	*P*
Age (years)	4.8 (0.6–11.8)	6.8 (0.4–16.0)	.07
Body weight (kg)	20.5 (2.3–70.2)	16.8 (1.1–62.0)	.11
Female, intact	5 (9%)	5 (5%)	.27
Female, neutered	20 (38%)	41 (37%)	
Male, intact	4 (8%)	19 (17%)	
Male, neutered	24 (45%)	45 (41%)	
Vomiting with or without diarrhea	43 (81%)	88 (80%)	.87
Hematemesis or melena with or without hematochezia	6 (11%)	28 (26%)	.04
Depression, weakness, or lethargy	51 (96%)	85 (77%)	.002
Dehydration	10 (19%)	23 (21%)	.76
Abdominal pain	14 (26%)	45 (41%)	.07
Trembling with or without seizures	9 (17%)	15 (14%)	.57
Systolic blood pressure (mmHg)	90 (40–150)	140 (50–210)	<.001
Duration of hospitalization (h)	49 (16–240)	66 (3–312)	.02
Survived to hospital discharge	52 (98%)	100 (91%)	.11

the time of initial examination at MJR-VHUP (n = 9), prior treatment with glucocorticoids (n = 7), or a missing medical record (n = 3). Diagnoses in the 110 dogs without HA were gastrointestinal disease (n = 50, including 2 cases with intestinal parasitism), renal disease (n = 21), hepatic disease (n = 16), endocrine disease (n = 6), neoplasia (n = 5), cardiorespiratory disease (n = 3, including 2 cases with eosinophilic pneumonopathy), autoimmune disease (n = 3), and various other diseases (n = 6). HA was excluded in 94 (85%) dogs using basal cortisol concentration whereas 16 (15%) dogs required a subsequent ACTH stimulation test to exclude HA. The age, weight, and sex of dogs were not different between groups (Table 1).

Historical and Examination Findings

Historical and examination findings were similar between groups, although overt gastrointestinal bleeding was more common in dogs without HA, depression, weakness, or lethargy were more common in dogs with HA, systolic blood pressure was lower in dogs with HA, and duration of hospitalization was shorter in dogs with HA (Table 1).

Clinicopathologic Findings

Na : K ratio, hematocrit, neutrophil, lymphocyte and eosinophil counts, and neutrophil:lymphocyte ratio were all significantly different between dogs with and without HA (Table 2). ROC curve analysis produced an AUC of 0.873 (CI: 0.809–0.937) for Na : K ratio, 0.847 (CI: 0.787–0.907) for lymphocyte count, 0.840 (CI: 0.776–0.903) for neutrophil:lymphocyte ratio, 0.764 (CI: 0.684–0.844) for eosinophil count, and 0.631 (CI: 0.541–0.720) for neutrophil count. The ROC curve for Na : K ratio was not significantly different from the ROC curve of the lymphocyte count ($P = .55$), but both of these ROC curves were significantly better than the curves for neutrophils, eosinophils, or the neutrophil:lymphocyte ratio ($P < .05$). The sensitivity and specificity of the Na : K ratio and lymphocyte count for various cutoffs were calculated (Table 3). At the 100% sensitivity cutoff, the calculated specificity for lymphocyte count (35%) was higher than the calculated specificity for the Na : K ratio (15%, $P < .001$).

Forward stepwise binary logistic regression modeling was performed, using all variables that were hypothesized to predict HA. An initial model identified Na : K ratio ($\beta = -0.292$, $P < .001$), neutrophil count ($\beta = 0.149$, $P = .012$), and lymphocyte count ($\beta = 1.226$, $P < .001$) as the best predictors of HA with an AUC of 0.935 (CI: 0.897–0.973) (Y intercept = 6.935, Hosmer-Lemeshow $P = .535$). Removal of neutrophil count produced a model with Na : K ratio ($\beta = -0.267$, $P < .001$) and lymphocyte count ($\beta = 1.108$, $P < .001$) with an AUC of 0.927 (CI: 0.875–0.962) (Y intercept = 4.943, Hosmer Lemeshow $P = .977$). The ROC curve for the logistic model combining the Na : K ratio and lymphocyte count was superior for identifying dogs with HA compared to the Na : K ratio ($P = .02$) or lymphocyte count ($P = .005$) alone at almost all cutoffs (Fig 1).

Discussion

The Na : K ratio is widely used to raise suspicion for HA and this study supports its use as a screening tool.[1,3–7] This study identified a dog's absolute lymphocyte count at the time of initial examination as an additional screening test for HA, which is more specific than the Na : K ratio at high sensitivity cutoffs. Furthermore, the study found that a screening test for HA combining the Na : K ratio and lymphocyte count is superior to either screening test alone.

This study found that dogs with HA have a significantly higher lymphocyte count than dogs without HA, even though the majority of dogs in this study had a normal lymphocyte count. Dogs with HA might have a higher lymphocyte count than dogs without HA because glucocorticoids, which cause the lymphopenia commonly encountered in sick dogs, are absent in dogs with HA.[3,6,11] Lymphocyte count was the most diagnostically useful leukocyte count in this study and we hypothesize that it is the variable most indicative of glucocorticoid activity in these dogs. Although electrolyte disturbances occur only in 76% of cases of HA, there is only 1 reported case of a dog with HA that did not have a cortisol deficiency.[4,16] In light of this, it is unsurprising that the absence of

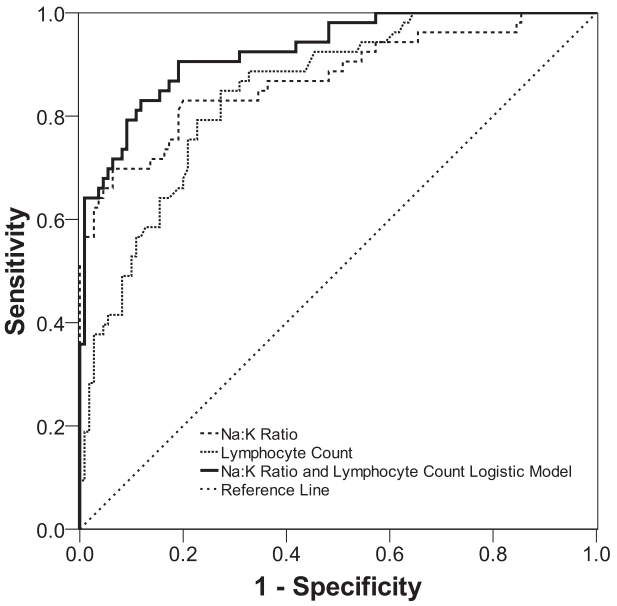

Fig 1. Receiver operating characteristic (ROC) curves for the Na : K ratio (coarse dashed line), absolute lymphocyte count (fine dashed line), and a logistic regression model combing both of these variables (solid bold line) for discerning dogs with hypoadrenocorticism (HA) from dogs with a clinical suspicion of HA. The combined Na : K ROC curve is above and to the left of the other ROC curves at almost all values, indicating consistently superior sensitivity and specificity when compared to either variable alone.

lymphopenia, which can be viewed as an indicator of glucocorticoid deficiency in this population, is a more sensitive detector of HA than Na : K ratio abnormalities, which are an indicator of mineralocorticoid activity. In addition, it might be reasonable to assume that the combination of lymphocyte count and the Na : K ratio provides a superior screening test because it assesses both glucocorticoid and mineralocorticoid activity when screening for dogs with HA.

A previous study reported that a Na : K ratio <27 is 89% sensitive and 97% specific for detection of HA.[1] In contrast, the sensitivity reported for the same ratio in this study is only 70%, while the specificity was similar at 94%. This difference is expected as the previous study examined exclusively dogs with HA and electrolyte derangements. In contrast, the current study examined all dogs with cortisol deficiency, regardless of their electrolyte concentrations. The specificity of the Na : K ratio reported in this study might also be lowered because of a selection bias in the control population; dogs in the control group could have had a baseline cortisol measured solely because of an abnormally low Na : K ratio, without other clinical signs suggestive of HA.

Eosinophilia or the lack of eosinopenia has been postulated to be an indicator of HA in sick dogs. Absence of a decrease in eosinophil count in response to ACTH administration has been used to support a diagnosis of HA.[2,3,11] This study found that eosinophil counts were significantly higher in dogs with HA compared with the control population, but that the difference was not useful as a discriminatory test. It is possible that a relatively high eosinophil count in the control population, which included dogs with intestinal parasitism and eosinophilic bronchopneumopathy, contributed to this finding.

The neutrophil counts in dogs with HA were significantly lower than in the control dogs and logistic regression identified the neutrophil count as a useful component of the model to identify dogs with HA. The median neutrophil counts in both groups were within the normal reference range and the ROC analysis did not find neutrophil counts alone to be a useful discriminatory test, perhaps reflecting that neutrophil counts can vary for many reasons and are therefore nonspecific.[11]

There are several potential limitations to this study. The data were collected from a referral and emergency hospital population, which might not reflect the dog population elsewhere. In particular, dogs seen in primary care practices might be under less physiologic stress, and therefore the reduction in their lymphocyte counts could be less pronounced,[11] decreasing the specificity of lymphocyte counts in an alternative population.

The sensitivity and specificity of the Na : K ratio reported in this study are also influenced by the fact that data were collected in a tertiary care center. It is possible that dogs with obvious electrolyte abnormalities are not referred to tertiary care centers, and are diagnosed and treated with their primary veterinarian. If this is indeed the case, than mineralocorticoid deficiency might be more common in dogs with HA

Table 2. Comparison of the Na : K ratio and selected blood cell counts between dogs with and without hypoadrenocorticism (HA). Data are expressed as median (range).

Variable	Dogs with HA (n = 53)	Dogs without HA (n = 110)	*P*
Na : K ratio	19.7 (12.0–39.4)	33.1 (20.5–61.6)	<.001
Hematocrit (%) (reference range: 40.3–60.3%)	46.1 (20.1–68.8)	42.2 (14.1–61.5)	.006
White blood cells count (cells $\times 10^3/\mu L$) (reference range: 5.3–19.8)	11.7 (5.6–31.2)	12.6 (0.9–64.2)	.87
Neutrophils (cells $\times 10^3/\mu L$) (reference range: 3.1–14.6)	7.75 (2.77–25.90)	9.87 (0.68–53.93)	.007
Lymphocytes (cells $\times 10^3/\mu L$) (reference range: 0.9–5.5)	2.38 (0.80–8.20)	1.07 (0–6.00)	<.001
Eosinophils (cells $\times 10^3/\mu L$) (reference range: 0–1.6)	0.57 (0–4.00)	0.12 (0–7.00)	<.001
Monocytes (cells $\times 10^3/\mu L$) (reference range: 0.1–1.4)	0.52 (0.07–2.80)	0.65 (0–9.63)	.174
Neutrophil: lymphocyte ratio	3.00 (0.76–14.59)	9.51 (1.23–95.15)	<.001

Table 3. Sensitivity and specificity of the Na : K ratio or lymphocyte count for predicting hypoadrenocorticism (HA) in dogs with a clinical suspicion of HA.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Na : K ratio		
<40	100 (93–100)	15 (9–23)
<35	94 (84–99)	35 (26–44)
<28	74 (60–85)	84 (75–90)
<27	70 (56–82)	94 (87–97)
<24	62 (48–75)	96 (91–99)
<20	51 (37–65)	100 (97–100)
Lymphocyte count (cells $\times 10^3/\mu L$) (reference range: 0.9–5.5)		
>0.75	100 (93–100)	35 (27–45)
>1.0	92 (82–98)	46 (37–56)
>1.2	89 (77–96)	56 (47–66)
>1.4	87 (75–95)	69 (60–78)
>1.6	79 (66–89)	77 (68–84)
>1.8	64 (50–77)	83 (74–89)
>2.0	58 (44–72)	85 (76–91)
>2.2	57 (42–70)	89 (82–94)
>2.4	49 (25–63)	92 (85–96)
>5.0	19 (9–32)	99 (95–100)
>6.0	9 (3–21)	100 (97–100)

diagnosed in a primary care practice, making the Na : K ratio changes more common and more sensitive in that setting.[3,7] Furthermore, the suspicion and screening for HA might be more common in a tertiary care center compared to a primary care setting, and this might have affected control selection and lowered the specificity calculated for the Na : K ratio.

The retrospective nature of this study means that the rationale for testing for HA is not always clear. The control population was restricted to dogs for which a basal cortisol measurement was requested, because the only indication for the test at the authors' institution is a clinical suspicion of HA. Control dogs were identified by searching for cases in which a basal cortisol and not an ACTH stimulation test was performed. This approach was chosen because the population of dogs in which an ACTH stimulation test is performed includes not only dogs with a clinical suspicion of HA, but also dogs with a clinical suspicion of hyperadrenocorticism or relative adrenal insufficiency, as well as dogs monitored for treatment of hyperadrenocorticism. Nevertheless, some dogs might have had cortisol concentration measurements solely because of their leukogram or electrolyte changes without other clinical suspicion of HA, lowering the identified specificity of lymphocyte count or Na : K ratio, respectively. In addition, our control population was selected from the hospital population of dogs that initially had only a resting cortisol measurement. Some dogs in which a strong suspicion of HA existed might have had an ACTH stimulation test performed immediately rather than a resting cortisol measurement and these dogs would not have been included in this study if they did not have HA.

Control dogs were not selected based on clinical signs, because these are not specific. Selection of control dogs based on clinical signs would have resulted in inclusion of dogs with conditions such as foreign body obstruction or viral infection, which do not usually require screening for HA. The goal of this study was to improve the screening for HA within a population of dogs truly suspected of having this condition. Results of this study (Table 1) suggest that selecting controls from the population of dogs in which a basal cortisol concentration was measured did ultimately yield a control group with great clinical similarities to dogs with HA.

During the study period, basal cortisol concentration was measured in 706 of 108,169 dog visits, but only 53 dogs were definitively diagnosed with HA. It is possible that in this particular study population there was overtesting for HA, and that cortisol was measured in the absence of appropriate clinical indication. Given the retrospective study design, it is not possible to determine whether testing was indicated in every dog in which it was performed, or whether it was overused. However, if testing was overused, it could have led to falsely low specificity of the parameters evaluated.

In conclusion, combining the Na : K ratio and lymphocyte count provides a screening test for HA that is superior for identifying dogs with HA compared to the Na : K ratio or lymphocyte count alone. Within this particular population of physiologically stressed animals that required hospitalization for fluid treatment administered IV, the diagnostic potential of the Na : K ratio or lymphocyte count alone is equal in differentiating dogs with HA from dogs that do not have HA.

Footnotes

[a] Florinef, Bristol-Myers Squibb Company, Princeton, NJ
[b] Percorten-V, Novartis Animal Health, Greensboro, NC
[c] Synacthen, Alliance Pharmaceuticals Limited, Chippenham, Wiltshire, UK
[d] IBM SPSS Statistics 19, IBM Corporation, Somers, NY
[e] Chemistry analyzer, Kodak Ektachem 250, Eastman Kodak Co, Rochester, NY
[f] Stat Profile, NOVA Biomedical Corporation, Waltham, MA
[g] Cell-Dyn 3700, AbbottLaboratories, Abbott Park, IL
[h] Immulite, DPC, Los Angeles, CA
[i] Medcalc for Windows 11.5, MedCalc Software, Mariakerke, Belgium

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