

Standard Article

J Vet Intern Med 2017;31:582–592**Prognostic Value and Development of a Scoring System in Horses With Systemic Inflammatory Response Syndrome**

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Background: Despite its widespread use in equine medicine, the clinical value of the systemic inflammatory response syndrome (SIRS) concept in horses remains unknown.

Objectives: To study the prognostic value of measures of SIRS in horses and identify the best model of severe SIRS to predict outcome.

Animals: A total of 479 consecutive adult horse emergency admissions to a private primary referral practice.

Methods: Prospective observational study. All adult horses admitted for emergency treatment over the study period were included. Multivariate logistic regression and stepwise model selection were used.

Results: Each of the 4 SIRS criteria was associated with outcome in this population. Thirty-one percent of emergency cases had 2 or more abnormal SIRS criteria on admission and were defined as SIRS cases. SIRS was associated with increased odds of death (odds ratio [OR] = 8.22; 95% CI, 4.61–15.18; $P < .001$), an effect mainly found for acute gastrointestinal cases. SIRS cases were assigned a SIRS score of 2, 3, or 4, according to the number of abnormal SIRS criteria fulfilled on admission, and SIRS3 and SIRS4 cases had increased odds of death compared to SIRS2 cases (OR = 4.45; 95% CI, 1.78–11.15; $P = .002$). A model of severe SIRS including the SIRS score, blood lactate concentration, and color of the mucous membranes best predicted outcome in this population of horses.

Conclusions and Clinical Importance: Systemic inflammatory response syndrome is associated with an increased risk of death in adult horses presenting with acute gastrointestinal illnesses. The model of severe SIRS proposed in this study could be used to assess the status and prognosis of adult equine emergency admissions.

Key words: Equine; Lactate; Mucous membranes; Outcome.

The systemic inflammatory response syndrome (SIRS) is a complex pathophysiologic response that develops after a variety of acute and severe insults such as trauma, burn, infection, or exposure to bacterial products. The concept of SIRS was introduced in the early nineties at the American College of Chest Physicians and Society of Critical Care consensus conference.¹ The goal of the conference was to introduce simple definitions for SIRS, sepsis, severe sepsis, septic shock, and multiple organ dysfunction, using clinical variables that would be easy to measure and accessible to any clinician.² These simple definitions would

Abbreviations:

| | |
|--------|---|
| 95% CI | 95% confidence interval |
| AIC | Akaike's information criterion |
| ROC | receiver operating characteristic |
| SIRS | systemic inflammatory response syndrome |

ensure uniformity in the terminology used in publications and across clinicians and lead to early identification of patients at risk for critical illness and sepsis that could benefit from early therapeutic intervention. The definitions were intentionally chosen to be quite sensitive and not too specific, to ensure identification of as many at-risk patients as possible. This high sensitivity and poor specificity of the SIRS and sepsis definitions led to many criticisms, with some suggesting that SIRS, as currently defined, is useless.³

Despite these criticisms, SIRS was widely adopted by human clinicians and researchers.^{4–8} The case fatality rate of patients in an intensive care unit was found to increase with the number of SIRS criteria met—the SIRS score—as well as with the progression from sepsis to severe sepsis and septic shock, suggesting that the consensus definitions were clinically useful and meaningful.⁹ Equine clinicians and researchers were also quick to adopt the human SIRS and sepsis definitions,^{10,11} leading to widespread use in research, clinic, and veterinary curriculums. Recently, it was suggested that SIRS should replace the widely used term endotoxemia to describe the clinical status of horses with severe colic.¹²

Despite its widespread use in equine medicine, there is still no adult horse-specific consensus SIRS definition, although such definition was recently proposed for foals.¹⁰ As a result, a wide variety of heterogeneous

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definitions are currently used, and while most authors follow the original human SIRS definition in terms of numbers of criteria, the cutoffs for each criterion have varied between authors,^{13–16} with some also including markers of poor perfusion in their SIRS definition.^{15,17} Moreover, to our knowledge, the clinical value of the SIRS concept in terms of prediction of death in adult horses remains unknown.

The main objective of this study therefore was to investigate the prognostic value of SIRS in a population of adult equine emergency admissions to a private primary referral practice. Additionally, we investigated the use of the SIRS score (ie, the number of abnormal SIRS criteria) for identifying horses with more advanced SIRS and increased risk of death. Finally, using markers of tissue perfusion in addition to the SIRS score, we aimed to identify the best model of severe SIRS for outcome prediction in this population.

Materials and Methods

Study Population, Data, and Sample Collection

This study consisted in the prospective collection of case information, diagnostic tests results, diagnosis, and outcome, followed by retrospective analysis of all data. All horses, aged 1 year or older, admitted on an emergency basis between June 2012 and May 2014 to a private equine referral center were included. Clinical data recorded included the horse's signalment, ownership, admission date, presenting complaint, physical examination findings, final diagnosis, outcome, discharged (or death) date, and reason for euthanasia if applicable. For analysis, horses that were

euthanized for poor prognosis and horses that died were treated as the same nonsurvivor or died group.

Attending clinicians were encouraged to collect venous blood on admission for CBC and, if indicated, measurement of venous blood lactate. All laboratory tests were performed in-house.^{a,b} The study protocol was approved by the Veterinary Science Animal Care Committee of our institution. Signed owner or agent consent was obtained at the time of admission.

Diagnostic Categories

To refine the data analysis, the emergency admissions were grouped into 3 broad diagnostic categories (Table 1): (1) gastrointestinal cases; (2) musculoskeletal and skin cases (wounds and lacerations, septic joints or tendon sheaths, fractures, and others); and (3) other systems cases (liver, respiratory, reproductive, urogenital, immune system, multisystemic, and other or unknown). The gastrointestinal cases were further subdivided into colics, colitis, and "other gastrointestinal." The colic cases included surgical colics and medical colics. The surgical colics were divided into strangulating colics (small and large intestine), surgical nonstrangulating large colon displacement or impactions, other surgical colics (nonstrangulating small intestinal lesions, small colon lesions, and large colon ulcers), and ruptured colics (colic cases with ruptured stomach, colon, or cecum upon arrival). Some cases with surgical colic lesions died or were euthanized (because of grave prognosis) before surgery; however, they were still included in the surgical colic cases. Colic cases were categorized as medical colics if they recovered without surgical intervention, and this category included mainly spasmodic colics, large colon impactions, and nonsurgical suspected large colon displacements. The "other gastrointestinal" category included a wide variety of noncolic gastrointestinal cases such as esophageal obstructions, intra-abdominal abscesses,

Table 1. Diagnostic categories, case fatality rates, and systemic inflammatory response syndrome (SIRS) status for the study population.

| Diagnostic Category | Total (n) | Case fatality Rate (%) | SIRS ^a (n) | Non-SIRS ^a (n) | SIRS Rate (%) |
|--|-----------|------------------------|-----------------------|---------------------------|---------------|
| All emergency admissions | 464 | 17.7 | 121 | 265 | 31.3 |
| Gastrointestinal | 308 | 17.9 | 76 | 186 | 29.0 |
| Colics | 247 | 13.4 | 49 | 155 | 24.0 |
| Surgical colics—All | 78 | 42 | 30 | 25 | 55 |
| Strangulating colics | 35 | 57 | 16 | 8 | 67 |
| Surgical NS large colon lesions ^b | 20 | 15 | 6 | 11 | 35 |
| Other surgical colics | 18 | 28 | 3 | 6 | 33 |
| Ruptured colics | 5 | 100 | 5 | 0 | 100 |
| Medical colics | 169 | 0 | 19 | 130 | 12.8 |
| Colitis | 30 | 53 | 17 | 13 | 57 |
| Other gastrointestinal | 31 | 19 | 10 | 18 | 36 |
| Musculoskeletal and skin | 93 | 12 | 16 | 50 | 24 |
| Wounds and lacerations | 52 | 6 | 9 | 30 | 23 |
| Septic joint or tendon sheath | 22 | 27 | 4 | 9 | 31 |
| Fracture | 6 | 17 | 0 | 3 | 0 |
| Other musculoskeletal | 13 | 8 | 3 | 8 | 27 |
| Other systems | 63 | 25 | 29 | 29 | 50 |
| Liver | 6 | 33 | 2 | 4 | 33 |
| Respiratory | 15 | 13 | 7 | 7 | 50 |
| Reproductive | 9 | 0 | 4 | 4 | 50 |
| Urogenital | 6 | 50 | 4 | 2 | 67 |
| Immune system | 5 | 20 | 2 | 3 | 40 |
| Other and unknown | 13 | 15 | 6 | 6 | 50 |
| Multisystemic | 9 | 67 | 4 | 3 | 57 |

^aSome cases did not have enough information recorded on admission to allow classification as SIRS or non-SIRS cases.

^bSurgical nonstrangulating large colon displacements or impactions.

primary peritonitis, neoplasia, and ill-defined gastrointestinal symptoms.

Systemic Inflammatory Response Syndrome Criteria

Physical examination values and WBC count of admission were used to investigate the clinical value of SIRS in horses, based on the previously published human SIRS criteria,¹ where SIRS is defined by the alteration of 2 or more of the following: heart rate, respiratory rate, temperature, and WBC count. The optimal cutoffs for the heart rate and respiratory rate for outcome prediction (survived or died) were established by a criterion based on the equality of sensitivity and specificity.¹⁸ For temperatures and WBC counts, because an abnormal value can be either below or above the reference range, using the same criterion for selection of a single cutoff would result in a value in the middle of the reference range, which would not be clinically meaningful. Therefore, we elected to define the cutoffs for these 2 physiologic measures based on normal reference ranges.

Not all cases had sufficient admission information recorded to allow classification as a SIRS or non-SIRS case, and these were assigned an “unknown” SIRS status. The unknown cases were, however, still included in the analysis of the individual SIRS or severe SIRS criteria for association with outcome and in the calculation of case fatality rates. Some cases with missing admission information were still assigned a SIRS or non-SIRS status, if it was determined that the SIRS status of the horse would stay the same regardless of the value of the missing criteria.

Systemic Inflammatory Response Syndrome Score

The number of abnormal SIRS criteria fulfilled on admission was used to assign a SIRS score⁵ to each horse. Horses with 0 or 1 abnormal SIRS criterion on admission were considered as a single, non-SIRS group, in agreement with the SIRS definition. Cases with 2, 3, or 4 abnormal SIRS criteria on admission were categorized as SIRS2, SIRS3, or SIRS4 cases, respectively. Not all horses had enough information to allow assignment of a SIRS score, and only those with enough information were used in the analysis of the SIRS score.

Severe Systemic Inflammatory Response Syndrome Criteria

In addition to the 4 SIRS criteria used to assign a SIRS score, admission blood lactate concentration and color of the mucous membranes were used in the study of an optimal model of severe SIRS to predict outcome in horses. The optimal cutoff for blood lactate was selected by a criterion of equal sensitivity and specificity,¹⁸ whereas the mucous membranes were considered abnormal if any of the following adjectives were used to describe them in the medical record: bright pink, injected, purple, muddy, pink, red, or white. Mucous membranes described as pale pink or icteric were not considered abnormal for this study. Not all cases had enough information recorded to be included in analysis of the models of severe SIRS, and only those with enough information were used.

Statistical Methods

Systemic inflammatory response syndrome category and case fatality rates are presented as percentage. Individual admission values for each of the SIRS criteria are presented as dot plots with median and interquartile range. Differences between survivors and nonsurvivors for the admission SIRS criteria values were assessed

by the Mann–Whitney test. The optimal cutoffs for the heart rate, respiratory rate, and lactate were computed by a criterion based on the equality of sensitivity and specificity.¹⁸ As specificity might not be exactly equal to sensitivity, the absolute value of the difference between them is minimized. Logistic regression models were used to examine the effects of the SIRS and severe SIRS criteria on the clinical outcomes (died/survived). Stepwise model selection by the Akaike’s information criteria (AIC), applying both forward and backward elimination approaches, as well as the model’s sensitivity and specificity was used to choose the best model for outcome prediction. Differences in survival proportions for SIRS and non-SIRS cases within diagnostic categories were compared by the Fisher’s exact test and reported as odds ratio (OR) with 95% confidence intervals (CIs) and associated *P* value. The same approach was used to investigate the association between the SIRS score (non-SIRS, SIRS2, SIRS3, and SIRS4) and outcome. The chi-square test for trend was used to test for an association between increasing SIRS score and case fatality rates. The survival proportion during hospitalization for various SIRS groups was plotted on Kaplan–Meir survival curves and compared by the log-rank test. The log-rank test for trend was used to test for a linear trend for decreasing median survival with increasing SIRS score. For comparisons of multiple survival curves, a Bonferroni-corrected *P* value threshold was used. For all other statistical analyses, a 2-sided *P* value < .05 was taken to indicate statistical significance. Statistical analyses were performed by Prism version 6^c and R version 3.3.0^d; “OptimalCutpoints” package version 1.1-3^e was used for computing the optimal cutoffs for the heart rate, respiratory rate, and lactate; “MASS” package version 7.3-45^f was used for model selection; “ROCR” package^g was used to plot the receiver operating characteristic (ROC) curves.

Results

Study Population

From June 2012 to May 2014, 479 adult horses were admitted on an emergency basis. Fifteen horses (all surgical colics) were euthanized after refusal of surgical treatment because of financial constraints. These horses were removed from further analysis, leaving a total of 464 emergency admissions. Twenty-one horses were hospitalized 2 (*n* = 13) to 5 (*n* = 1) times, and therefore, 432 individual horses accounted for the 464 emergency admissions. For 85% of the repeated admissions (*n* = 45), colic was the reason for presentation. The average time between admissions for these cases was 136 days (median, 118 days; range, 4–363 days). Because of the time interval between repeated admissions and because these cases were deemed to have recovered by the time they were discharged, each subsequent admission was considered as a new admission with new SIRS status. The emergency admission population included a variety of breeds with Quarter Horses being the most common (*n* = 176), followed by Warmbloods (*n* = 85), Thoroughbreds (*n* = 53), Paints (*n* = 17), Ponies and Miniatures (*n* = 15), Arabians (*n* = 12), and Draft breeds (*n* = 7). Twenty-five horses were of mixed breeds, and 27 horses were from a variety of other breeds. The breed was not recorded for 15 horses. Fifty-three percent of the horses were geldings (*n* = 228), 40% were mares (*n* = 171), and 8% were stallions (*n* = 33). The age of the horses ranged from 1 to 28 years, with a median of 9 years. The age was not recorded for 25 horses.

The number of cases and case fatality rates for all emergency admissions and each final diagnostic category are shown in Table 1. The most common reason for emergency admission was colic ($n = 247$) followed by musculoskeletal and skin problems ($n = 93$). The overall case fatality rate for all emergency admissions was 17.7% ($n = 82$). Seven horses died (surgical colics perioperatively [$n = 3$], colitis [$n = 2$], diffuse neoplasia with coagulopathy [$n = 1$], and ventricular tachycardia [$n = 1$]), whereas 75 cases were euthanized because of poor prognosis, the combination of poor prognosis and cost of treatment or failure of the condition to improve despite treatment. The case fatality rates varied according to the final diagnostic category with, for instance, high fatality rates in strangulating surgical colics (57%) and colitis cases (53%) and low fatality rates in medical colics (0%) or wounds and lacerations cases (6%).

Selection and Evaluation of the Systemic Inflammatory Response Syndrome Criteria

Considering the widely used human SIRS criteria (heart rate, respiratory rate, temperature, and WBC count) for defining equine SIRS, we first investigated

whether each of them would be associated with outcome in this population. The available admission values for the SIRS criteria for all emergency admissions are shown in Figure 1, comparing survivors and nonsurvivors. Horses that survived had statistically significant lower admission heart rates, respiratory rates, and WBC counts compared to nonsurvivors. The optimal cutoffs for outcome prediction for the abnormal heart rate and respiratory rate, based on the equal sensitivity and specificity criterion, were >52 bpm and >20 bpm, respectively. For the rectal temperature, we used the normal adult horse temperature range commonly used in our practice (37 – 38.5°C), similar to published values.¹⁹ Therefore, for the SIRS definition, an abnormal temperature was either below or above this reference range. For the WBC count, we used the reference range provided for our hematology analyzer (5 – $11 \times 10^9/\text{L}$), extending the upper limit slightly to allow for the common excitement-associated neutrophilic leukocytosis often seen in horses recently admitted to the clinic. Therefore, for the purpose of defining the SIRS criteria, an abnormal WBC count was either below or above 5 – $12.5 \times 10^9/\text{L}$ (Table 2).

These dichotomized (normal or abnormal) equine SIRS criteria were tested for an association with

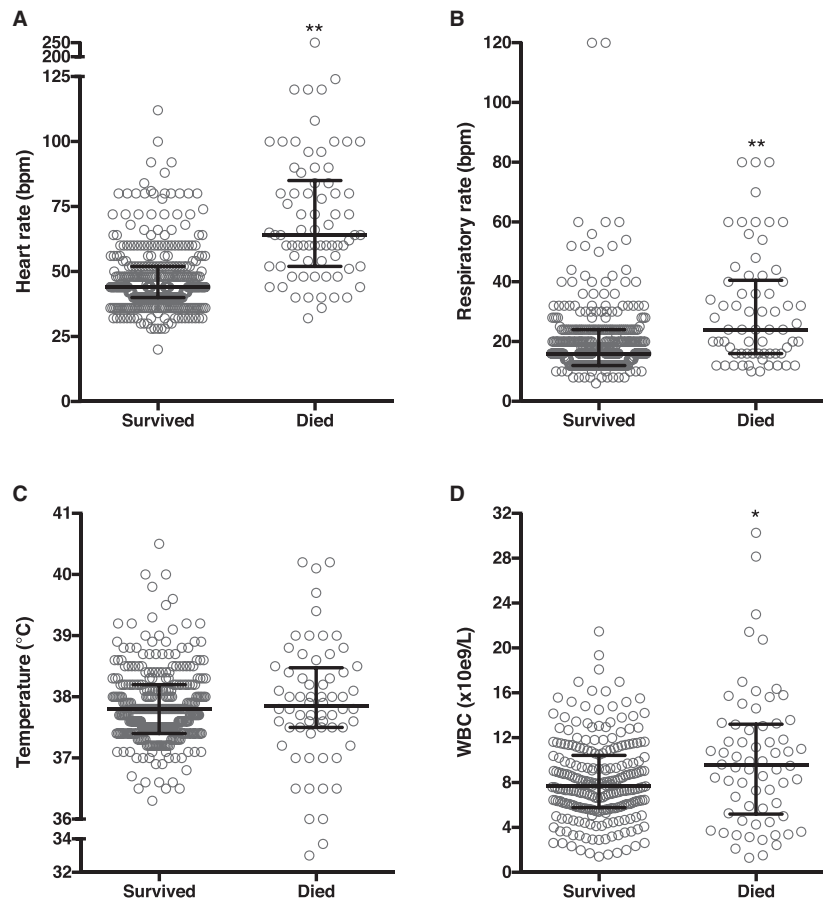


Fig 1. Admission values for the systemic inflammatory response syndrome criteria, comparing cases that survived with cases that died. Individual values, median, and interquartile range are shown. (A) $n = 438$; (B) $n = 421$; (C) $n = 386$; (D) $n = 307$. Mann-Whitney test, ** $P < .001$; * $P = .027$.

Table 2. Results of univariate logistic regression analyses for the individual systemic inflammatory response syndrome (SIRS) criteria and for the SIRS status of the horses.

| Variable | Total (n) | Case Fatality Rate (%) | OR | 95% CI | P Value |
|---------------------------------|-----------|------------------------|-------|------------|---------|
| Heart rate | | | | | |
| Abnormal (>52 bpm) | 130 | 42.3 | 11.15 | 6.35–20.36 | <.001 |
| Normal (≤52 bpm) | 308 | 6.2 | 1.00 | – | – |
| Respiratory rate | | | | | |
| Abnormal (>20 bpm) | 134 | 26.9 | 3.15 | 1.84–5.42 | <.001 |
| Normal (≤20 bpm) | 287 | 10.5 | 1.00 | – | – |
| WBC | | | | | |
| Abnormal (<5 or >12.5 × 10e9/L) | 103 | 33.0 | 2.65 | 1.52–4.64 | <.001 |
| Normal (5–12.5 × 10e9/L) | 204 | 15.7 | 1.00 | – | – |
| Temperature | | | | | |
| Abnormal (<37 or >38.5°C) | 69 | 32 | 3.06 | 1.66–5.57 | <.001 |
| Normal (37–38.5°C) | 317 | 13.2 | 1.00 | – | – |
| SIRS status | | | | | |
| SIRS ^a | 121 | 38.8 | 8.22 | 4.61–15.18 | <.001 |
| Unknown ^b | 78 | 21 | 3.34 | 1.61–6.88 | .001 |
| Non-SIRS | 265 | 7.2 | 1.00 | – | – |

^aSIRS is defined as having 2 or more abnormal results for any of the following: heart rate, respiratory rate, WBC, and temperature.

^bUnknown cases are cases for which not enough information was recorded on admission to allow classification as a SIRS or non-SIRS case.

outcome by univariate logistic regression. Taken individually, each of them showed a statistically significant association with outcome and horses admitted with an abnormal value for any of the 4 SIRS criteria were at increased odds of death compared to horses admitted with a normal value (Table 2).

Systemic Inflammatory Response Syndrome Rates and Prognostic Value

The information recorded on admission allowed identification of 386 horses with enough clinical data to allow classification as SIRS or non-SIRS cases, based on the selected criteria (Table 2). Among these cases, 121 horses fulfilled 2 or more SIRS criteria on admission for an overall SIRS rate of 31.3% (Table 1). The SIRS rates varied across diagnostic categories, with for instance a high SIRS rate of 67% for strangulating colics and a low SIRS rate of 12.8% in medical colics. There were 78 cases with unknown SIRS status.

The case fatality rate for SIRS cases (38.8%) was much higher compared to non-SIRS cases (7.2%), whereas cases with unknown SIRS status had an intermediate fatality rate (21%; Table 2). Univariate logistic regression indicated that SIRS on presentation was associated with increased odds of death compared to non-SIRS cases (OR = 8.22; 95% CI, 4.61–15.18; $P < .001$) in this population (Table 2). There was a statistically significant association of SIRS with outcome for gastrointestinal emergencies (OR = 21.11), colics (OR = 19.00), all surgical colics (OR = 6.91), surgical colics excluding ruptured cases (OR = 5.09), colitis cases (OR = 25.67), and other gastrointestinal cases (OR = 11.33), all with $P < .05$ (Table 3). A statistically

significant association between SIRS and outcome could not be identified for the musculoskeletal-skin and “other systems” groups. The statistically significant association of the SIRS status on admission with outcome for all emergencies was also confirmed by comparisons of Kaplan–Meir survival curves (Figure 2).

Systemic Inflammatory Response Syndrome Score

After the identification of an association between SIRS and outcome in this population, we investigated whether there was a direct relationship between the SIRS score (ie, the number of abnormal SIRS criteria) and case fatality rates. The SIRS score was directly related to the case fatality rate, with horses fulfilling increasing numbers of SIRS criteria having statistically significant increasing case fatality rates (Figure 3A). Additionally, survival analysis for the various SIRS score groups showed that median survival decreased with increasing SIRS score (Figure 3B). Statistically significant differences in pairwise comparisons of the survival curves were found between all groups, except for the comparison between the SIRS3 and SIRS4 groups which presented overlapping survival curves. The SIRS3 and SIRS4 groups (SIRS3/4) were at increased risk of death compared to the non-SIRS cases (OR = 19.80; 95% CI, 9.18–42.74, $P < .001$) or the SIRS2 cases (OR = 4.45; 95% CI, 1.78–11.15; $P = .002$; Table 4).

Severe Systemic Inflammatory Response Syndrome

To identify horses with more advanced SIRS and increased risk of death, we investigated whether we could define a severe SIRS category for horses using the

Table 3. Odds ratio^a of death for horses fulfilling the systemic inflammatory response syndrome (SIRS) criteria on admission.

| Diagnostic Category | SIRS Status | Total (n) | Case Fatality Rate (%) | OR | 95% CI | P Value | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|-------------|-----------|------------------------|-------|------------|---------|---|------|----|----|-------|------------|-------|----------|-----|-----|---|------|----|----|-------|------------|-------|----------|-----|-----|---|------|----|----|-------|------------|------|----------|----|----|---|------|----|----|-------|------------|------|----------|----|----|--------------------------|------|----|----|-------|------------|------|----------|----|----|--------------------------|------|----|----|-------|------------|------|----------|----|----|--------------------------|------|----|----|------|-----------|------|----------|----|----|---------------|------|----|----|------|-----------|
| All emergency admissions | SIRS | 121 | 38.8 | 8.22 | 4.55–14.88 | <.001 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 265 | 7.2 | | | | Gastrointestinal | SIRS | 76 | 49 | 21.11 | 9.12–48.86 | <.001 | Non-SIRS | 186 | 4.3 | Colics | SIRS | 49 | 39 | 19.00 | 6.58–54.87 | <.001 | Non-SIRS | 155 | 3.2 | Surgical colics—All | SIRS | 30 | 63 | 6.91 | 2.02–23.63 | .002 | Non-SIRS | 25 | 20 | Surgical colics (w/o ruptured) ^b | SIRS | 25 | 56 | 5.09 | 1.45–17.93 | .019 | Non-SIRS | 25 | 20 | Colitis | SIRS | 17 | 82 | 25.67 | 3.63–181.5 | .001 | Non-SIRS | 13 | 15 | Other gastrointestinal | SIRS | 10 | 40 | 11.33 | 1.05–122.6 | .041 | Non-SIRS | 18 | 6 | Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | Non-SIRS | 50 | 10 | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 |
| Gastrointestinal | SIRS | 76 | 49 | 21.11 | 9.12–48.86 | <.001 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | Non-SIRS | 155 | 3.2 | | | | Surgical colics—All | SIRS | 30 | 63 | 6.91 | 2.02–23.63 | .002 | Non-SIRS | 25 | 20 | Surgical colics (w/o ruptured) ^b | SIRS | 25 | 56 | 5.09 | 1.45–17.93 | .019 | Non-SIRS | 25 | 20 | Colitis | SIRS | 17 | 82 | 25.67 | 3.63–181.5 | .001 | Non-SIRS | 13 | 15 | Other gastrointestinal | SIRS | 10 | 40 | 11.33 | 1.05–122.6 | .041 | Non-SIRS | 18 | 6 | Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | Non-SIRS | 50 | 10 | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | |
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| Surgical colics (w/o ruptured) ^b | SIRS | 25 | 56 | 5.09 | 1.45–17.93 | .019 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 25 | 20 | | | | Colitis | SIRS | 17 | 82 | 25.67 | 3.63–181.5 | .001 | Non-SIRS | 13 | 15 | Other gastrointestinal | SIRS | 10 | 40 | 11.33 | 1.05–122.6 | .041 | Non-SIRS | 18 | 6 | Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | Non-SIRS | 50 | 10 | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Colitis | SIRS | 17 | 82 | 25.67 | 3.63–181.5 | .001 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 13 | 15 | | | | Other gastrointestinal | SIRS | 10 | 40 | 11.33 | 1.05–122.6 | .041 | Non-SIRS | 18 | 6 | Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | Non-SIRS | 50 | 10 | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Other gastrointestinal | SIRS | 10 | 40 | 11.33 | 1.05–122.6 | .041 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 18 | 6 | | | | Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | Non-SIRS | 50 | 10 | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal and skin | SIRS | 16 | 19 | 2.08 | 0.44–9.88 | .39 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 50 | 10 | | | | Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Other systems | SIRS | 29 | 24 | 1.22 | 0.35–4.20 | 1.00 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Non-SIRS | 29 | 21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

^aFisher's exact test.

^bSurgical colics, excluding 5 cases that had a ruptured stomach, colon, or cecum upon arrival, diagnosed during surgery or necropsy.

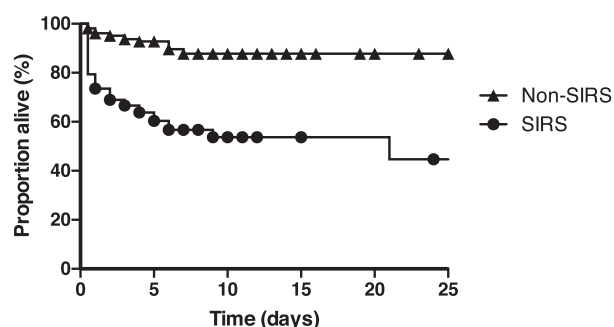


Fig 2. Kaplan–Meier survival curves, comparing systemic inflammatory response syndrome (SIRS) cases and non-SIRS cases. The survival curves are significantly different. Log-rank test, $P < .001$. The graph shows survival up to 25 days. Seven cases that stayed in the clinic for more than 25 days (up to 108 days) are not shown on this graph but were included in the analysis.

SIRS score and easily available markers of altered tissue perfusion such as the admission blood lactate concentration and color of the mucous membranes. First, we looked at the impact of having abnormal mucous membranes upon admission on outcome among all cases for which this information had been recorded ($n = 416$). Results from univariate logistic regression showed that horses with abnormal mucous membranes on admission had statistically significant increased odds of death (OR = 17.11; 95% CI, 9.42–31.89, $P < .001$) compared to horses with normal mucous membranes (Table 5). We also studied the horses for which blood lactate had been measured on admission ($n = 95$) and identified an optimal cutoff of 2.06 mmol/L for outcome prediction in this population based on the equal sensitivity and specificity criterion as mentioned in the Materials and Methods section. Within this smaller population, horses with blood lactate >2.06 mmol/L

had a statistically significant increased likelihood of death (OR = 5.65; 95% CI, 2.38–14.13, $P < .001$) compared to normolactatemic horses (Table 5).

Using multivariate logistic regression, we tested 3 different models of severe SIRS to predict outcome in this population. Increased blood lactate was significantly associated with increased risk of death, after adjusting for the SIRS score (OR = 6.03; 95% CI, 2.08–19.58, $P = .001$, Table 5, Model [I]). Abnormal mucous membranes were also associated with increased risk of death, after adjusting for the SIRS score (OR = 10.50; 95% CI, 5.47–20.51, $P < .001$, Table 5, Model [II]). Finally, we considered all 3 variables in a third model (Model [III] in Table 5), combining the SIRS score, blood lactate concentration, and mucous membrane color. In this third model, the SIRS score and the mucous membranes had statistically significant association with outcome prediction.

The final model selection was performed by a stepwise model selection approach based on the lowest AIC value. In addition, the clinical performance of the models was also assessed by looking at their sensitivity and specificity in predicting outcome. For this approach, only cases with complete dataset (ie, cases with no missing values for the severe SIRS criteria) could be used. Because of concerns that the subpopulation of cases with complete admission dataset ($n = 71$) might not be representative of the whole population of horses admitted on emergency over the study period, we compared the distribution of each continuous variable (heart rate, respiratory rate, temperature, WBC count, and blood lactate) between the 2 populations for survivors and nonsurvivors and found them to be very similar (data not shown). Additionally, univariate logistic regression identified similar association for SIRS, mucous membranes, and lactate with outcome in the complete admission dataset compared to the whole population

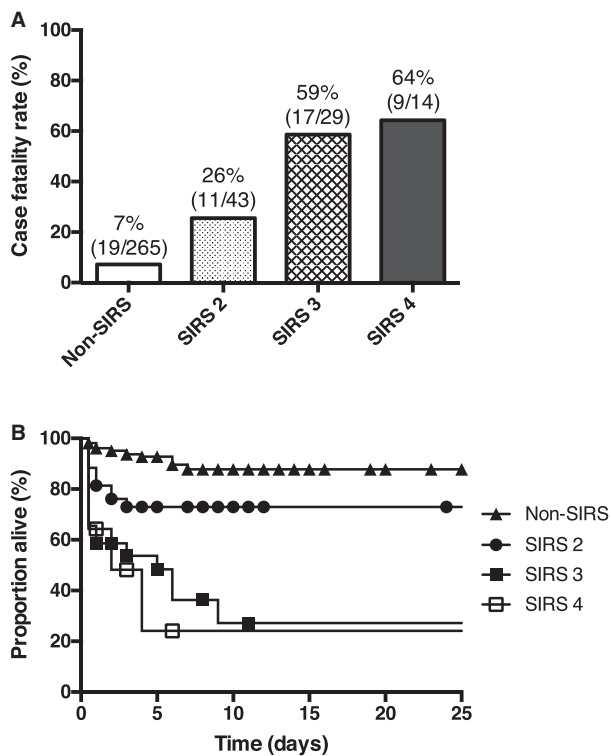


Fig 3. Systemic inflammatory response syndrome (SIRS) score. (A) The case fatality rate increases with increasing number of abnormal SIRS criteria (SIRS score). Chi-square test for trend, $P < .001$ (chi-square = 79.57, $df = 1$). The case fatality rates as well as the number of death and the total number of horses in each group are shown above the bars. (B) Kaplan-Meier survival curves for different SIRS score groups. The survival curves are significantly different, and median survival is found to decrease with increasing SIRS score (log-rank test for trend, $P < .001$). All pairwise comparisons are also significantly different (Bonferroni-corrected threshold: $P = .008$) except for the SIRS3 versus SIRS 4 pairwise comparison. Log-rank tests: non-SIRS versus SIRS2: $P = .001$; non-SIRS versus SIRS3: $P < .001$; non-SIRS versus SIRS4: $P < .001$; SIRS2 versus SIRS3: $P = .003$; SIRS2 versus SIRS4: $P = .003$; SIRS3 versus SIRS4: $P = .581$. Survival shown up to 25 days. Five cases that stayed in the clinic for more than 25 days (up to 108 days) are not shown on this graph but were included in the analysis.

(data not shown). This indicated that the subpopulation of horses with complete admission dataset was overall representative of the whole emergency population. Using this complete dataset, Model (III) with the SIRS score, lactate, and mucous membranes was identified as the best model for predicting outcome with the lowest AIC and the best combination of sensitivity and specificity (Table 6). The ROC curves for each models of severe SIRS are shown in Figure 4, and our final model (Model III) has the largest area under the curve among all the other possible severe SIRS models.

Discussion

In this study, we investigated the clinical relevance of SIRS in a population of adult equine emergencies admitted to a private primary referral practice. We

Table 4. Odds ratio^a of death for horses admitted with a systemic inflammatory response syndrome (SIRS) score of 3 or 4.

| SIRS Score ^b | Total (n) | Case Fatality Rate (%) | OR | 95% CI | <i>P</i> value |
|-------------------------|-----------|------------------------|-------|------------|----------------|
| SIRS3/4 | 43 | 60 | 19.80 | 9.18–42.74 | <.001 |
| Non-SIRS | 265 | 7.2 | | | |
| SIRS3/4 | 43 | 60 | 4.45 | 1.78–11.15 | .002 |
| SIRS2 | 43 | 26 | | | |

^aFisher's exact test.

^bThe SIRS score is based on the number of abnormal SIRS criteria among the following: heart rate >52 bpm, respiratory rate >20 bpm, temperature below or above 37.0–38.5°C, WBC above or below $5.0\text{--}12.5 \times 10^9/L$; non-SIRS: 0–1 abnormal criteria; SIRS2: 2 abnormal SIRS criteria; SIRS3/4: 3 or 4 abnormal SIRS criteria.

found that each of the SIRS and severe SIRS criteria used in this study was associated with increased risk of death. Using SIRS defined by the presence of 2 or more abnormal criteria, we found that 31% of our emergencies had evidence of SIRS on presentation and showed that SIRS cases were more likely to die than non-SIRS cases, an effect mainly identified for acute gastrointestinal cases. We also showed that SIRS3 and SIRS4 cases appeared to have more severe disease and increased risk of death compared to non-SIRS or SIRS2 cases. Finally, using multivariate logistic regression and stepwise model selection, we identified a model of severe SIRS for horses that includes the SIRS score, blood lactate concentration, and color of the mucous membranes as the best model for outcome prediction in this population.

We believe that the results of this study are highly relevant to equine clinicians and researchers as they demonstrate the clinical value of SIRS in horses while also proposing a model of severe SIRS for outcome prediction in horses. Given that the SIRS and severe SIRS criteria discussed here are simple, easy to remember, inexpensive to measure, and widely available, we believe they can be used in any clinical setting to help identify and monitor critically ill horses, especially for acute gastrointestinal disease cases.

The criteria used for the equine SIRS and severe SIRS definitions are not new to equine veterinary medicine, and experienced clinicians have and continue to use them in the clinical evaluation of their cases. Several previous studies have highlighted the importance of some of the SIRS and severe SIRS criteria reappraised in the current study, although not in the context of assigning a SIRS status. For instance, a previous study identified heart rate, mucous membranes, blood lactate concentration, and peritoneal fluid total protein concentration as the 4 variables associated with outcome in colics.²⁰ Three of these 4 criteria were evaluated in the present study and found to be associated with outcome. Several other studies investigating the prognostic values of clinical and clinicopathological variables in colics have been performed and were reviewed.²¹ Whereas the

Table 5. Results of logistic regression analyses for the severe systemic inflammatory response syndrome (SIRS) criteria and models.

| Variable | Total (n) | Case | | OR | 95% CI | P Value |
|--|-----------|-------------------|-------|------------|--------|---------|
| | | Fatality Rate (%) | | | | |
| Univariate logistic regression | | | | | | |
| Blood lactate | | | | | | |
| >2.06 mmol/L | 44 | 66 | 5.65 | 2.38–14.13 | <.001 | |
| ≤2.06 mmol/L | 51 | 25 | 1.00 | – | – | |
| Mucous membranes | | | | | | |
| Abnormal ^a | 74 | 59 | 17.11 | 9.42–31.89 | <.001 | |
| Normal | 342 | 7.9 | 1.00 | – | – | |
| SIRS score ^b | | | | | | |
| SIRS3/4 | 43 | 60 | 18.77 | 9.13–40.05 | <.001 | |
| SIRS2 | 43 | 26 | 4.32 | 2.12–8.81 | <.001 | |
| Unknown | 113 | 23 | 3.34 | 1.61–6.88 | .001 | |
| Non-SIRS | 265 | 7.2 | 1.00 | – | – | |
| Multivariate logistic regression | | | | | | |
| Model (I): SIRS score ^b and Lactate | | | | | | |
| SIRS score | | | | | | |
| SIRS3/4 | 43 | 60 | 19.20 | 5.28–87.31 | <.001 | |
| SIRS2 | 43 | 26 | 1.00 | 0.23–3.98 | .99 | |
| Unknown | 113 | 23 | 4.72 | 0.91–26.41 | .065 | |
| Non-SIRS | 265 | 7.2 | 1.00 | – | – | |
| Lactate | | | | | | |
| >2.06 mmol/L | 44 | 66 | 6.03 | 2.08–19.58 | .001 | |
| ≤2.06 mmol/L | 51 | 25 | 1.00 | – | – | |
| Model (II): SIRS score ^b and mucous membranes | | | | | | |
| SIRS score | | | | | | |
| SIRS3/4 | 43 | 60 | 9.25 | 3.93–22.27 | <.001 | |
| SIRS2 | 43 | 26 | 3.23 | 1.43–7.26 | .004 | |
| Unknown | 113 | 23 | 2.46 | 0.89–6.32 | .069 | |
| Non-SIRS | 265 | 7.2 | 1.00 | – | – | |
| Mucous membranes | | | | | | |
| Abnormal ^a | 74 | 59 | 10.50 | 5.47–20.51 | <.001 | |
| Normal | 342 | 7.9 | 1.00 | – | – | |
| Model (III): SIRS score ^b , mucous membranes, and lactate | | | | | | |
| SIRS score | | | | | | |
| SIRS3/4 | 25 | 84 | 7.74 | 1.82–38.31 | .007 | |
| SIRS2 | 14 | 36 | 1.16 | 0.23–5.40 | .85 | |
| Non-SIRS | 32 | 25 | 1.00 | – | – | |
| Mucous membranes | | | | | | |
| Abnormal ^a | 34 | 76 | 5.78 | 1.69–21.09 | .006 | |
| Normal | 37 | 22 | 1.00 | – | – | |
| Lactate | | | | | | |
| >2.06 mmol/L | 35 | 66 | 3.06 | 0.87–11.45 | .085 | |
| ≤2.06 mmol/L | 36 | 31 | 1.00 | – | – | |

^aThe mucous membranes were considered abnormal if they were described as bright pink, injected, purple, muddy, toxic, red, or white.

^bThe SIRS score is based on the number of abnormal SIRS criteria fulfilled among the following: heart rate >52 bpm, respiratory rate >20 bpm, temperature below or above 37.0–38.5°C, WBC above or below $5.0\text{--}12.5 \times 10^9/\text{L}$; non-SIRS: 0–1 abnormal criteria; SIRS2: 2 abnormal SIRS criteria; SIRS3/4: 3 or 4 abnormal SIRS criteria.

results have differed between studies, the cardiovascular status of the horse upon admission as indicated by heart rate,^{22–25} capillary refill time,²⁵ abnormal mucous membrane color,²⁶ or packed cell volume^{22,23} was often associated with outcome. In colitis cases, several factors

Table 6. AIC, sensitivity, and specificity for the models of severe systemic inflammatory response syndrome (SIRS).

| Model | AIC ^a | Sensitivity | Specificity |
|---------------------------|------------------|-------------|-------------|
| SIRS score ^b : | 82.22 | 0.62 | 0.89 |
| SIRS score + lactate: | 79.04 | 0.74 | 0.76 |
| SIRS score + | 74.28 | 0.71 | 0.84 |
| mucous membranes: | | | |
| SIRS score + lactate + | 73.25 | 0.82 | 0.81 |
| mucous membranes: | | | |

^aAIC: Akaike's information criteria; the smaller the value, the better the model fits the data.

^bThe SIRS score is based on the number of abnormal SIRS criteria fulfilled among the following: heart rate >52 bpm, respiratory rate >20 bpm, temperature below or above 37.0–38.5°C, WBC above or below $5.0\text{--}12.5 \times 10^9/\text{L}$; non-SIRS: 0–1 abnormal criteria; SIRS2: 2 abnormal SIRS criteria; SIRS3/4: 3 or 4 abnormal SIRS criteria.

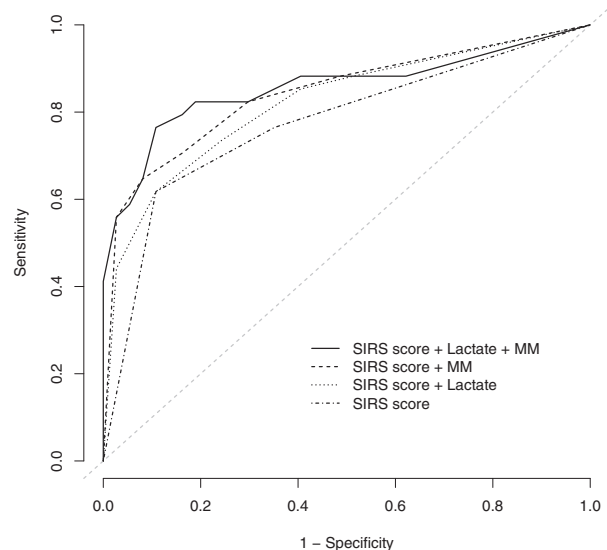


Fig 4. Receiver operating characteristic curves showing the performance of the various models of severe systemic inflammatory response syndrome (SIRS) in predicting outcome in adult equine emergency admissions. SIRS score: number of abnormal SIRS criteria fulfilled among the following: heart rate >52 bpm, respiratory rate >20 bpm, temperature below or above 37.0–38.5°C, WBC above or below $5.0\text{--}12.5 \times 10^9/\text{L}$. MM: mucous membranes. The mucous membranes were considered abnormal if they were described as bright pink, injected, purple, muddy, toxic, red, or white.

have also been associated with outcome, including heart rate, packed cell volume, blood creatinine concentration, band neutrophils, and base excess.^{27,28} Blood lactate concentration, used here in the final model of severe SIRS, has been extensively studied in horses and was found to be associated with outcome in colics,^{20,29–32} colitis cases,³³ and adult equine emergency admissions.³⁴ The results of this study reinforce the previously demonstrated importance of assessing the cardiovascular status of horses at the time of clinical

examination and demonstrate that the clinical parameters of the SIRS and severe SIRS definitions are important in evaluating the status of equine gastrointestinal emergencies.

In the present study, we looked at the impact of SIRS on outcome for all adult horses admitted on an emergency basis over the study period. This resulted in a very heterogeneous population presenting with a variety of acute to subacute or chronic illnesses. While the impact of SIRS on outcome was detected when applied to the whole population, a finer analysis according to broad diagnostic categories revealed that SIRS was mainly a predictor of outcome in acute gastrointestinal emergencies. For the musculoskeletal-skin group, we did not detect a statistically significant effect of SIRS on outcome. It is conceivable that the low number of cases with known SIRS status and low number of deaths within this category contributed to the lack of significant association, even though the mortality rates appeared different between non-SIRS (10%) and SIRS cases (19%). For the "other systems" group, SIRS did not appear to be associated with outcome, with comparable mortality rates for non-SIRS (21%) and SIRS (24%) cases. Multiple factors probably contributed to this lack of association between SIRS and outcome in this category. First, with a lower number of cases in this category, we could have had insufficient power to identify such association. Second, these cases were heterogeneous in terms of diagnosis, chronicity, and comorbidities, and therefore, it might not be surprising that the same set of criteria would not perform equally well for such diverse cases. For instance, some non-SIRS cases presented with incurable diseases or failed to respond to treatment and were euthanized, illustrating that the non-SIRS status does not guarantee a positive outcome. Other cases presented with SIRS but responded well to treatment with normalization of physiologic variables and positive clinical outcomes. Finally, in this study, we only looked at admission SIRS status; however, especially for cases that survived several days, this initial SIRS status might not have been related to outcome because it changed through time as the condition of the horse improved or deteriorated. This illustrates that disease severity scores, such as the SIRS and severe SIRS criteria presented here, should not supersede clinical judgment and continuous patient monitoring for deterioration or improvement of the horses' condition. Moreover, disease severity scores should not be used as single time point prognostic indicators but should rather be seen as a tool to assess and monitor the horse's condition, prompting more aggressive treatment if indicated, and helping in the discussion of the horse's clinical status and prognosis with the owner.

Development of a systemic inflammatory response that progresses to organ failure or shock is not the only cause of death in horses, which is also why the SIRS criteria might not perform equally well in all types of emergencies. It appears, however, to be particularly well suited as a severity illness score in acute gastrointestinal illnesses where the development of SIRS can indicate a

more serious pathophysiological process such as intestinal strangulation, rather than a simple displacement, that demands immediate attention and aggressive treatment.

While our study brings a better understanding of the clinical relevance of SIRS in horses, it also has some limitations. First, many horses did not have all of the SIRS or severe SIRS criteria recorded on admission, which precluded at times assignment of a SIRS status or inclusion in the models of severe SIRS. The main reasons for incomplete admission records included staff shortage, priority given to patient treatment in critical emergencies, incomplete medical record entries, and cost considerations in the choice of diagnostic tests. We verified whether the missing data introduced a bias in the subpopulation of cases with different sets of clinical parameters measured. For instance, it is likely that the measurement of blood lactate was biased toward horses presenting with more severe disease. However, we found no difference comparing a subset of cases with a full complement of admission data versus the emergency population as a whole (see Results section for details). This indicated that the subpopulation of horses with complete admission dataset was overall representative of the whole emergency population and suggests that the results of this study are overall valid for this population despite the missing admission data.

Second, this study only looked at the blind application of the SIRS criteria upon admission, without any regard to other factor that could have influenced the measured parameters. Based on the original human SIRS definition, to assign a SIRS status, the physiologic changes measured must represent an acute alteration from baseline in the absence of other known causes for such abnormalities.¹ Thus, the abnormalities in the physiologic measures of SIRS can only be attributed to systemic inflammation if there is no other explanation to account for the observed alterations. In these cases, several factors likely influenced the values of the SIRS criteria, including pain, stress, organ dysfunction, and prior administration of analgesics or sedatives by referring veterinarians. In the clinical setting, the attending veterinarian would need to assess each case individually in order to decide whether the observed changes are acute physiologic alterations likely caused by systemic inflammation or if other factors are possibly contributing. Using clinical judgment to weigh the probability of SIRS in each case, it is possible that the proposed SIRS and severe SIRS criteria could also be used as illness severity markers in nongastrointestinal emergencies, although further studies would be needed to confirm or refute this hypothesis.

A third limitation of this study is that we did not include band neutrophils as an indicator of abnormal WBC count in the SIRS criteria even though it is included in the original human SIRS definition. Unfortunately, in a private practice setting, blood smears are not routinely performed upon admission and we felt we did not have enough blood smears collected from these cases to include band neutrophils in this analysis. However, band neutrophils are indicators of acute and

severe inflammatory response in horses, and we showed, in a previous smaller study, that band neutrophils and neutrophil toxic change are associated with outcome in adult equine emergency admissions.³⁵ Whether including band neutrophils in the equine SIRS definition would improve its clinical performance in defining SIRS in horses is unclear; however, this addition should likely be considered.

Despite the limitations of this study, we demonstrated the clinical relevance of SIRS in horses, which should help appraise past and future studies using SIRS for case selection or categorization. Because the host systemic inflammatory response can progress through time, we sought to capture this progression by exploring the use of the SIRS score and selecting the best model of severe SIRS for outcome prediction in horses. From these results, it appears that this equine model of severe SIRS that includes the SIRS score, blood lactate concentration, and color of the mucous membranes can help identifying horses with more severe disease.

In conclusion, this study showed that the concept of SIRS is clinically relevant in horses and that acute gastrointestinal disease cases presenting with SIRS have an increased risk of death. We also showed that the risk of death increases with increasing number of abnormal SIRS criteria fulfilled on admission (the SIRS score), and we identified a model of severe SIRS that includes the SIRS score, blood lactate concentration, and color of the mucous membranes as the best model for predicting outcome in this population. While these findings would need to be replicated in different populations, it seems that the SIRS criteria and the model of severe SIRS proposed in this study can be used to objectively assess the status and prognosis of critically ill adult horses presenting for acute gastrointestinal illnesses.

Footnotes

^a IDEXX ProCyt Dx™ Hematology Analyzer, IDEXX Laboratories, Markham, ONT, Canada

^b VetScan i-STAT 1 Handheld Analyzer, Abaxis North America, Union City, CA

^c Prism 6 for Mac OS X, GraphPad software Inc., La Jolla, CA

^d R Foundation for Statistical Computing, Vienna, Austria 2016

^e OptimalCutpoints: Monica Lopez-Raton, Maria Xose Rodriguez-Alvarez, Carmen Cadarso Suarez, Francisco Gude Samperdo (2014). OptimalCutpoints: An R Package for Selecting Optimal Cutpoints in Diagnostic Tests. *Journal of Statistical Software*, 61(8), 1–36. <http://www.jstatsoft.org/v61/i08/>

^f MASS: Venables, W. N. & Ripley, B. D. (2002) *Modern Applied Statistics with S*. Fourth Edition. Springer, New York. ISBN 0-387-95457-0.

^g ROCR: Sing T, Sander O, Beerenwinkel N and Lengauer T (2005). ROCR: visualizing classifier performance in R. *Bioinformatics*, 21(20), pp. 7881. <http://rocr.bioinf.mpi-sb.mpg.de>

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The results reported herein have not been previously presented at a conference.

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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