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RESEARCH ARTICLE

Immunolabeling of Survivin in Ulcerated and Healthy Gastric Mucosa of Equids: A Comparative Study of Species (Horses, Donkeys, And Mules)

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Survivin, an inhibitor of apoptosis, plays a key role in mucosal renewal and resistance to cell death. This study investigated the participation and dynamics of this protein in the squamous and glandular ulcerated gastric mucosa of horses, donkeys, and mules to compare and determine the similarities and differences between each species of equids. Sixty samples of the stomachs of these equids (10 from each species), both healthy and ulcerated, were analyzed, and immunohistochemical and histological techniques were used to determine the location and intensity of survivin expression in the different gastric regions. The results revealed a significant presence of survivin in the gastric mucosa of almost all equids. However, it was more consistently found in the glandular mucosa, both in healthy and ulcerated conditions. Additionally, immunolabeling predominated in the cytoplasmic subcellular location, although a minimum number of individuals presented a nuclear location. This study provides a basis for future research on the role of survivin in gastric pathology and its potential impact on gastrointestinal diseases in equids. Furthermore, these findings suggest that survivin may serve as a potential biomarker of gastric mucosal integrity in equids.

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INTRODUCTION

Survivin is a protein that participates in cell division and the inhibition of apoptosis; it was initially described in abundance in embryonic and fetal cells and low proportions in some differentiated or adult tissues of humans and mice (O'Driscoll *et al*., 2003; Yang *et al*., 2006; Kondapuram *et al.,* 2023). Owing to its bifunctional nature, it is also highly expressed in various types of cancer, characterized by its aggressiveness and malignancy (Adida *et al*., 1998; Kawasaki *et al*., 1998; Sarela *et al*., 2000; Velando *et al*., 2008; Cherukuri and Guttikonda, 2017; Fang *et al.,* 2024). Therefore, it is considered a biomarker of interest in cancerology (Ambrosini *et al*., 1997; Zhou *et al.,* 2024).

In other species of veterinary interest, survivin has been detected in pigs, chickens, and canines, mainly in different types of neoplasms (O'Driscoll *et al*., 2003; Rebhun *et al*., 2008; Annkathrin *et al*., 2021; Rösch *et al.,* 2025). Among the differentiated tissues that express survivin, the healthy stomach has been studied in humans and mice (O'Driscoll *et al*., 2003; Yang *et al*., 2006). It is considered a gastric cytoprotective mechanism because it maintains integrity and regulates the cellular renewal of the mucosa (Chiou *et al*., 2003; Chiou *et al*., 2005). However, a recent study identified the presence of survivin in healthy squamous and glandular gastric mucosa in equids (Medina-Bolivar *et al.,* 2025). Therefore, this is the first study to attempt to elucidate the behavior of this protein in ulcerated gastric tissue.

Ulcerative lesions in the stomach of equids are highly prevalent (Van den Boom, 2022; Vokes *et al*., 2023; Medina *et al*., 2024), with differences depending on the mucosa, due to defense mechanisms that determine pathways of injury; therefore, equine gastric ulcer syndrome (EGUS) comprises glandular gastric mucosa disease (GGMD) and squamous gastric mucosa disease (SGMD) (Sykes *et al*., 2015). However, it is common to observe individuals or populations of equids that do not develop lesions when subjected to recognized ulcerogenic factors, which has encouraged the study of possible components involved in gastric integrity and protection, such as the survivin protein, which has been widely studied in other animal species.

Previous studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and ethanol, inhibit the expression and proteasomal

degradation of survivin, leading to gastric injury in murine models and cell culture (Chiou *et al*., 2005; Chiou and Mandaya, 2007; Jones *et al*., 2008), despite being the only factors described in this mechanism. These findings confirmed the participation of this protein in the phenomena of cytoprotection and gastroadaptation (Jones *et al*., 2008; Garcia-Bonete, 2019). These processes have not been explored in equids; however, the use of NSAIDs is common in these animals, with ulcerogenic potential due to different mechanisms of injury to the gastric mucosa, although some controversial findings exist (Nieto *et al*., 2012; Martinez *et al*., 2014; Pedersen *et al.*, 2018). The preceding motivates the exploration of these mechanisms within the multifactorial nature of EGUS.

Given the importance of the survivin protein in the protection of the gastric mucosa in other animal species, this study aimed to determine the participation and dynamics of this protein in the squamous and glandular ulcerated gastric mucosa of horses, donkeys, and mules to compare and determine the similarities and differences between each species of equids, and, in this sense, to validate the possible participation of survivin in aspects of cytoprotection and gastroadaptation in these species.

MATERIALS AND METHODS

Sampling of gastric tissue: A total of 60 stomachs of equids (horses, donkeys, and mules) were used, which were divided into two groups: Group 1 included 30 ulcerated stomachs, and Group 2 included 30 healthy stomachs, corresponding to 10 samples of each species in each group. All stomachs were obtained from a processing plant immediately after slaughter. Each stomach was cut between the cardia and the pyloric antrum through the greater curvature to expose the gastric surface fully, and the contents were removed and washed with abundant water for subsequent macroscopic inspection and selection for both groups.

The stomachs in Group 1 were classified considering both gastric diseases, namely, SGMD and GGMD. The SGMD was classified by number (0-4) and severity of the lesions (0-5), according to MacAllister *et al*. (1997), and for GGMD, the classification suggested by the consensus of the European College of Internal Medicine was considered (Sykes *et al.*, 2015). Additionally, all findings related to chronic and acute gastritis, hyperkeratosis, and observations in the gastric lumen were recorded. The stomachs of Group 2 had intact surfaces, without evidence of inflammation, erosions, ulcers, or hyperkeratosis.

Histological and immunohistochemical analysis: Two samples of approximately 1cm in length were taken by dissection from the squamous and glandular gastric mucosa for immunohistochemical and conventional histopathological analysis, which involved dehydration, embedding, sectioning, and hematoxylin and eosin staining, and were subsequently examined under a light microscope to determine the integrity and viability of the tissues. For the determination of the survivin protein in the gastric mucosa, survivin (monoclonal rabbit anti-human antibody, Clone EP119, Vitro Master Diagnóstica®, Spain) and the polymer method were used. Subsequently, deparaffinization, rehydration, and antigen recovery were performed via a water bath for 30min in Tris-EDTA buffer solution containing the survivin antibody (10mmol/L Tris base, 1mmol/L EDTA at pH 9.0). The deactivation of endogenous peroxidase was carried out with the application of hydrogen peroxide for 5min. The slides were then covered with survivin (ready to use) for 1 hour in a humidified chamber. The immunoreactivity of the positive controls was revealed with equine fetal kidney tissue via the "Master Polymer Plus Detection System" of Vitro Master Diagnóstica®, Spain. The negative controls were treated with rabbit IgG instead of anti-survivin antibodies.

The immunoreaction in the squamous and glandular gastric mucosa was located in the cytoplasm and nucleus, and the classification was adapted according to Alan and Liman (2012), according to the intensity between grades 0 and 5: negative (0), weak (1), weak-moderate (2), moderate (3), moderate-intense (4), and intense (5). The survivin index was obtained as the percentage of positive cells in a population of 1,000 total cells (Sokołowska and Urbanska, 2017) in 10 fields at 40×.

Statistical analysis: The variables were analyzed via descriptive statistics, contingency tables, means, standard deviations, and percentages, using R Studio software. Shapiro-Wilk test was used to determine the normality of the data. Transformation of data (logarithmic and square root transformation) in cases that did not show a normal distribution was used to compare the variables. Student t-test and Kruskal-Wallis tests were used to determine significant differences between the mean of the survivin index and the degree of intensity between the gastric mucosa of each species of equid and between healthy and ulcerated conditions. A P-value of <0.05 was considered statistically significant.

RESULTS

Macroscopic examination of the stomachs allowed for the classification of the samples into the respective study groups. Histopathological evaluation was used to evaluate the integrity of the collected tissues for subsequent immunohistochemical analyses. The classification of ulcerated stomachs is presented in Table 1, where it is shown by the gastric mucosa, species of equid, and degrees of injury. Donkeys and mules presented the highest degrees of ulcerative lesions in both mucosae, whereas the three species presented higher degrees of gastric lesions in the squamous mucosa. Regarding the presence of gastritis, the glandular mucosa was the only mucosa compromised, where the horses presented the highest frequency.

Table 1: Classification of the degrees of ulcerative lesions in both the gastric mucosa of the selected equids

Classification	Gastric glandular mucosa*			Gastric squamous mucosa**		
Grade	Horses	Donkeys	Mules	Horses	Donkeys	Mules
0	2	0	2	2	0	2
I	0	0	0	0	0	0
II	0	1	2	5	4	1
III	0	7	1	3	4	4
IV	1	1	5	0	2	3
Gastritis	7	1	2	0	0	0

*Sykes *et al.* (2015) **MacAllister *et al.* (1997).

Survivin protein is expressed in the gastric mucosa of almost all equids; however, survivin protein is more highly expressed in the glandular mucosa in both healthy and ulcerated mucosa, however, with no statistically significant differences (P=0.602). In addition, immunolabeling was predominantly localized in the cytoplasm (90%), with only a small proportion observed in the nucleus (10%). The results of the cytoplasmic indices and intensity grades in the gastric mucosa of horses (Table 2), donkeys (Table 3), and mules (Table 4), under both ulcerated and healthy conditions, are presented. Additionally, Fig. 1 presents the classification used for the intensity of immunoreactivity, and Fig. 2 shows the cytoplasmic and nuclear localization of survivin in each species.

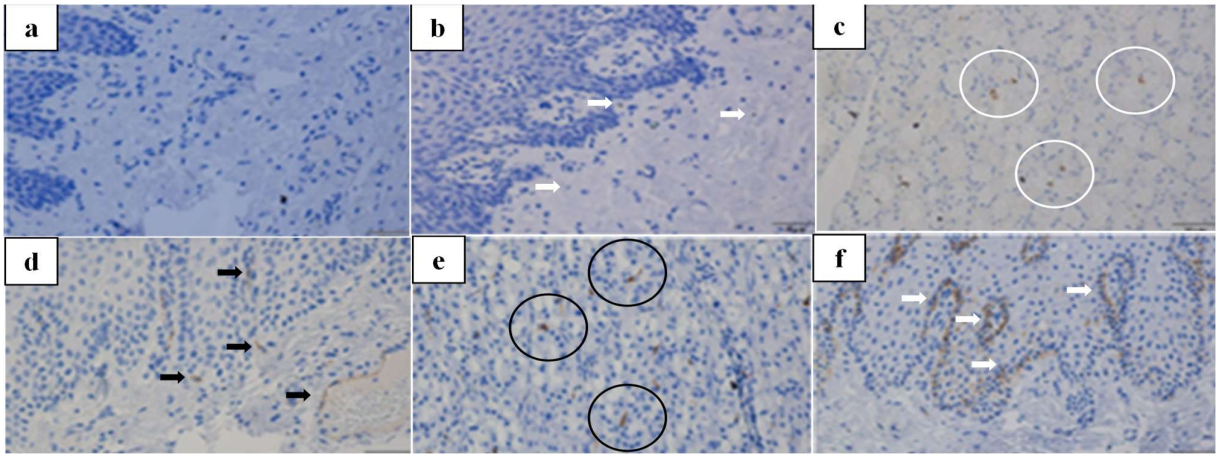

Fig. 1: Immunoreactivity intensity scale (grades 0–5) based on Alan and Liman (2012), applied to survivin expression in the gastric mucosa of equids (horses, donkeys, and mules) using immunohistochemistry with the EP119 antibody. 40x magnification. a) Negative (grade: 0), b) Weak (grade: 1) (white arrows), c) Weak-moderate (grade: 2) (white circles), d) Moderate (grade: 3) (black arrows), e) Moderate-intense (grade: 4) (black circles) and f) Intense (grade: 5) (white arrows). Weak-moderate (grade 2) intensity was most commonly observed.

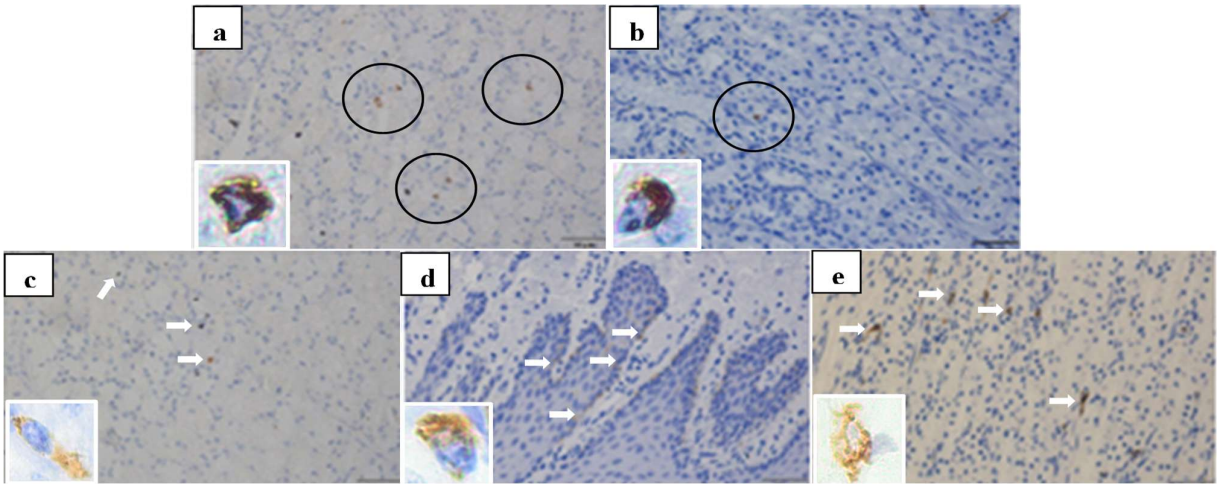

Fig. 2: Cytoplasmic and nuclear expression of survivin in ulcerated gastric mucosa of equids (horse, donkey and mule) detected by immunohistochemistry using the EP119 antibody. 40x magnification. a) and b) Nuclear expression of survivin in lamina propria and epithelial layer in a horse and a donkey, respectively (black circles). Inset: Detail at higher magnification showing nuclear staining. c), d) and e) Cytoplasmic expression of survivin in a horse (lamina propria layer), donkey (epithelial layer), and mule (lamina propria layer), respectively (white arrows). Inset: Cytoplasmic immunoreactivity observed at higher magnification.

Table 2: Degrees of intensity and localization of the survivin protein in the ulcerated and healthy gastric mucosa of horses

Horses	Gastric glandular mucosa				Gastric squamous mucosa			
	Ulcerated		Healthy		Ulcerated		Healthy	
	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.
Horse 1	5	1	67	2	2	2	0	0
Horse 2	88	2	105	2	1	1	2	2
Horse 3	57	1	93	2	1	2	2	2
Horse 4	65	2	1	1	2	2	24	1
Horse 5	50	2	18	2	2	2	15	2
Horse 6	21	2	9	2	3	2	26	2
Horse 7	16	2	0	0	60	2	1	1
Horse 8	28	2	28	2	40	2	2	1
Horse 9	20	2	155	2	0	0	39	2
Horse 10	11	1	115	4	0	0	44	3
Mean±SD.	36.1±27.3	1.7±0.48	59.1±55.4	1.9±0.99	11.1±21.0	1.5±0.84	15.5±16.8	1.6±0.84

Cyto. Ind.: Cytoplasmic index, Int: Intensity. 0: negative, 1: weak, 2: weak-moderate, 3: moderate, 4: moderate-intense, 5: intense.

Table 3: Degrees of intensity and localization of the survivin protein in ulcerated and healthy gastric mucosa of donkeys

Donkeys	Gastric glandular mucosa				Gastric squamous mucosa			
	Ulcerated		Healthy		Ulcerated		Healthy	
	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.
Donkey 1	9	2	41	2	43	2	21	2
Donkey 2	287	4	22	2	101	4	0	2
Donkey 3	483	2	110	2	61	4	0	0
Donkey 4	548	2	133	2	94	4	66	2
Donkey 5	559	2	89	2	107	4	37	2
Donkey 6	92	2	183	4	110	2	90	2
Donkey 7	940	2	202	3	60	4	66	2
Donkey 8	76	4	140	2	136	2	0	0
Donkey 9	303	2	144	3	89	2	0	0
Donkey 10	61	2	121	3	128	2	127	1
Mean±SD.	335.8±297.0	2.4±0.8	118.5±56.5	2.5±0.7	92.9±30.2	3±1.05	40.7±44.9	1.3±0.9

Cyto. Ind.: Cytoplasmic index, Int: Intensity. 0: negative, 1: weak, 2: weak-moderate, 3: moderate, 4: moderate-intense, 5: intense.

Table 4: Degrees of intensity and localization of the survivin protein in ulcerated and healthy gastric mucosa of mules

Mules	Gastric glandular mucosa				Gastric squamous mucosa			
	Ulcerated		Healthy		Ulcerated		Healthy	
	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.	Cyto. Ind.	Int.
Mule 1	4	1	12	2	3	1	3	2
Mule 2	14	2	13	2	15	2	4	2
Mule 3	51	2	72	3	0	0	11	1
Mule 4	95	2	114	4	230	2	8	1
Mule 5	146	4	57	3	194	2	42	4
Mule 6	169	4	72	3	46	2	56	3
Mule 7	259	4	12	2	88	4	4	2
Mule 8	126	5	13	2	165	4	11	2
Mule 9	137	4	72	3	138	5	8	1
Mule 10	150	2	114	4	44	3	42	1
Mean±SD.	115.1±77.0	3±1.3	55.1±40.9	2.8±0.78a	92.3±87.0	2.5±1.5	18.9±19.7	1.9±0.99b

Cyto. Ind.: Cytoplasmic index, Int: Intensity. 0: negative, 1: weak, 2: weak-moderate, 3: moderate, 4: moderate-intense, 5: intense. Different superscripts within a row/column indicate significant differences ($P<0.05$).

Survivin was consistently detected in both gastric mucosa types across horses, donkeys, and mules, with the highest index generally observed in the glandular mucosa (Table 2-4). In horses, a decreasing trend was noted in ulcerated tissues compared to healthy ones, whereas donkeys and mules showed the opposite pattern, though only mules exhibited statistically significant differences ($P=0.03$). Staining intensity varied between mucosal types and species, ranging from weak to moderately intense. Lack of immunoreactivity was mainly observed in the squamous mucosa of some individuals, particularly in horses and donkeys.

DISCUSSION

The survivin protein was initially described in the gastric tissue of humans and mice and is thought to participate in maintaining the integrity and renewal of the mucosa by participating in the cell cycle (Rafatmanesh *et al.,* 2019). In addition, it is considered a possible pathway of ulcerative injury caused by indomethacin, which decreases the expression of this protein in the same species (Chiou *et al.,* 2005), and later, it was linked to the processes of gastroprotection and gastroadaptation in experiments with ethanol in mice (Robert *et al.,* 1983; Jones *et al.,* 2008). Despite being reported in embryonic and neoplastic tissues in other animals (Aida *et al.,* 1998; Kawasaki *et al.,* 1998), the present study reports the presence of this protein in differentiated, mature tissues such as the gastric mucosa of equids. To the best of our knowledge, this is the first report describing survivin expression in the gastric mucosa of ulcer-injured equids.

The variability in the intensity of the immunostaining independent of the type of mucosa and the absence of immunoreactivity in some animals was possibly due to factors related to the depth, site of the sampling, and technique of histological sections. Furthermore, the number of samples, per mucosa was not representative of the entire gastric surface, since 6 to 8 samples have been recommended for each mucosa (Rodrigues *et al.*, 2009). The limitations of this work should be considered in the interpretation of the results; however, unpublished information should be explored in future studies.

Given the importance of survivin in the maintenance of the gastric mucosa and the revelation of its presence on all the gastric surfaces of equids, knowledge of the dynamics of this protein in the ulcerated and inflamed mucosa is encouraged because of the high prevalence of EGUS, in addition to its presence in the processes of cytoprotection and gastroadaptation, which are poorly explored in these species. In this sense, survivin was detected in ulcerated mucosa and had the same distribution pattern as previously reported in healthy mucosa (Medina-Bolivar *et al.,* 2025), with the glandular mucosa having a higher immunolabeling index, which could indicate that this protein may be involved in various efficiency mechanisms of this mucosa (Buchanan and Andrews, 2003; Murray, 2009; Videla and Andrews; 2009); however, it remains speculative, as this study only determined presence, not functionality.

The high index of survivin in the glandular mucosa coincided with the low percentage of ulcers compared with the squamous mucosa in the three species of equids, corroborating what is reported in the literature that it is the most compromised mucosa in EGUS. However, ulcerative lesions were present in both mucosa types, indicating that the inducing or predisposing factors of ulcers exceeded the defense mechanisms of the gastric mucosa, regardless of

how efficient they are and through different injury routes (Laine *et al.*, 2008; Aranzales and Silveira, 2013); thus, SGMD and GGMD are currently considered separately (Sykes *et al.*, 2015).

Since survivin is involved in epithelial integrity (Garcia-Bonete, 2019), a higher marker index was expected in healthy mucosa than in ulcerated ones; however, this behavior was observed only in both mucosa in horses, whereas the opposite was observed in donkeys and mules, where ulcerated mucosa presented high indices. The degree of ulceration differed across species of equids, being more severe and chronic in donkeys and mules since most horses presented gastritis. Therefore, it cannot be inferred whether the increase in survivin in the ulcerated mucosa was due to the process of repair, re-epithelialization, or evolution of the lesion, although survivin participates in the regulation of cell division (Chiou *et al*., 2003). Further studies in well-managed donkeys and mules are needed to clarify survivin's role in EGUS, as these animals may be less prone to gastric ulcers under normal conditions (Calixto-Vega and Martínez-Aranzales, 2024a; Medina *et al*., 2024).

The gastric epithelium is constantly challenged by harmful local and systemic substances and factors (Aranzales and Silveira, 2013). Therefore, it possesses several defense mechanisms, among which the renewal of epithelial cells plays a key role in maintaining the integrity and repair of the mucosa. This process involves several growth factors (EGFR, FCT-α, and FCI-1) acting through active myogenic protein kinases (Pai *et al.*, 2002), as well as peptides and proteins (heat shock proteins, cathelicidin, β-defensins, and survivin), which also have important functions in the mucosa (Yang *et al.,* 2004; Chiou *et al*., 2005; Yang *et al.*, 2006; Tanaka *et al.*, 2007). Therefore, the high intensity and elevated expression of survivin in the gastric tissues of equids are due to death and continuous cell renewal for the maintenance of homeostasis in the epithelium damaged by multiple factors.

Gastroprotection and gastroadaptation with the participation of survivin have not been described in equids, as in other species (Robert *et al*., 1983; Jones *et al*., 2008). However, several events have been described, such as the natural repair of gastric ulcers without medical intervention (Sharbine *et al.*, 2022), the presence of gastritis before weaning, which influences the low presentation of gastric ulcers in the postweaning period (Campos de Araújo *et al*., 2022), and the individual variability in response to predisposing factors of EGUS, which translates into different prevalence rates around the world (Graaf-Roelfsema *et al*., 2010; Van den Boom, 2022; Vokes *et al*., 2023; Calixto-Vega and Martínez-Aranzales, 2024a). These findings encourage the exploration of these aspects in equids because of their high frequency of gastric lesions.

Neurohormonal interactions with the defense mechanisms of the gastric mucosa, including the survivin protein, have been extensively studied in humans and mice (Johnson and Howerth, 2004; Garcia-Bonete, 2019). However, in horses, studies have focused on the effects of stress on the gastric mucosa, specifically hormones such as cortisol and adrenocorticotropic hormone (ACTH) (Scheidegger *et al.*, 2017; Prinsloo *et al.*, 2019; Calixto-Vega and Martinez-Aranzales, 2024b), and the effects of anti-inflammatory agents on cytoprotective prostaglandins (MacAllister and Sangiah, 1993; McConnico *et al.*, 2008); however, how these factors influence or impact the expression of survivin has not been studied to better understand the behavior of this protein on the surface of the equids studied, as well as its dynamics during the process of evolution of ulcerative lesions.

The inhibition of survivin is considered another mechanism of NSAID-induced gastric injury in mice (Chiou *et al*., 2005). These drugs are commonly used in equines, and their gastric effects are widely known, but no relationship has been sought with the concentration of this protein. Although one study addressed the phenomenon of gastroadaptation to Phenylbutazone, it did not consider the determination of survivin (Martinez *et al*., 2014). Importantly, the main mechanism of injury associated with NSAIDs has become controversial, leading to the description of other routes of injury (Nieto *et al*., 2012; Martinez *et al*., 2014; Pedersen *et al.*, 2018). This aspect requires further study in future work.

The stomachs analyzed came from equids destined for slaughter, which allowed for an exhaustive postmortem examination; however, owing to the conditions of these animals, no relevant information was obtained on the predisposing factors of EGUS, such as management and feeding systems, the use of NSAIDs and stressors, and the time of evolution, which could somehow impact the expression of survivin, avoiding inferring about its participation in the induction or resolution of ulcerative lesions. Additionally, owing to the storage conditions and destinations of the equids, the prevalence and degree of severity do not represent the natural prevalence of ulcerative lesions in these animals. Future studies using transendoscopic gastric biopsies in equids under ideal management conditions are warranted to further elucidate the role of survivin in gastric health.

Conclusions: Survivin is consistently expressed in the gastric mucosa of equids, regardless of health status, suggesting a constitutive role in mucosal maintenance. Future studies should explore its functional role in healing and gastroprotection and gastroadaptation.

Conflict of interest statement: The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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Authors contribution: ALMB: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. VMUM: Writing – review & editing, Writing – original draft, Supervision,

Methodology, Investigation, Formal analysis. JRMA: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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