Polycythemia, emperipolesis and extramedullary haematopoiesis caused by acute shock: the first record in the Northern white-breasted hedgehog *Erinaceus roumanicus* Barrett-Hamilton, 1900

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Abstract

An adult female hedgehog *Erinaceus roumanicus*, was found in a city traffic zone, exhibiting severe injuries consistent with a vehicular collision. Rapid diagnostics, including X-ray imaging, were performed at the veterinarian clinic to rescue the animal. Due to multiple traumatic injuries and poor prognosis, the animal was anesthetized for blood sampling and then euthanized. Polycythaemia, platelet aggregation, rare megakaryoblasts, neutrophilia, lymphocytosis, and a high red blood cell (RBC) and white blood cell (WBC) count were found in peripheral blood. Eosinophilia and the physiological phenomenon of emperipolesis were detected in the femur bone marrow, while the liver biopsy confirmed the extramedullary haematopoiesis (EMH). Acute hypovolemic shock results in rapid changes in hematological and biochemical parameters, endangering the patient's life. Treatment of hypovolemic shock and intensive care of small and exotic animals is further complicated by their small size, physiological diversity, lack of research and clinical data on their response to therapy. Given the increased vulnerability of the small mammal fauna as a result of expanding urbanization, this case study aims to facilitate the recognition of this life-threatening condition, the possible physiological response in hedgehogs and the adequate care of injured animals. Raising awareness of the fragmentation and decline of their populations in the habitats they share with humans can contribute to finding solutions to mitigate their road mortality, and improve their well-being and conservation.

Shock is generally considered a syndrome caused by systemic tissue hypoperfusion leading to widespread cellular dysoxia and vital organ dysfunction (7). Following severe trauma, increased production of catecholamines, particularly norepinephrine, has been associated with bone marrow dysfunction due to prolonged mobilization of haematopoietic progenitor cells and decreased proliferation of erythroid progenitor cells in the bone marrow (3). After a traumatic injury, mainly caused by haemorrhagia, anaemia occurs very early and often lasts for months (16). However, bleeding can increase bone marrow activity and lead to accelerated erythropoiesis up to several times the usual rate, and if blood loss continues, anaemia develops. While the JAK2/STAT5 pathway has been shown to activate genes fundamental for erythroid progenitor survival, proliferation and differentiation (8), STAT5 phosphorylation is essential for erythropoiesis acceleration during the hypoxic stress.

Emperipolesis is an extraordinary biological process in which one cell invades another living cell. A penetrated cell is maintained inside another and can come out anytime without structural and functional abnormalities (17). Moreover, emperipolesis is now understood as a mechanism to improve cell survival and help prevent apoptosis of cells within the host cell (12). This phenomenon also occurs in certain pathological conditions such as autoimmune haemolytic anaemia, leukemia, myeloma (9) and inbreeding (18). More detailed research is needed to determine whether emperipolesis is the result of an existing pathological process or acute shock, which was not feasible in this case. Furthermore, it is already known that various haematopoietic stressors, such as infection, can induce extramedullary haematopoiesis (EMH) (2). In contrast, hypoxia can induce EMH in the presence of anaemia, particularly in the spleen. Splenic erythropoiesis secondary to hypoxia, also known as "stress EMH," has been thoroughly studied in mice (4, 10).

To the best of our knowledge, there are no previous studies on the effect of acute haemorrhagic shock on the change of haematological and biochemical parameters of the northern white-breasted hedgehog *Erinaceus roumanicus* Barrett-Hamilton, 1900. While only a few studies have reported average reference values for several haematological and biochemical parameters on few species of family Erinaceidae such as European hedgehog *E. europaus* (13, 26), desert hedgehog *Paraechinus aethiopicus* (19), and African pygmy hedgehog *Atelerix albiventris* (22), there are no data on hepatocytes and haematopoietic cell alterations in the hedgehog bone marrow as the output of severe injuries. In this study, it has been noted for the first-time different features as a result of the acute hypovolemic shock in the northern white-breasted hedgehog *Erinaceus roumanicus*, such as polycythaemia in peripheral blood, the physiological phenomenon of emperipolesis in the bone marrow as well as extramedullary haematopoiesis in the liver.

An adult female hedgehog *Erinaceus roumanicus*, weighing 2300 g, was found at the end of May 2022 in a city traffic zone with serious injuries, most likely caused by being struck by a vehicle. The animal hid in the nearby vegetation, but it is unknown how much time passed from being wounded to being found. External examination of the animal revealed a massive separation of the ventral fur integument from the dorsal skin with quills along the left flank, showing fully exposed muscle fascia in the lower abdominal region, partially torn. The skin of the left hind leg was wholly peeled off, which in addition to the pathological mobility of the femur, made movement extremely difficult. The exhausted and dehydrated hedgehog was transported to the veterinary clinic for examination assessment. External examination revealed a large deep purple ecchymotic area, of the left ventral part. The abdominal bleeding was immediately assumed based on the findings of a swollen, tight abdomen, accompanied by tachycardia and rapid, shallow breathing. A skeletal X-ray of the skeleton showed an open pelvic fracture with a large sacroiliac (SI) dislocation followed by a left hip dislocation. The caudal vertebrae were mostly bruised, even crushed, while the damage to the internal organs was difficult to assess (Fig. S1A). Due to multiple traumatic injuries and poor prognosis, the animal was anesthetized for blood sampling and then euthanized.

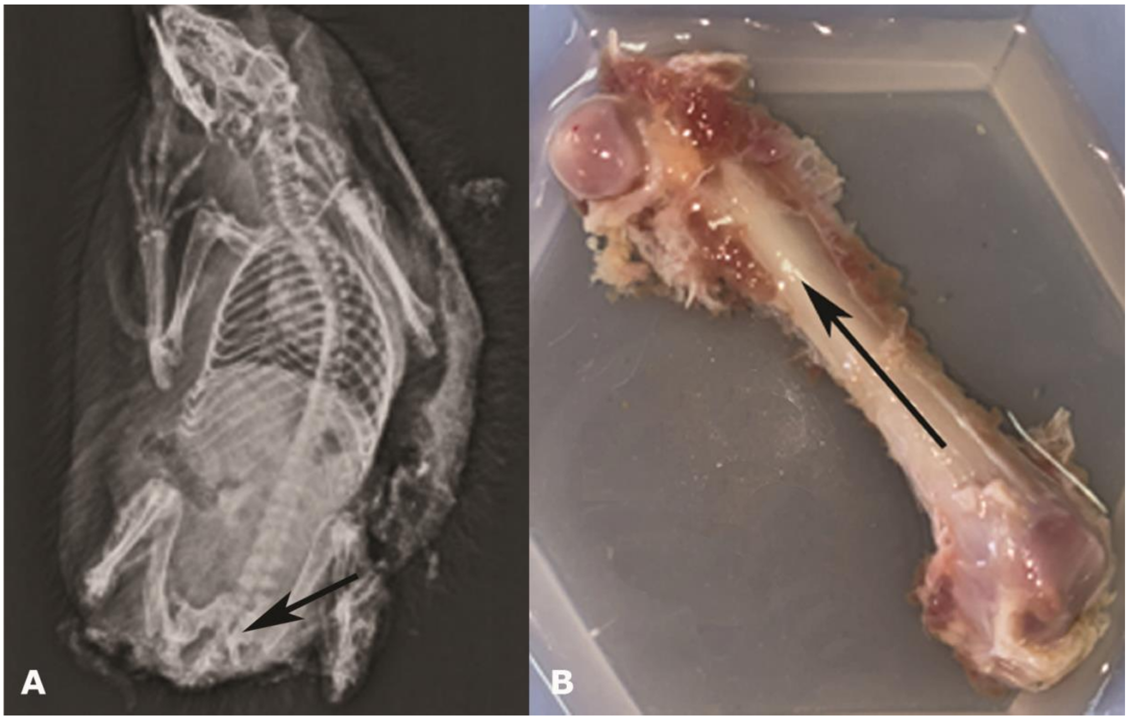

Figure S1. A - X-ray imaging of the skeleton of the northern white-breasted hedgehog (*Erinaceus roumanicus*) exhibited open pelvis fracture with massive sacroiliac (SI) dislocation with crushed caudal vertebrae (marked with black arrow). **B** - Presentation of longitudinal dissection of the femur for the purpose of bone marrow biopsy. The length of the dissection is indicated by a black arrow.

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A combination of 60 mg/kg ketamine (Intervet International) and 7 mg/kg diazepam (Alkaloid), intraperitoneally (i.p.) has been used for long-lasting analgesia prior to cardiac puncture, according to the University of Minnesota Research Animal Resources; repeated dose administrated for euthanasia, as recommended by the American Veterinary Medical Association (AVMA). After sedation, blood obtained by cardiac puncture immediately before euthanasia was centrifuged and serum was separated for spectrophotometric analysis of biochemical parameters, such as total protein, albumin, globulin, A/G ratio, glucose, creatinine and urea. A drop of fresh blood with EDTA (100:1) for the May-Gruenwald-Giemsa stain of blood smear was taken for microscopic examination with manual blood count/percentage of peripheral cells. In parallel, the total number of erythrocytes and leukocytes was confirmed by a haemocytometer.

Necropsy and partial dissection (excluding head region) showed that the massive abdominal bleeding was most likely caused by rupture and crushing of the spleen, which therefore could not be sampled. Pelvic fracture with severe SI dislocation, along with severe injuries to the surrounding structures, contributed to blood loss and the onset of acute hypovolemic shock. Apart from ectoparasites common in hedgehogs (mites), no endoparasites, obvious pathological formations or neoplasms were found during dissection. A bone marrow (BM) biopsy was performed from the middle part of the femur (Fig. S1B) and smeared with the touch technique (28). The longitudinal dissection of the femur showed that the central region contains most of the BM, while the *caput femoris* and *collum femoris* lack a sufficient BM amount for analysis. A liver biopsy was performed, and hepatocytes were analyzed by the imprint method (28).

Although there is no information on time since injury, significant erythrocytosis and mild leukocytosis followed by lymphocytosis and neutrophilia are most likely caused by the onset of acute hypovolemic shock. The haematological and biochemical parameters of the northern white-breasted hedgehog *E. roumanicus* from this case study, compared to healthy specimens of the same and related species of the family Erinaceidae, are shown in Table 1. Given that differences between biochemical parameters may be due to physiological conditions, sex differences and a season, obtaining values for *E. roumanicus* should be taken with reservation because the values are changed as a consequence of acute hypovolemic shock and dehydration, as indicated by the high value of urea (28.30 mmol/L) and mild hypoglicemia (4.07 mmol/L). Table 2 contains morphological observations focusing on the percentage of different forms of erythrocytes and platelets in the peripheral blood. In addition to normal erythrocytes, rare macrocytes and a large proportion of microcytes (38%) were observed. The appearance of different stages of erythrocytes may indicate anaemia or accelerated erythropoiesis, with the latter being the more likely scenario. However, rare megakaryoblasts present in peripheral blood, app. 1% is a phenomenon that has not been described so far. It remains unknown how such large cells can reach the circulation (Figure 1A). The platelets were shown different morphological changes with 90% average sized, 10% extra small and 9% large forms, and their notable aggregation (Table 2; Figure 1B). The total number of platelets could not be calculated due to pronounced aggregations.

Table 1. Obtained haematological and biochemical values of northern white-breasted hedgehog *Erinaceus roumanicus* in acute hypovolemic shock, in comparison to the healthy specimens of related species from the family Erinaceidae (except for 6. *E. europaeus* # (24) with notably tick-induced blood loss and regenerative anaemia).

	1. ***Er****	**2.** ***Ec/Er*(23)**	**3.** ***Ee^a^* (29)**	**4.** ***Ee^b^* (13)**	**5.** ***Ee^c^* (14)**	**6.** ***Ee^d^#* (24)**	**7.** ***Ee^e^* (26)**	**8.** ***Aa* (22)**	**9.** ***Pe* (19)**
RBC (10^{12}/L)	16.41	-	5.1	9.64	8.06	6.39-8.02	8.1	5.13	5.90
WBC (10^{9}/L)	10.96	-	4.7	8.20	7.69	10-11	8.4	14.35	6.00
Neut %	62	23.9	65	45	-	39-43	35.1	64.08	51.36
segs %	51	-	-	-	-	-	-		-
bands %	11	-	-	-	-	-	-		-
LYM %	29	65.5	29	51	-	38-46	50	33.17	41.9
MONO %	4	1.80	4	0	-	4-5	2.7	1.08	6.88
BASO %	2	1	-	3	-	2-4	3.5	0.42	-
EOS %	3	9	2	2	-	6	7.5	0.75	-
PLT (10^{9}/L)	-	-	-	-	135	301-334	230.7	-	150
Albumin (g/L)	33.67	-	-	-	-	-	35.00	34.3	18.30
Globulin (g/L)	29.55	-	-	-	-	-	33.80	26.30	47.70
Total protein (g/L)	63.22	-	-	-	-	-	68.80	59.80	66.10
A/G ratio	1.13	-	-	-	-	-	1.07	1.30	0.38
Glucose (mmol/L)	4.07	-	-	-	-	-	5.9	8.60	7.15
Urea (mmol/L)	28.30	-		-	-	-	-	4.7	14.40
Creatinine (µmol/L)	59.53	-		-	-	-	-	67	44.20

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Table 2. Percentage and morphological characteristics of erythrocytes and platelets in peripheral blood of northern white-breasted hedgehog *E. roumanicus* as a result of acute shock.

	Cell types	Surface area (µm^2)	%	Description
Erythrocytes	Macrocytes	28.16-33.26	2%	Very large, round, often with a central pallor
	Normal erythrocytes	19.04-21.36	50 %	Round, rarely with a central pallor
	Microcytes (spherocytes)	11.20-14.40	38%	Very small, round, without central pallor
Platelets	Extra small	8.39-9.01	10%	Single, small and round
	Normal	7.16-9.90	90%	Standard size, irregular round shape, often in clusters
	Large	20.46-29.56	9%	Large than normal, the membrane often regular round
	Megakaryoblasts (Shown in Fig 1. A1)	70.23-77.45	1%	Largest cells, rarely present, significantly smaller than bone marrow megakaryocytes, regular round shape with few visible nuclei

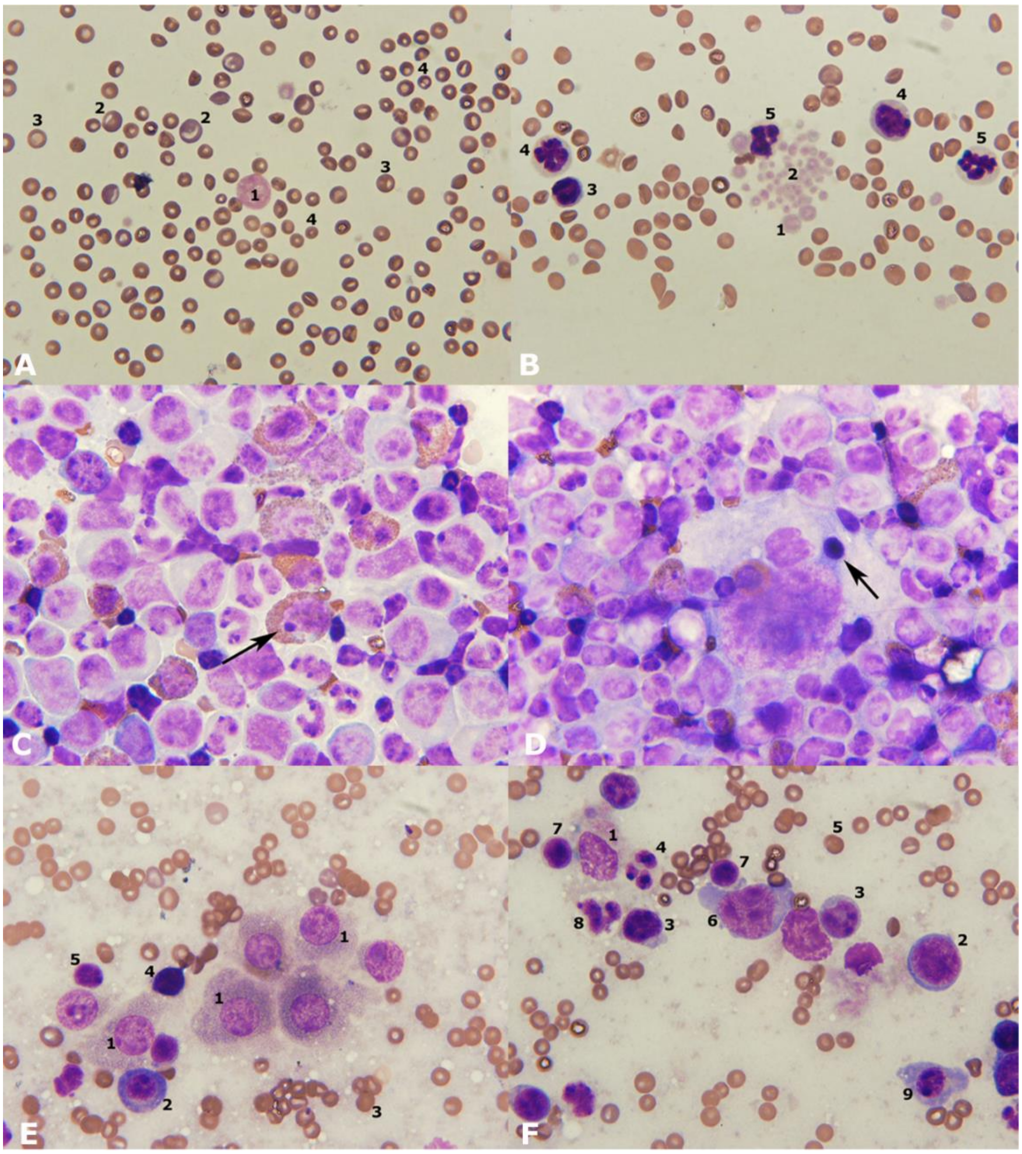

Figure 1. A-B Overview of hedgehog blood cells features. A – Polycythaemia; 1. megakaryoblast, 2. macrocyte, 3. normal erythrocyte, 4. microcyte. **B -** Leukocytes and platelets aggregation; 1. – large platelets, 2 – normal platelets, 3. lymphocyte, 4. non-segmented granulocyte, 5. segmented granulocyte; **C-D Overview of hedgehog bone marrow features. C -** The arrow indicates eosinophilic blasts; **D** - The arrow indicates emperipolesis. Inside the active megakaryocyte are basophilic erythroblast, undifferentiated blast, lymphocyte, and eosinophilic granulocyte; **E-F Overview of hedgehog liver features. E –** 1. hepatocytes, 2. erythroblast, 3. mature erythrocytes, 4. lymphoblast, 5. mature lymphocyte; **F -** extramedullary haematopoiesis in liver: 1. macrophage, 2. proerythroblast, 3. lymphoblast, 4. acidophilic erythroblast, 5. mature erythrocyte, 6. myeloblast, 7. prolymphocyte, 8 neutrophilic granulocyte (immature), 9. basophilic erythroblast.

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Increased production of eosinophilic blasts was found in the bone marrow (Figure 1C). Emperipolesis (Figure 1D) detected in all types of megakaryocytes: acidophilic, basophilic and thrombocytopenic, involved engulfment of immature and mature blood cells of the erythrocyte and leukocyte line in the bone marrow. Cunin et al. (5) recently established that emperipolesis accelerates platelet production both *in vitro* and *in vivo* which is common to several conditions associated with high platelet demand, such as blood loss and hemorrhagic shock.

Hedgehog hepatocytes (Figure 1E) are large, usually with 1-2 nucleoli, structurally very similar to the hepatocytes of other mammals. Numerous hepatoblasts have been observed in the liver indicating EMH (Figure 1F). Present EMH in the liver can be associated with acute shock and a pronounced emperipolesis phenomenon in the bone marrow. In addition to blasts, immature erythrocytes and leukocytes were also observed during different developmental stages. Although a recent study reported the presence of megakaryocytes indicating EMH in the liver in two specimens of the African small hedgehog (27), megakaryocytes or megakaryoblasts in the liver of *E. roumanicus* were not identified in our study. Future studies should elucidate whether EMH in the liver is possible for all types of leukocytes and platelets.

The most crucial aspect of acute shock appears to be the presence of relative polycythemia, probably caused by hypovolemia followed by prolonged dehydration, haemoconcentration and stress. The blood smears (Figure 1A and Figure B) showed mild poikilocytosis, while present polychromasia indicates that RBCs are being released prematurely from the BM during formation. Therefore, in this case study we hypothesized that different forms of erythrocytes in peripheral blood are associated with their high production, indicating extramedullary erythropoiesis with increased production of erythrocytes in the bone marrow. Acute hypovolemic shock leads to polycythaemia with significantly increasing RBC and WBC count. We identified different forms of platelets and the presence of megakaryoblasts in the peripheral blood, eosinophilia, as well as the emperipolesis observed in the BM. Moreover, the finding of a robust BM response in protecting immature blood cells (emperipolesis) with the aim of preserving future mature cells crucial for blood loss replacement is another novelty of this study that has not been previously reported in response to acute hypovolemic shock in small mammals. It seems *E. roumanicus* appears to possess robust physiological and biochemical mechanisms of defence against acute shock at several levels, ranging from blood cells and variations in biochemical parameters in the blood to significant hematopoietic processes in the bone marrow, aided by extramedullary haematopoiesis detected in liver. Although data on extramedullary erythropoiesis after severe injury and/or disease are very scarce, a recent study on male Sprague-Dawley rats exposed to chronic stress, lung contusion and haemorrhagic shock showed the occurrence of extramedullary erythropoiesis in spleen (1). EMH of unknown origin, common in hedgehogs and other small mammals, can also appear during systemic infections and active immune response, most often occurring in the spleen and liver (11). Thus, the presence of EMH in *A. albiventris* has been reported for the spleen (25) and liver (27). Although the studies provide data for EMH, mainly in the spleen, detailed data for this phenomenon in the liver have been reported for the toad *Bufo bufo* (28). Since, in our study, the location of tissue sampling in the liver was chosen randomly, the authors tentatively conclude that EMH occurs only in certain liver regions. Future research should determine whether this mechanism is prevalent throughout the liver tissue and whether it also occurs in the spleen. As noted above, the spleen was not analyzed in this study due to tissue damage and profuse bleeding.

The results presented here are based on a case report of single animal specimen and therefore the obtained values cannot be generalized to other animals of the same or different species. Nevertheless, we strongly believe that EMH is a consequence of acute hypovolemic shock, although possible existing pathological conditions cannot be completely excluded. Distinguishing EMH from chronic myeloid and erythroid leukemia is a rare diagnostic problem due to the low frequency of such neoplasia in animals (10), and possible only using immunochemical techniques. However, the existence of a malignant tumor cannot be completely excluded, especially as neoplasia is the most common pathological finding of *A. albiventris* (21).

Hedgehogs are nocturnal animals with maximum activity after midnight. They prefer forest edges, hedgerows, suburban, but they also inhabit urban habitats. In recent decades, they are certainly the most prominent accidental victims of human activities (6), with thousands of them killed on our roads each year. The season from April to July is thought to have the highest rate of road fatalities for hedgehogs because of increased activity and reduced visibility at night (30). Considering the increased vulnerability of small mammals in urban areas, recognition of acute shock and rapid response is necessary to avoid animal suffering and mortality (20). Treatment of hypovolemic shock and monitoring of intensive care in exotic pets is hampered by their fragility, physiological diversity and lack of clinical data on their response to therapy (15). Veterinarians who work with exotic animals or practice emergency care need to be well-versed in the pathophysiology of shock since many exotic pets appear with an acute crisis or an acute manifestation of a chronic condition that results in poor organ perfusion.

This case report also aims to raise awareness of the importance of hedgehogs and other small mammals in the ecosystem, and the problem of fragmentation and/or loss of their habitats, accompanied by the decline of their populations, especially in suburban and urban areas. Therefore, improving the care of injured animals and applying timely therapy can significantly contribute to their preservation and well-being.

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Conflict of Interest

The authors declared that there is no conflict of interest.

Author Contributions

DS, LLB and MF conceived and planned the experiments. DS and MF carried out the experiments. DS and MF contributed to sample preparation. DS and LLB contributed to the interpretation of the results. LLB took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethical Statement

This study does not present any ethical concerns.

Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

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