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REVIEW ARTICLE

Impact of ruminal impaction syndrome on ruminant livestock productivity: Evaluation of protocols for rapid diagnosis and treatment

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ABSTRACT

Ruminal impaction syndrome (RIS) is an emerging, severe, and potentially fatal gastrointestinal disorder affecting ruminants in urban, semi-urban and peri-urban settlements, with increasing spread into rural communities in developing regions. RIS arises from ingestion of indigestible objects that accumulate in the rumen and obstruct the flow of ingesta through the lower digestive tract; resulting in severe impaction, indigestion, persistent tympany, protracted morbidity, lethargy, and, in severe cases, death. Additionally, RIS results in animal losses, reduced milk and meat production, and costly, often ineffective treatments. Moreover, RIS exhibits a high prevalence propagated via a vicious cycle. Definitive diagnosis and treatment often rely on exploratory rumenotomy. Affected animals are frequently presented in a terminal condition, limiting therapeutic options. Surgical outcomes are often poor and are commonly associated with postoperative complications. Furthermore, microplastics, nanoplastics, xenobiotic chemicals and heavy metals leach into ruminal fluid, bioaccumulate in tissues and enter food chain through milk and meat products to exert detrimental toxic effects in animals and humans. Despite its high incidence and severe strain on economy and animal health, there are no established government regulations or standardized guidelines governing the diagnosis and treatment of RIS, making it a major yet neglected disorder that is often managed empirically by veterinarians. Integrating rumenoscopy alongside nanotechnology, diagnostic markers and modified abdominal ballottement technique can advance accurate diagnosis, while therapeutic laparoscopy may facilitate prompt treatment. This review evaluates the profound impact of RIS on the health and productivity of ruminant livestock. Ultimately, it aims to establish effective diagnostic pathways and therapeutic protocols that can be adopted by veterinarians and policymakers to restore livestock health, improve animal welfare, and ensure sustainable productivity of ruminant livestock systems.

Keywords: Diagnosis, impaction, productivity, ruminal, treatment

INTRODUCTION

Ruminal Impaction Syndrome (RIS) (also known as Non-Penetrating Foreign Body Syndrome, Plastic-Induced Ruminal Impaction or Ruminal Impaction Disease Syndrome) is a major emerging threat to health and welfare of ruminants, including free-range and semi-intensively reared livestock in developing regions (Bokko et al., 2025). The rapid growth of plastic production and the expansion of "take-make-dispose" consumption patterns generate enormous amounts of plastic waste that litter the environment, thereby contributing to the incidence of RIS (Adane and Muleta, 2011). Ruminal impaction syndrome remains a challenging high prevalence gastrointestinal disorder, primarily driven by ingestion and accumulation of indigestible, non-biodegradable materials in the rumen, leading to severe secondary metabolic disturbances and high mortality if left untreated (Jyothi et al., 2025). Ruminal impaction syndrome rapidly degrades the body condition of affected animals and consequently undermines farmers' livelihoods, representing a significant impediment to ruminant livestock productivity. Moreover, sustainable ruminant livestock production remains crucial for attainment of global food security and safeguarding the livelihoods of many households in low- and middle-income countries where RIS is endemic (Kamalakar et al., 2021).

Beyond its detrimental effects on animal health, plastic debris, particularly microplastics and nanoplastics, together with xenobiotic chemicals and heavy metals leached from ingested plastics, may enter the human food chain via meat and milk, posing a risk of irreversible metabolic, endocrine, and developmental abnormalities (Allen et al., 2022; Coffin et al., 2022; Walker et al., 2022). Thus, RIS exerts multi-dimensional impact on animal and human health. Traditional diagnostic procedures like clinical examination, ruminal fluid analysis, and biochemical screening have significant limitations due to non-specificity of assay outcomes (Lakhpati et al., 2019; Jyothi et al., 2025; Marzok and Tharwat, 2025). Radiography and ultrasonography are used only as complementary diagnostic tools, as neither modality provides a definitive diagnosis of RIS. Modern diagnostic protocols need to evolve to overcome these barriers by employing multimodal approaches that provide greater diagnostic accuracy and improve overall survival rates (Sagar et al., 2024). This review appraises the impact of RIS in ruminants and explores emerging diagnostic frameworks and therapeutic strategies, including laparoscopy, nanotechnology, putative diagnostic markers and modified abdominal ballottement techniques, to identify the most effective protocols for restoring animal health, enhancing welfare, and safeguarding livestock productivity.

AN OVERVIEW OF RUMINAL IMPACTION SYNDROME (RIS)

ETIOLOGIC AGENTS OF RIS

The incidence of RIS begins with the indiscriminate ingestion of indigestible materials by ruminants. The principal etiologic agent, polyethylene or polythene (IUPAC name: polyethene or poly[methylene]; abbreviated PE) accounts for 79.2% of the foreign mass associated with RIS (Negash et al., 2015). The ethylene double bond allows untrammeled polymerization into Low-Density Polyethylene (LDPE), a soft, flexible, lightweight thermoplastic polymer that can be easily melted, moulded and reshaped through the application of heat and pressure into a wide range of consumer plastic products (plastic bags, films, sheets, wraps, films, membranes) primarily used for food packaging (Achilias et al., 2007; Araújo et al., 2008; Adane and Muleta, 2011). LDPE is noted for its low temperature flexibility, water resistance, durability, corrosion resistance and transparency (Adane and Muleta, 2011). Plastic originates from fossil fuels buried deep beneath the Earth's surface and ultimately ends up as deadly anthropogenic debris in landfills, refuse dumps, and aquatic ecosystems. While the foreign mass is predominantly composed of polythene intertwined with feed particles, it may also contain other indigestible materials, such as synthetic ropes and cords, fabric, leather, rubber**,** stone, trichobezoars and metals (Tiruneh and Yesuwork, 2010), which make up 20.8% of the foreign mass content (Mushonga et al., 2015; Negash et al., 2015; Duresa et al., 2022). The tangled polythene network acts as an ever-present matrix that traps other indigestible items in the rumen.

PROPENSITY OF RUMINANT LIVESTOCK TO RIS

Numerous factors play imperative roles in the predisposition of ruminants to RIS. These include:

Breed, Age and Sex Predisposition

Ruminants are prone to RIS, with cattle more susceptible than sheep and goats. This is attributable to cattle having least sensitive prehensile organs (lips and tongues) to distinguish feed from inedible items and having more indiscriminate, non-selective feeding habits (Uzal et al., 2016). Crossbred cattle are also more vulnerable than indigenous breeds owing to higher nutritional and energy demands (Mendonça et al., 2019). Sheferaw et al. (2014) showed that the prevalence of polythene masses in slaughtered animals was significantly higher in cattle (41.8%) than in sheep (20.6%) and goats (11.9%). Similarly, post-mortem prevalence of ruminal polythene mass at Addis Ababa abattoir was 35.7% in cattle, 18.6% in sheep and 15.3% in goats (Mekuanint et al., 2017; Kamalakar et al., 2021).

Furthermore, cattle older than 10 years and sheep and goats older than 4 years exhibit a higher prevalence (46.7%) than younger age groups (12.9%) (Duresa et al., 2022). This is attributable to the continual ingestion and cumulative load of indigestible material in the rumen over their lifespan. Additionally, the absence of diagnostic signs exacerbates the occurrence of higher prevalence of RIS in older animals (Mekuanint et al., 2017; Priyanka and Dey, 2018; Kamalakar et al., 2021).

RIS are more prevalent in cows, ewes and does than in bulls, rams and bucks (Tiruneh and Yesuwork, 2010; Mekuanint et al., 2017). For instance, the frequency of recovered plastic at Batna slaughterhouse in Algeria was 79.06% in cows and 23.92% in bulls (Zahra et al., 2022). Female animals show higher propensity to RIS due to greater nutritional demand, negative energy balance and susceptibility to mineral deficiency aggravated by gestation and lactation (Remi-Adewumi et al., 2004; Tiruneh and Yesuwork, 2010; Mekuanint et al., 2017).

Ruminant Livestock Rearing System

Ruminant livestock reared under free range or semi-intensive farming are at a higher risk of developing RIS. They roam waste-polluted open areas and refuse dumps, where they indiscriminately scavenge or freely graze any feed matter, including erratic ingestion of predominantly polythene garbage laced with residual salt, sugar and seasoning mistaken for feed. The repeated ingestion of such indigestible materials leads to their accumulation in the rumen. In contrast, ruminant livestock reared by intensive systems without access to indigestible material rarely develop RIS (Bokko et al., 2025).

Nutritional Imbalances

Fodder scarcity, poor nutritional supplementation and deficiencies of essential minerals like calcium, phosphorus and other micronutrients can lead to *pica* and increased energy requirement with resultant negative energy balance status (Otsyina et al., 2015). Such ruminants resort to ingesting indigestible items resembling feed in an attempt to offset energy deficits (Otsyina et al., 2017). Additionally, the RIS cycle is propagated in a "vicious cycle" as a self-perpetuating, negative feedback loop that links malnutrition to compulsive, indiscriminate ingestion of indigestible materials. Nutritional buffering with mineral licks and supplementary feeding minimizes consumption of non-feed items.

Industrialization and Urbanization

Since the 1950s, global plastic industry has experienced exponential growth. For instance, plastic production reached 390.7 million metric tons in 2021, from 2 million tons in 1950, generating $609.2 billion with attendant enormous polythene wasteland (Kamalakar et al., 2021). Plastic waste generation exacerbated by population explosion, "take-make-dispose" consumer actions, and urbanization, has resulted in a global plastic pollution crisis, outpacing the global waste management systems and exerting adverse effects on the environment, climate and public health (Borrelle et al., 2020; Sequeira et al., 2020; Walker, et al., 2022; Kibria et al., 2023). Plastic waste, together with poor animal husbandry, aggravates the incidence of RIS and consequently represses productivity and profitability of the free range or semi-intensive ruminant livestock systems (Borrelle et al., 2020; Lau et al., 2020). The high preponderance of RIS is a direct reflection of poor waste management practices and environmental plastic pollution, highlighting a broader public health failure in waste disposal systems, particularly in urban areas of developing countries. The issue underscores the interconnectedness of environmental, animal and human health.

Furthermore, rapid urbanization through extensive haphazard constructions has diminished natural grazing lands while discarded anthropogenic debris, principally

plastic waste, is ingested by ruminants (Bokko et al., 2025). Moreover, the free range and semi-intensive rearing methods have not been synchronized with the urban growth trends.

PREVALENCE OF RUMINAL IMPACTION SYNDROME

Slaughterhouse prevalence of RIS in ruminant livestock in developing regions has been extensively reported. Studies have shown that abattoir prevalence rates range from 19.3% to 87.32%; while the hospital RIS detection rates are 0.4% to 13.5% (Table 1). The vast disparity in detection of RIS with up to 90% prevalence post-mortem compared to under 14% in veterinary hospitals/ clinics highlights a high disease overall incidence that is severely masked by poor clinical detection of active cases in living animals; a critical flaw in clinical diagnostics.

Table 1 Prevalence rates of RIS in ruminant livestock in veterinary hospitals or abattoir post-slaughter in selected developing countries

Country	Abattoir postmortem prevalence	Prevalence in hospitals/ clinics	Source reference
Algeria	52.24%	**No data**	Zahra et al., 2022
Ethiopia	30.73% – 79.2%	0.44% - 13.22%	Hussain & Uppal, 2012 Tesfaye and Chanie, 2012 Nugusu et al., 2013 Negash et al., 2015 Kamalakar et al., 2021 Ame et al., 2022 Duresa et al., 2022 Vakare et al., 2022
Kenya	72.3%	0.5 – 13.5%	Otsyina et al., 2015
Malawi	80.7%	7.8%	Airs et al., 2024
Nigeria	19.3% – 87.32%	0.7 – 11%	Aminu et al., 2024 Igbokwe et al., 2003 Rabana et al., 2022
Rwanda	65.5%	0.4% - 3.2%	Mushonga et al., 2015

The massive gap between the high prevalence of RIS observed post-slaughter (up to 90%) and the low number of cases documented in veterinary hospitals and clinics (<14%) indicates that the condition is widespread but frequently undetected in the field. The lowest RIS prevalence post-slaughter was more than the highest prevalence detected in the veterinary hospitals and clinics in all countries. Despite a high incidence of RIS, the majority of cases go undetected in clinical settings.

ECONOMIC IMPACT OF RIS ON RUMINANT LIVESTOCK

Ruminal impaction syndrome severely impedes animal health and production in several ways. The physical presence of foreign mass in the rumen reduces functional capacity, obstructs fermentation and hinder production and absorption of volatile fatty acids (VFA), leading to low milk yield, poor weight gain, reduced draft ability and microbiota dysbiosis (Ali et al., 2024). Ruminants experiencing RIS exhibit increased susceptibility to other diseases (Martin Martel et al., 2021). In severe or

untreated cases, RIS may lead to mortality rates as high as 100% (Bokko et al., 2025).

Furthermore, RIS impedes ruminant productivity. Its high prevalence results in substantial economic losses for livestock farmers. For instance, the prevalence of 67.46±7.32% translates to an estimated US$538.75 million (₦820.675 billion) loss annually amongst the 152.48 million cattle, sheep and goats in Nigeria alone (Rabana et al., 2022; Aminu et al., 2024; Bokko et al., 2025). The losses arise from infertility, foetal loss, low milk yield, stagnated weight gain, emaciation, poor meat quality, high morbidity, high health costs and high mortality (Remi-Adewunmi et al., 2004; Bokko, 2011). Ruminal impaction syndrome can also result in "phantom" live weight inclusive of the foreign mass and rumen distension masking actual body mass.

Untreated RIS negatively impact animal welfare causing significant distress and protracted suffering amongst ruminants (Terra and Reynolds, 2020). RIS also puts significant strain on potentials for international trade since contaminated milk and meat products as export commodity fall short of the global WTO agreement standards (Tibebu et al., 2024).

EFFECTS OF RIS IN RUMINANTS

Plastic forms (megaplastics >50mm and macroplastics >25mm – 50mm) in the rumen exposed to churning, ruminal contractions, microbial action, oxidation, mechanical degradation and enzyme activity, undergo continual subtle disintegration into mesoplastics (>5mm – 25mm), microplastics (1µm – <1mm), nanoplastics (1nm – <1µm) or plastic nanoparticles (≤100 nm), even into monomeric forms (Walker et al., 2022; Ali et al., 2024). Microplastics and nanoplastics are the key breakdown forms that cross into circulation and enter tissues. At the same time, plastic polymerization additives, including xenobiotic chemicals such as bisphenol A (BPA), di-(2-ethylhexyl) phthalate (DEHP), polychlorinated biphenyl's (PCBs), triphenyl phosphate (TPP), dioxins,per- and polyfluoroalkyl substances (PFASs), and heavy metals (lead, mercury, chromium, radium, copper, cobalt, barium, arsenic, cadmium) are uncoupled and continually leached into the ruminal fluid, absorbed into the bloodstream, eventually bioaccumulating in tissues and body fluids (Vandenberg et al., 2012; Wiesinger et al., 2021; Dey et al., 2022; Ali et al., 2024). Microplastics and nanoplastics as well as xenobiotic chemicals and heavy metals have been detected in sheep faeces (Beriotet al., 2021), cow follicular fluid (Grechiet al., 2023), blood, ruminal fluid, milk, liver, kidney, and muscle tissues of ruminants (Kunisue et al., 2004; Muleke et al., 2013; Da Costa Filho et al., 2021; Glorio Patrucco et al., 2024). Microplastics, nanoplastics, xenobiotic chemicals and heavy metals are highly toxic, non-biodegradable, and eventually cause lethal effects in ruminants (Allen et al., 2022; Leslie et al., 2022; Walker et al., 2022). Such include immunosuppression, endocrine dysfunction, metabolic insufficiencies, disrupted neurodevelopment, increased reactive oxygen species production and DNA damage, infertility, carcinogenicity and teratogenicity (Matthews, 2021). Microplastics, nanoplastics, xenobiotic chemicals and heavy metals may exert putative, yet to be determined, toxic synergism in livestock with RIS.

IMPACT OF RIS ON HUMAN HEALTH

The RIS carries significant public health importance. RIS itself is not contagious, infectious or zoonotic, but microplastics, nanoplastics, xenobiotic chemicals and heavy metals pose long-term threat to human health. Although humans are vulnerable to exposure through multiple routes, such as inhalation and skin contact dietary ingestion has been recognized as a major sources of exposure. Ingestion is principally the route of exposure to microplastics, nanoplastics, xenobiotic chemicals and heavy metals in water supplies, the environment and food chain including meat and milk products from ruminants with RIS. Humans unknowingly consume 39,000 – 52,000 microplastics annually (Cox et al., 2019). Additionally, airborne particulates originate from synthetic textiles, rubber tyres, landfills and waste incineration are inhaled into the lungs (Kole et al., 2017; Prata, 2018). The vast and thin (<1 µm) alveolar surface area of the lungs is permeated by plastics and chemicals to enter blood stream and reach the entire body (Lehner et al., 2019). Inhalation of plastic particles can push up the figures to 74,000 – 121,000 particles per year (Cox et al., 2019). Similarly, dermal exposure occur where plastic particles and chemicals in personal care products pass through the skin barrier, skin wounds, sweat glands or hair follicles (Schneider et al., 2009).

Microplastics, nanoplastics, xenobiotic chemicals and heavy metals have the inclination for widespread dispersal, non-biodegradability, persistence and high toxicity (Kolandhasamy et al., 2018; Wang et

al., 2020; Yee et al., 2021). Bioaccumulation and biomagnification occur in vital organs with potential to cause an array of adverse, irreversible and severe health damage over time (Adane and Muleta, 2011; Muleke et al., 2013; Priyanka and Dey, 2018). These toxic agents have been detected in liver, spleen, lungs (Amato-Lourenço, 2021; Horvatits, 2022), kidneys, heart, gonads, blood (Leslie et al., 2022; Walker et al., 2022; Codrington et al., 2025) and human placenta (Ragusa et al., 2021). Each of these agents have been reported to cause discrete deleterious effects that mirror the other; such that microplastics and nanoplastics cause effects analogous to xenobiotic chemicals and/or heavy metals. For instance, *in vitro* and *in vivo* studies have shown that microplastics and nanoplastics induced myocardial pyroptosis, mitochondrial damage and adverse immune response in humans (Matthews, 2021). Additionally, they cause endocrine dysfunction, infertility, metabolic insufficiencies, disrupted neurodevelopment (Deng et al., 2017; Lu et al., 2018; Goodes et al., 2022) and tumours of the liver, testes, prostrate, breast, ovaries and increased cardiovascular disease risk (Oskam et al., 2005; Vandenberg et al., 2012; Yee et al., 2021). Furthermore, exposure can trigger the release of reactive oxygen species (ROS) production that can set off DNA damage (Srinivas et al., 2019; Ali et al., 2024). Similarly, continuous long-term exposure to picomolar to nanomolar doses of xenobiotic chemicals or heavy metals have been linked to infertility, birth defects, growth and cognitive impairment (Oskam et al., 2005; Vandenberg et al., 2012; Rani et al., 2015; Ali et al., 2024), immunosuppression, increased cardiovascular disease risk, stroke, as well as hepatocellular carcinoma, testicular carcinoma, prostate, breast and ovarian tumors (Oskam et al., 2005; Vandenberg et al., 2012; Priyanka and Dey, 2018).

The adverse human health effects of microplastics, nanoplastics, xenobiotic chemicals and heavy metals due to RIS remain largely undefined owing to lack of definitive evidence-based data. While microplastics, nanoplastics, and associated leached chemicals or heavy metals are known to be harmful individually, they likely act in combination to produce additive or synergistic toxic effects that amplify overall risks to human health. Currently, there is no comprehensive data to distinguish standalone detrimental effects attributable to individual agent. Further research is required to determine the distinct toxicological effects of xenobiotic chemicals, heavy metals, and plastic particles (microplastics/nanoplastics) on the human physiology. Deciphering the discrete effects of plastic particles, heavy metals and other xenobiotic chemicals is a critical research challenge, as these pollutants rarely occur in isolation and often act synergistically. Moreover, microplastics and nanoparticles pose greater threat by acting as vectors for chemical contaminants (xenobiotic chemicals and heavy metal) adsorbed on their surfaces.

SIGNS AND SYMPTOMS OF RIS

Ruminants harboring little quantities of indigestible materials, most notably polythene waste in the rumen, remain asymptomatic. Once the intraruminal load attains significant threshold, clinical signs start to appear. Although such animals initially appear healthy, they gradually develop a range of nonspecific, low grade, non-diagnostic clinical signs starting out as mild forms of depression, inappetence, indigestion, recurrent bloat, ruminal stasis, ruminal impaction, weight loss, reduced fecal output (Kamalakar et al., 2021; Vakare et al., 2022) or even dyschezia (Babayani and Nyange, 2019). As RIS assumes a more severe form, exhibited signs increase in severity as anorexia, persistent impaction, doughy to firm rumen on palpation, suspended rumination, reduced or absent rumen motility, recurrent severe tympany, distended abdomen, progressive emaciation, dehydration, constipation, lethargy and death (Otsyina et al., 2017; Sasikala et al., 2018; Matthews, 2021). In severely protracted RIS, the actual muscular wall of the rumen can become shrunken or atrophied because the walls remain adhered to the foreign material. The severity of RIS varies greatly depending on the quantities, location and duration of the foreign mass in the rumen, and the extent of interference of ingesta flow (Otsyina et al., 2017). These also produce the variation in duration of clinical RIS of 31 ± 1.24 days (Kamalakar et al., 2021) and 3.7 ± 4.6 months (0.5 to 24 months) in the affected animal (Ismail et al., 2007). The resulting abdominal distension in RIS is frequently misdiagnosed as pregnancy especially amongst female small ruminants (Navarre et al., 2012).

Additionally, rumen movement against the polythene mass lead to mechanical injuries on the ruminal mucosae and papillae (Martin Martel et al., 2021) causing a significant reduction of rumen papillae length (1.243 units) in comparison to the long, slender, regular, white to grey, healthy rumen papillae (3.097 units) (Uzalet al., 2016), thereby reducing rumen functionality. Rumenitis, thinning of ruminal wall, (Martin Martel et al., 2021),

erosion, dystrophy, ulceration, sloughing of ruminal papillae, as well as vacuolar degeneration (spongiosis), increased keratinocytic layers and intense acanthosis of the squamous epithelium of the ruminal mucosae have also been reported (Sheferaw et al., 2014; Mahadappa et al., 2020).

CURRENT PROTOCOLS FOR DIAGNOSIS AND TREATMENT OF RIS

Unlike other diseases, RIS offers no pathognomonic or signature clinical signs. Diagnosis in living animals is difficult because the symptoms are often non-specific or obscure. Instead, RIS is frequently an accidental finding during rumenotomy, necropsy, identified at "the fag end" (Priyanka & Dey, 2018) or as incidental finding during routine abdominal surgeries. Even the inadvertent diagnosis only occurs when a substantial quantity of foreign mass is already present in the rumen and the animal is mortally ailing (Bokko et al., 2025).

Diagnosis of RIS relies on a combination of primary diagnostic procedures including clinical examination and laboratory tests; and complementary imaging techniques (ultrasonography and radiography).

Primary Diagnostic Methods

Clinical Indicators: The animal's history, rearing methods, such as free range or semi-intensive rearing systems, access to plastic waste, other indigestible materials and garbage dumps, or consumption of poor-quality fibrous feed, are crucial indicators. Chronic progressive anorexia, considerable left abdominal distension, "doughy" to hard mass felt on deep abdominal palpation, chronic recurrent bloat, ruminal stasis and/or constipation with scanty or dry feces are key signs.

Evaluation of Rumen Fluid

Methylene Blue Reduction Time (MBRT) in RIS is significantly prolonged due to the disrupted microbial activity and fermentation processes (Bayne and Edmondson, 2020; Jyothi et al., 2025). Reduction in protozoal (Entodinomorphs such as *Entodinium* and Holotrichs like *Isotricha*) count and activity are suggestive of RIS (Ivan et al., 2000). Reduced Total Volatile Fatty Acid (TVFA) concentration indicates impaired digestion and fermentation (Ivan et al., 2000). The indicators used today are a measure of function and activities in the rumen. These tests neither confirm presence or size of polythene mass and other indigestible material, nor the duration, location or severity of RIS.

Complementary Diagnostic Methods

Utility of Non-Invasive Diagnostic Imaging

Radiography and ultrasonography are frequently employed to visualize foreign bodies in the rumen. Their effectiveness, however, is limited as primary diagnostic methods as detailed below:

Ultrasonography

Ultrasonographic scanning of the rumen utilizes linear or convex transducer with a 3.5 to 5.0 MHz on a B-mode to acquire the echogenicity of rumen, its morphology and contents (Li et al., 2018). The rumen topography, motility, wall thickness and contents are visualized in the 8th through 12th intercostal spaces (ICS) and flank on the left; and from 12th ICS and flank on the right (Bayne and Edmondson, 2020). The rumen wall appears as thick, distinct, hyperechoic, smooth line (Marzok and Tharwat, 2025). The gas cap is hyperechoic, characterized by reverberation artifacts that run parallel to the rumen wall, the fiber mat appears as an echogenic, heterogeneous mass with gas inclusions, while fluid phase appears anechoic to hypoechoic (Bayne and Edmondson, 2020; Marzok and Tharwat, 2025). The gas content often creates acoustic shadowing, making it difficult to properly assess the contents or the far wall (Gomaa and Abdelaal, 2015)**.**

In RIS cases, significant reduction in wall thickness has been observed (Gomaa and Abdelaal, 2015). The stratification of ruminal contents (gas, fiber mat, fluid layers) is often not clearly visible with contents appearing as a heterogeneous mixture of echogenic material (Wong et al., 2024). Entangled plastic mass appears as hyperechoic band with characteristic "dirty" acoustic shadowing mostly observed at ventro-lateral aspect of left 11th-12th ICS and lower left paralumbar fossa (Abdelaal and EL-Maghawry, 2014; Gomaa and Abdelaal, 2015; Li et al., 2018; Kamalakar et al., 2023; Wong et al., 2024). Ultrasonography may not reveal characteristic differences in the size or appearance of the polythene or other indigestible materials. Detecting specific materials like plastics can be difficult as they often lack a distinct sonographic signature.

Radiography

Radiography is a valuable diagnostic tool for ruminal impaction caused by radio-opaque (e.g., metallic) foreign bodies (Makhdoomi et al., 2018). Radiography

of the abdomen may also demonstrate the displacement, distortion, distention or superimposition of abdominal structures, as well as the presence of soft tissue opacities, gas-fluid interfaces, or abnormal gas inclusions (Bayne and Edmondson, 2020). In cases where foreign bodies can be seen, radiography serves as a definitive diagnostic method, precluding exploratory surgeries. However, it has limitations for diagnosing RIS caused by plastics; non-radio-opaque (radiolucent or low radiopacity) material, not readily evident on standard radiographs (Lakhpati et al., 2019). The polythene material often appears as non-discrete, non-specific radiolucent or low radiopacity areas, that often merge with existing fluid and soft tissue densities, making them difficult to distinguish between the fluid and soft tissue in the rumen. The radiographs might show generalized dilated rumen with fluid shadows but cannot specifically identify the foreign material itself. Radiography can also confirm a dilated stomach distended with food material, which may displace other abdominal organs, such as the intestines caudally (Navarre et al., 2012). The use of radiography for RIS diagnosis in pregnant dams, especially during the first trimester, poses radiation hazard to the fetus. Radiography may be supportive but not highly diagnostic, often inconclusive for RIS (Lakhpati et al., 2019). Other methods are necessary for a definitive diagnosis. This significantly limits the utility of radiography alone.

Current Treatment Protocols

Treatment of RIS with anti-bloat agents, laxatives or purgatives intended to aid the passage of polythene

Figure 1 Foreign mass recovered via rumenotomy from a 5 year old Sahel Buck (32kg bodyweight). The recovered mass was washed to reveal the composition. A). A 3.8kg foreign mass with feed material (yellowish), B). Polythene weighing 3.1 kg accounting for 81.6 % of the mass, C). Indigestible plant fibres, D). Fabric/Cloth (red), E). Synthetic cords and F). Polyester mesh.

or other indigestible materials is not successful in resolving RIS. Moreover, polythene or other indigestible materials cannot be excreted, hence remain as such. Rumenotorics and probiotics may help restore rumen microflora and motility, but only after the removal of the foreign mass (Dagnaw Fenta et al., 2023). At the moment, rumenotomy is the sole therapeutic protocol that guarantees resolution of RIS, where the rumen is surgically opened to physically remove the accumulated indigestible material with a good prognosis for recovery if addressed in time. In practice, the affected animal will mostly be terminally ill with a huge quantity of the foreign material and surgical intervention success rate is very low.

Foreign mass recoveries via rumenotomy weighed as much as 5.5kg in sheep and goats with 12 liter rumen capacity (Martin Martel et al., 2021; Bokko et al., 2025). This is a considerable load for small ruminants with a bodyweight range of 18–52kg. Similarly, a team of veterinarians in Vepery, Tamil Nadu, India recovered 52kg of foreign mass from a 150 liter sized rumen of a 600kg cow via rumenotomy (Sasikala et al., 2018). The foreign mass is typically large, hard, compact, irregular, roughly spherical to oblong shaped; and conforming to the ruminal environment - usually the ventral sac, composed of tightly intertwined materials with polythene as the main component (Figure 1).

Rumenotomy in animals with poor body condition is frequently associated with complications like severe peritonitis, abscessation, hemorrhage, seromas, infection, dehiscence of suture lines and adhesions between the rumen and abdominal wall. The exteriorization of the rumen, *per se* a tremendous stressor may culminate in hypovolaemic shock (Bokko et al., 2025). These are exacerbated by pre-existing conditions (severe emaciation, dehydration or chronic impaction) before intervention. Furthermore, foreign body mass is typically substantial, frequently exceeding1kg in small ruminants (Figure 1) and above 10kg in cattle. These loads reduce rumen functional volume; interfering with ruminal movements and inhibiting fermentation and VFA production. Moreover, their sudden removal can trigger physiological imbalances predisposing to emergencies. Even after removal of the foreign bodies, the damage to the rumen wall (atrophy of papillae) or chronic impairment of absorption may not be reversed, leading to poor productivity. Furthermore, the animal requires intensive care following rumenotomy, including antibiotics and potential transfaunation to re-establish the flora and accelerate recovery. These are rarely performed.

These challenges reinforce the necessity for developing efficient protocols for early diagnosis of RIS where the indigestible material load is detected before occurrence of any damage to the rumen architecture, function and contents. Although rumenotomy is valuable as treatment, it has setbacks as a diagnostic tool for early stage RIS, including the cost, expediency and skill.

NEWER PROPOSITIONS FOR DIAGNOSIS AND TREATMENT OF RIS

Advances in science, medicine and biotechnology have led to higher degree of accuracy in diagnosing and treating intra-abdominal masses. However, not much progress has occurred in the rapid diagnosis and treatment of RIS in ruminants, despite its high incidence and the untoward impact on the livestock economy. Endeavours are mainly about reportage of prevalence and quantization of economic losses from repressed ruminant livestock productivity. Today, emerging technologies can be harnessed to develop early and definitive diagnostic techniques and expeditious therapeutic approaches for RIS in the ruminants (Figure 2). Such interventions will help prevent ruminants from going through deleterious, debilitating and even fatal course of RIS, while enhancing welfare and restoring ruminant health.

In this review, laparoscopy, nanotechnology, putative diagnostic markers and modified abdominal ballottement techniques are appraised. Laparoscopy and nanotechnology offer twofold roles for diagnosis and treatment for RIS (Figure 2). Diagnostic markers and abdominal ballottement provide only a presumptive diagnosis (Figure 2). The multi-faceted modalities constitute a comprehensive framework for the contemporary diagnosis and management of RIS.

DUAL ROLE OF LAPAROSCOPY FOR DIAGNOSIS AND TREATMENT OF RIS

The advent of laparoscopy (syn: minimally invasive procedure, band-aid surgery, keyhole surgery) represents a milestone in surgery that initiated a shift from the open abdominal operation era to minimally invasive surgery revolution (Kelley, 2008). Laparoscopy, a cornerstone of minimally invasive surgery, has emerged as a gold standard and versatile technique offering numerous benefits over conventional surgery. Moreover, laparoscopy is handy for diverse applications

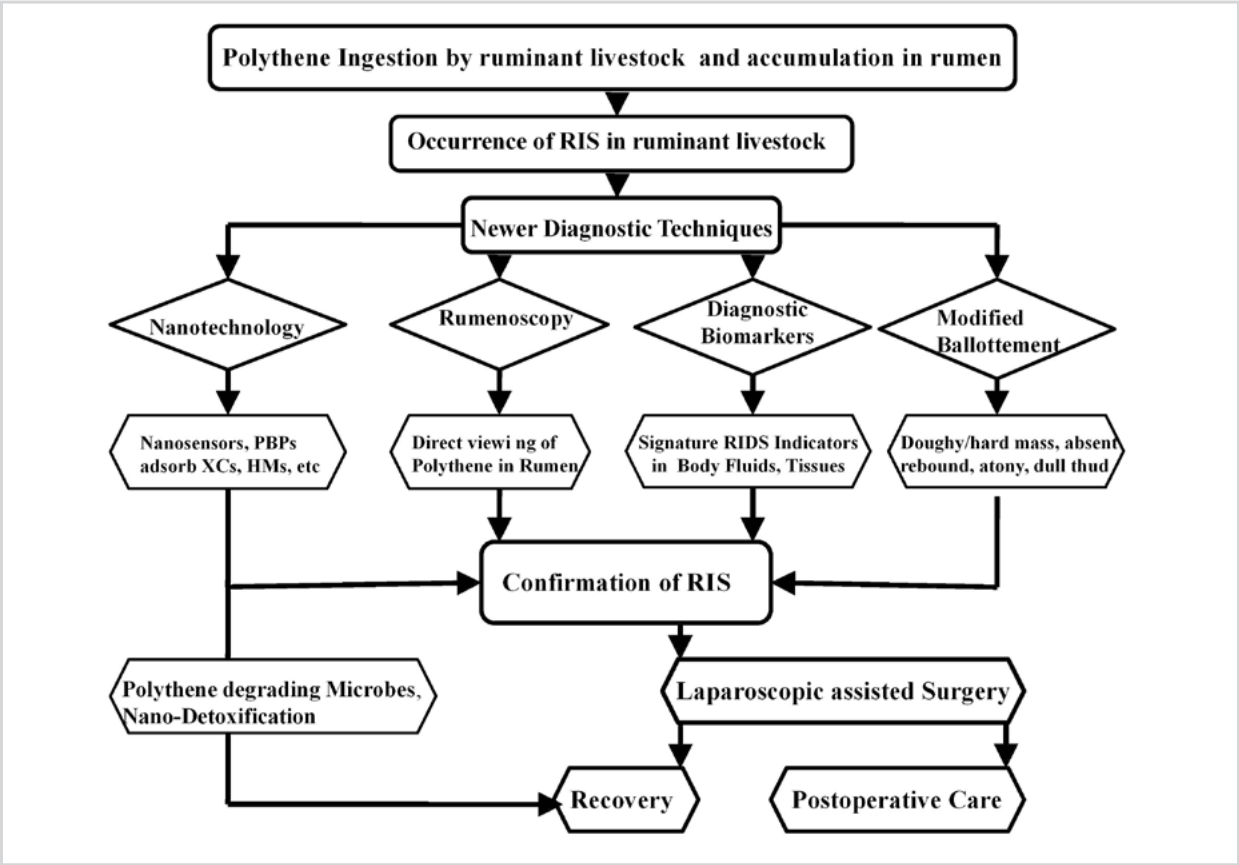

Figure 2 Flowchart of non-invasive diagnosis and minimally invasive treatment of RIS in ruminant livestock. Nanotechnology and laparoscopy offer both diagnostic and therapeutic prospects. Diagnostic markers and abdominal ballottement afford diagnosis. HMs – heavy metals, PBPs – plastic-binding peptides, RIS – ruminal impaction syndrome, XCs – xenobiotic chemicals.

in diagnosis, therapeutic interventions, and/or biopsy of organs of the abdominal cavity without the need for laparotomy.

Laparoscopy is accomplished with the aid of the cardinal tool, the laparoscope, either through the conventional telescopic rod lens system or the digital ("chip-on-the-tip") laparoscope, representing two distinct imaging technologies to visualize the abdomen **(**Sinha et al., 2017; Alkatout et al., 2021). The rod-lens-based laparoscopes dominate in practice for their fine optical resolution (50µm objective lens), trim contrast, better image quality and brightness (Soper et al., 2005). Also, the rod lens system has high-definition (HD) video camera (single- or three Charge-Coupled Device (CCD)) attached, with single chip cameras offering higher image sharpness (Soperet al., 2005). Equally, the digital laparoscope has a miniature digital video camera (CCD or Complementary Metal-Oxide-Semiconductor - CMOS) attached at the distal tip of the laparoscope, eliminating the rod lens system (Soperet al., 2005). Digital laparoscope offers ergonomically superior, often focus-free, lightweight and flexible imaging that provides enhanced resolution, finer color and, in many cases, HD grade images (Sinha et al., 2017; Singla et al., 2022). The digital laparoscopes are becoming standard for complex, precision surgeries, providing depth perception and faster procedure times. Furthermore, 3D laparoscopy employs either dual-channel rods or two sensors at the tip, that significantly improve depth perception, spatial orientation and precision, critical for identifying tissue planes, particularly for suturing (Sinha et al., 2017).

In this review, rumenoscopy (syn: diagnostic laparoscopy, exploratory laparoscopy) denotes to explore, visualize and diagnose conditions, while laparoscopic rumenotomy (laparoscopy-assisted

surgery; therapeutic/operative laparoscopy) implies minimally invasive surgery to treat, repair or remove diseased tissue or organs in the abdomen or pelvic area. Laparoscopy offers diagnosis and treatment (Figure 2). Often, a procedure begins as a diagnostic laparoscopy to determine the problem and continue as therapeutic laparoscopy during the same session.

Rumenoscopy is performed through multiple (2 - 5) elective 3-5cm stab incisions in selected regions of the abdomen, creating a minimally invasive access route that allows the placement of laparoscopic instruments (scissors, dissector, probes, hooks, retractors, etc.) (Figure 3). The real time view of the operating field, assessment of abdominal contents and digital recording is enhanced by pneumoperitoneum via CO_2 gas insufflation (Sinha et al., 2017; Yu et al., 2017). The navigation system permits two directional movement (180º upward and 100º downwards) to produce 2D viewing (Jayender et al., 2018) and the irrigation system facilitates rumen lavage (Sasikala et al., 2018). Larger incisions (>10 mm) may be employed for colectomy, nephrectomy, cholecystectomy or large specimen biopsy **(**El-Sharkawy et al., 2019)**.**

Rumenoscopy (Diagnostic Laparoscopy)

Rumenoscopy allows direct visualization and inspection of the abdominal cavity for diagnosing disorders like appendicitis, intra-abdominal adhesions, ascites, hernias, cirrhosis, bleeding, cancers or foreign body masses (Buia et al., 2015; Yaghobian et al., 2024). Laparoscopy also provides enhanced precision, surpassing physical examination or other imaging tests (radiography, computed tomography, ultrasonography, magnetic resonance imaging scans) to clarify pathologies (Allen et al., 2016; Bokko, 2018; Haruna et al., 2021). Laparoscopy has been shown to be more accurate than radiography for staging cancers of the digestive system (Kooby, 2006). Additionally, laparoscopy not only minimizes patient discomfort, but also allows for repeated examinations if required, providing a practical approach to ongoing abdominal assessments (Yaghobian et al., 2024). Thus, laparoscopy is well suited to evaluate the rumen for the presence of plastic masses and lesions associated with RIS by placement of the laparoscope alone (Yaghobian et al., 2024). Moreover, rumenoscopy is safe, quick and effective for establishing a conclusive diagnosis.

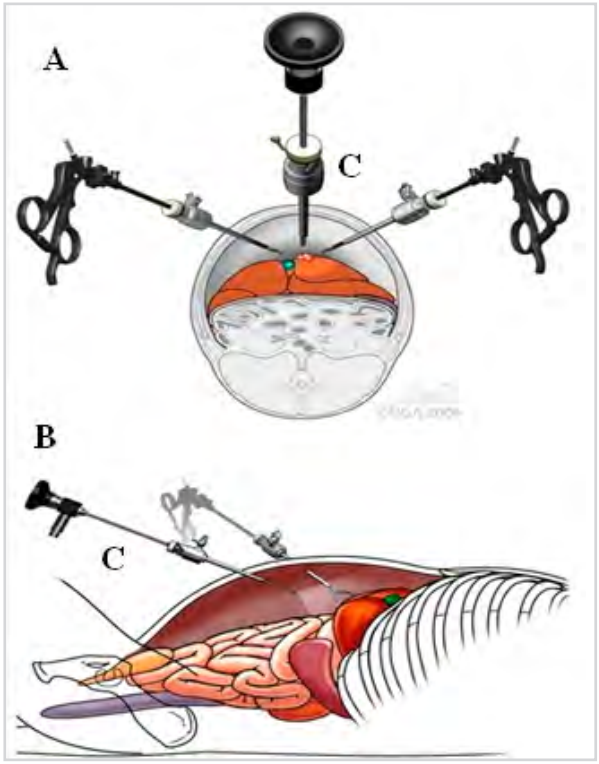

Figure 3: The laparoscopic image with triangulation depth perception of instruments orientation in the transverse (A), sagittal planes (B) and laparoscope (C)

The laparoscope illuminates the operation field view for correct lap instruments placement through the stab incisions while pneumoperitoneum with carbon dioxide gas elevates the abdominal wall to enhance visualization (https://veteriankey.com/laparoscopy).

Laparoscopic Rumenotomy (Laparoscopy-Assisted Surgery, Therapeutic/Operative Laparoscopy)

In addition to rumenoscopy, laparoscopy can double as a tool for removal of polythene and other indigestible materials from the rumen. Laparoscopic techniques have been widely employed for procedures such as herniorrhaphy, ovariectomy, hysterectomy, removal of certain cancers (including those affecting the colon, prostate, ovaries, liver), and the management of ectopic pregnancies in both humans and animals, while providing real-time visualization of the operative field (Sasikala et al., 2018).

Laparoscopy also reduces surgical trauma, bleeding, post-operative morbidity, pain and recovery time

compared to open surgery (Li et al., 2017). In addition, it provides superior cosmetic outcomes and facilitates a more rapid return to normal activity (Wang et al., 2017). Laparoscopic surgery for RIS treatment can significantly prevent complications like postoperative infections, risks to internal organs, fewer chances of wound dehiscence, peritonitis and postoperative hemorrhage (Martin Martel et al., 2021). Keyhole surgery also translates to shorter hospital stays, reduced cost and providing views of internal organs on a monitor (Yi et al., 2017; Yaghobian et al 2024). Complications such as aspiration pneumonia are avoided with laparoscopy (Sasikala et al., 2018).

The future of laparoscopy in veterinary medicine looks promising, with advancements in robotic surgery, advanced imaging, instruments accessibility and precision (Buia et al., 2015; Yaghobian et al., 2024). These innovations will improve surgical outcomes and expand the range of procedures that can be performed. The dual role of laparoscopy can therefore be a boon to veterinary surgery and ruminant animal practice for early, accurate diagnosis and instant treatment of RIS.

NANOTECHNOLOGY TOOLS FOR RIS DIAGNOSIS AND TREATMENT

Nanotechnology offers a wide range of highly sensitive advanced tools for early-stage diagnosis and precise, targeted treatment options operating at atomic or molecular scale (1–100nm) for RIS (Figure 2). Nanotechnological approaches are primarily driven by the inadequacies of existing diagnostic and therapeutic methods, which currently remain the only available options. Early detection of RIS is crucial for preventing severe structural and functional damage to the rumen.

Nanotechnology in RIS Diagnostics

Nanoparticles may be developed into diagnostic tools such as nanosensors/nanobiosensors that enable accurate, faster, low-cost and ultra-sensitive detection of indicators (Mekonnen, 2021). Nanosensors are high-precision tools that can be used for real-time, on-site monitoring of ruminal distress and early recognition of specific diagnostic markers for RIS in biological samples like blood, rumen liquor or saliva (Danchuk et al., 2023; Sharma et al., 2025). Prompt diagnosis via nano-sensors allows intervention before RIS becomes a clinical disease. Additionally, nanoparticles can be used as contrast agents in digital imaging to visualize non-penetrating foreign bodies within the rumen, replacing the need for invasive, exploratory rumenotomy.

Nanotechnology in RIS Treatment

Treatments focus on breaking down foreign matter, preventing secondary infections, and repairing damaged tissues. Nanoparticles can also be engineered into Nano-Detoxification Systems as high-affinity binders to adsorb, bind, neutralize, or remove toxins within the rumen by leveraging high surface area and specific affinities, preventing their absorption into the animal's system and the entry into food chain (Pashirova et al., 2023). In addition, prokinetic drugs or bioengineered nano-enzymes can be delivered directly into the rumen to target and break down polymeric plastics or fiber-based blockages that lead to impaction. Emerging research indicates that the use of nanoparticles enhances the ability of rumen microorganisms to degrade polythene by re-engineering their metabolic cycles (Graham et al., 2011). Furthermore, metal-based nanoparticles such as zinc oxide (ZnO-NPs) and selenium (Se-NPs) can be used to treat metabolic disorders associated with RIS and re-stabilize the ruminal microflora, which is often severely disrupted in RIS (Michalak et al., 2022; Kholif et al., 2025).

Nanotechnology, alongside other advanced techniques such as digital non-invasive imaging and laparoscopy, may form a comprehensive strategy to manage RIS more effectively (Figure 2). Overall, nanotechnology could offer significant improvements over existing diagnostic and treatment options for RIS.

DECIPHERING PUTATIVE DIAGNOSTIC MARKERS FOR RIS

Diagnostic markers are signature molecules that detect or confirm the presence of a disease or condition of interest. To date, there are no established signature molecules or diagnostic biomarkers for RIS in ruminants. Developing diagnostic markers for RIS focuses on identifying physiological, haematological and biochemical molecules arising from the chronic accumulation of polythene in the rumen. Putative diagnostic markers to identify RIS *in vivo* are emerging through research into metabolic, inflammatory, and molecular changes. The putative diagnostic marker that may provide a definitive diagnosis can be any of the polythene forms, plastic micropellets in the rumen fluid, rumen content or faecal material (Figure 2). Potential diagnostic markers may include polythene monomers, microplastics and nanoplastics, xenobiotic chemicals, heavy metals, biological agents, degradation products, reporter molecules, and enzymes, which may be triggered by RIS or by ingestion of polythene and other indigestible materials. These markers may be detectable

in blood, milk, urine, tissues, and ruminal fluid, and could potentially serve as indicators of RIS (Figure 2). Their concentration is expected to be directly or indirectly proportional to the state of RIS.

The diagnostic markers can be characterized, re-engineered or labeled, and then developed into a reliable, rapid, cost-effective and easy to use kit for early and spot-on diagnosis of RIS. Utility of specific diagnostic markers aid the early diagnosis of RIS and helps ensure timely treatment.

MODIFIED ABDOMINAL BALLOTTEMENT TECHNIQUE FOR DIAGNOSIS OF RIS

The term "Ballottement" derived from the French word *ballotter* ("to toss" or "to shake" or "to move about") originated in the 1830s (Cockcroft and Jackson, 2004). Traditional abdominal ballottement is a specialized physical palpation technique of a "push and feel" that relies on the principle of rapidly displacing fluid causing the underlying solid object to float away and then "rebound" or "bounce" back to tap the examiner's hand.

Conventional abdominal ballottement has been subjected to a variety of refinements to accurately decipher complex scenarios where the simple push and feel does not yield desired outcome or when such adjustments offer decisive conclusion. These refinements transform the technique into a more systematic, multi-step or positional maneuvers (Abdisa, 2017). Modifications or specialized versions of ballottement technique significantly enhance diagnostic accuracy particularly in complex clinical situations—such as pregnancy diagnosis, enlarged organs (kidney, liver), ascites or sizeable foreign mass in the rumen (Abdisa, 2017). Such modified techniques include a specialized bimanual ballottement technique executed using one hand to apply sudden pressure to produce "milking" motion or "toss" or displace internal structures against a stationary, feeling hand acting as a stabilizer on the opposite side to detect the "bounce" from enlarged organs (e.g. kidneys) or masses within an ascites-filled abdomen (Abdisa, 2017). Additionally, Ballottement and Simultaneous Auscultation (BSA) technique combines physical pushing with auscultation (stethoscope) to detect fluid-splashing sounds as in traumatic reticuloperitonitis or left-displaced abomasum (LDA) (Cockcroft and Jackson, 2004). Furthermore, Ballottement Percussion (Tactile Percussion) involves a "firm and interrupted" push, creating a wave-like fluid movement that allows the detection of organ enlargement (e.g., liver), masses, or pregnancy in small ruminants that cannot be felt through either method alone.

Modified abdominal ballottement enhances accuracy of RIS diagnosis, even in field situations or remote communities. The Modified Ballottement Technique involves locating the rumen, typically in the left paralumbar fossa and the region caudal to an imaginary line drawn from the point of the elbow to the top of the last rib (Bayne and Edmondson, 2020; Petzl et al., 2026). The technique involves applying deep, firm-pushing stroke, inward thrust using a clenched fist into the left paralumbar fossa, and upward pressure against the left flank, where foreign bodies are frequently located (Karadaev, 2015). Crucially, the hand should remain in contact with the abdomen after the initial push (Abdisa, 2017). The goal is to specifically detect the presence of dense, solid mass that is "doughy" to "hard" in consistency, which would indicate compacted foreign material in the rumen; distinct from normal rumen contents that can feel soft and soggy (Table 2). RIS will typically exhibit a lack of rebound, feeling solid and heavy against the hand from tightly packed palpable hard or doughy mass in the mid-to-caudal left abdomen that does not "bounce" or produce a fluid wave (Table 2). The key diagnostic finding for RIS therefore is the sensation of a solid hard or doughy mass of heavily impacted rumen (Figure 2). The polythene masses indicative of RIS usually occupy the flank and the lower quadrants (Terra and Reynolds, 2020).

Modified abdominal ballottement, a refined, low-cost technique has shown high accuracy rates—ranging from 80% to 95% of field cases, especially small ruminants, allowing for earlier detection of impacted masses before irreversible systemic damage occurs (Petzl et al., 2026). As a physical, manual technique, it requires no specialized equipment, making it highly suitable for field conditions and small holder farmers.

Modified ballottement technique serves a "triad of purpose". First, it can be utilized for the benefit of remote areas and rural communities to diagnose RIS in their ruminants, as most of the livestock are kept on a semi-intensive rearing. Second, this technique can be used in cases where equipment such as imaging devices, laparoscopy and diagnostic marker assay are not freely accessible. Third, ballottement can be employed by trained community-based animal health workers, veterinary nurses, veterinary technicians, field veterinary assistants or paraprofessionals to detect and report RIS in ruminant livestock.

Table 2 Findings following abdominal ballottement tests on healthy and RIS ruminants**:** distinctions between normal and RIS rumen reactions upon abdominal ballottement in the mid-to-caudal left flank. Succussion technique refers to vigorous shaking of the left flank by rocking side to side. Typical result is a splashing or fluid-sloshing sound on auscultation. In RIS, succusion yields a dull thud or lack of splashing sounds due to mass

Feature	Normal Rumen	RIS Rumen
Consistency	Dorsal resilient gas cap, mid doughy fiber mat of firmer fibrous material and bottom with rumen fluid.	Uniformly firm: hard mass or a very doughy in the mid-to-ventral abdomen
Rebound	Soft, elastic rebound or resilient "bounce". Rumen walls yield to pressure and returns quickly.	Indistinct, reduced or absent rebound. Mass moves as a single, sluggish unit.
Sound	Splashing or "tinkling" fluid wave	Dull or absent fluid wave/splashing
Rumen Motility	Normal, Regular, consistent ruminal contractions cycles (typically 1-3 per minute) in the left paralumbar fossa.	Reduced or absent (rumen stasis/ atony) due to the heavy, static mass.
Abdominal Contour	Normal symmetrical or slight filling of the left flank within a normal range.	Ventral left abdomen often visibly distended (bilateral in severe cases).
Succussion splash	a "slushy" or splashing sound	dull thud
Pain Response	Generally non-painful.	May show signs of abdominal discomfort during deep palpation.

CONCLUSION

Ruminal impaction syndrome (RIS) resulting from the ingestion of polythene materials remains an emerging and serious gastrointestinal disorder that threatens ruminant health, welfare, and sustainable production, particularly in developing regions where environmental plastic pollution is widespread. The high prevalence, neglect and "vicious cycle" continually and severely hamper the efficiency of extensive and semi-intensive ruminant livestock production systems, with colossal economic loss to livestock stakeholders and considerable health hazards to humans in endemic regions. Current identification and treatment methods have significant deficiencies. Laparoscopy, nanotechnology, establishment of specific diagnostic markers will provide non-invasive, high precision diagnosis and instant minimally invasive treatment of RIS. The integration of modified abdominal ballottement with the analysis of putative markers provides an effective field-level diagnostic framework to allow early detection of RIS. The multi-tiered, technology-driven approach for the management of RIS in ruminants represents the new standard of care to maximize long-term livestock health, improve individual survival rates and safeguard the economic viability of livestock production systems.

CONFLICT OF INTEREST

The authors declare no competing interests regarding the authorship, content or publication of this article.

CONTRIBUTORS

All content herein in this article is solely by the authors. PBB conceptualized and wrote the initial review manuscript draft. PBB also generated data on laparoscopy, nanotechnology, diagnostic markers prospects and the economics of RIS. AAH**,**

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Utjecaj sindroma ruminalne impakcije na produktivnost preživara: Evaluacija protokola za brzu dijagnostiku i liječenje

SAŽETAK

Sindrom ruminalne impakcije (RIS) je novonastali, težak i potencijalno smrtonosan gastrointestinalni poremećaj koji pogađa preživare u urbanim, poluurbanim i periurbanim naseljima, sa sve većim širenjem u ruralne zajednice u zemljama u razvoju. RIS nastaje uslijed ingestije neprobavljivih predmeta koji se akumuliraju u buragu i ometaju prolaz ingesta kroz donji probavni trakt, što dovodi do teške impakcije, poremećaja probave, perzistentnog timpanizma, produženog morbiditeta, letargije, a u teškim slučajevima i smrti. Dodatno, RIS dovodi do gubitaka životinja, smanjene proizvodnje mlijeka i mesa te skupih i često neefikasnih tretmana. Nadalje, RIS pokazuje visoku prevalenciju koja se održava kroz začarani krug. Definitivna dijagnoza i liječenje često se oslanjaju na eksplorativnu rumenotomiju. Pogođene životinje nerijetko dospijevaju u terminalni stadij bolesti, što ograničava terapijske mogućnosti. Hirurški ishodi su često nepovoljni i najčešće povezani sa postoperativnim komplikacijama. Nadalje, mikroplastika, nanoplastika, ksenobiotičke hemikalije i teški metali mogu dospjeti u ruminalnu tečnost, bioakumulirati se u tkivima i ući u prehrambeni lanac putem mlijeka i mesa, gdje ispoljavaju štetne toksične efekte kod životinja i ljudi. Uprkos visokoj učestalosti i značajnom ekonomskom i zdravstvenom opterećenju, ne postoje uspostavljeni državni propisi niti standardizirane smjernice za dijagnostiku i liječenje RIS-a, što ga čini važnim, ali zanemarenim poremećajem kojeg veterinari često tretiraju empirijski. Integracija rumenoskopije zajedno sa nanotehnologijom, dijagnostičkim markerima i modificiranom tehnikom abdominalne palpacije (ballottement) može unaprijediti tačnu dijagnostiku, dok terapijska laparoskopija može omogućiti pravovremeno liječenje. Ovaj pregledni članak procjenjuje značajan utjecaj RIS-a na zdravlje i produktivnost preživara. Konačno, cilj je uspostaviti učinkovite dijagnostičke puteve i terapijske protokole koji se mogu primijeniti od strane veterinara i donosilaca politika, kako bi se poboljšalo zdravlje životinja, unaprijedila dobrobit i osigurala održiva produktivnost sistema uzgoja preživara.

Ključne riječi: Burag, dijagnostika, impakcija, liječenje, produktivnost.

REVIEW ARTICLE

Clinical application of dog-assisted therapy – benefits for patients, healthcare professionals, and dogs: A review article

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ABSTRACT

A significant number of recent studies confirm the application of dog-assisted therapy in healthcare institutions. Dog-assisted therapy, as part of animal-assisted therapy (AAT), is increasingly gaining importance in clinical practice, both in working with patients and in supporting healthcare professionals. This systematic review analyzes 20 studies published between 2025 and 2026, with a focus on dog-assisted interventions in healthcare institutions involving various populations. The search was conducted in the PubMed, Google Scholar, and ScienceDirect databases. The selection process followed the PRISMA methodology: identification (n = 105), screening (n = 91), eligibility assessment (n = 36), and final inclusion (n = 20). Included studies involved children with autism (n = 4), children and adolescents (n = 1), oncology patients (n = 2), elderly patients (n = 3), individuals with mental health disorders (n = 2), healthcare professionals (n = 3), the general population (n = 3), and specific categories such as palliative care, chronic pain, cardiovascular rehabilitation, and special education (n = 2). The results show that dog-assisted therapy contributes to reduced stress and anxiety, improved emotional regulation, enhanced social skills, and better quality of life across different age groups. Among healthcare professionals, dog-assisted interventions were associated with reduced burnout and increased psychological resilience. Dog-assisted therapy has a significant positive effect on patients and healthcare professionals, with the need for further research and integration into multidisciplinary teams. In the context of Bosnia and Herzegovina, this form of therapy is underdeveloped, and no studies were identified in internationally indexed databases, indicating a research gap and the need for further development and implementation of this method in the healthcare system.

Keywords: Bosnia and Herzegovina, dog-assisted therapy, dog welfare, healthcare professionals, healthcare workers

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INTRODUCTION

The beneficial influence of animals on human psychology and health has been recognized since antiquity. The earliest documented inclusion of animals in therapeutic programs dates back to medieval Belgium, while in Germany, animals were engaged in therapeutic activities for socially disadvantaged individuals. Later, Boris Levinson and Konrad Lorenz emphasized the significance of animals in therapy as mediators between humans and nature (Bachi and Parish-Plass, 2017).

According to the American Veterinary Medical Association (AVMA, 2019), animal-assisted therapy (AAT) constitutes a targeted intervention in which the animal meets specific criteria and is integrated into the treatment process. Dog-assisted therapy, conducted by qualified professionals, is designed to enhance physical, social, emotional, and cognitive functioning.

AAT has been shown to improve neuromuscular abilities (strength, endurance, mobility), motor skills (fine and gross movements), cognitive functions (multitasking, problem-solving, attention), sensory functions (visual, auditory, olfactory, tactile), communication skills, balance, and carrying capacity (AVMA, 2019). Interaction with animals has been demonstrated to release beta-endorphins and activate lymphocytes, thereby fostering positive emotions and reducing pain perception (Braun et al., 2009).

Hospitalization and prolonged rehabilitation frequently result in separation from everyday environments, family, and pets, which may lead to loneliness and adverse psychological outcomes (Burres et al., 2020).

AAT programs employ teams of humans and animals to deliver targeted therapeutic interventions (IAHAIO, 2014). While interaction with animals can yield biological, psychological, and social benefits, the understanding of their application in hospital and rehabilitation practice remains limited (Gee et al., 2025).

Different species are utilized in AAT depending on therapeutic objectives and patient needs. Hippotherapy has proven effective in the rehabilitation of children with neurological impairments and developmental delays, with documented improvements in motor function, balance, and movement control (MacKinnon et al., 2019). Cats are employed in geriatric institutions and with patients experiencing anxiety, while birds such as parrots and canaries are incorporated into programs of emotional support and communication stimulation.

Dogs, however, are particularly suitable for therapeutic interventions due to their trainability, adaptability to diverse environments, and the existence of standardized training and certification programs, which enhance participant safety and intervention quality (Katica et al., 2025).

The most commonly employed therapeutic breeds are characterized by calm temperament, high sociability, and friendliness toward humans. Labrador Retrievers are distinguished by intelligence, composure, and their ability to bond with both children and adults, making them prevalent in hospitals and rehabilitation centers. Golden Retrievers are valued for patience and gentleness, rendering them suitable for work with children and the elderly. Poodles (standard, miniature, and toy) are appreciated for their hypoallergenic properties, intelligence, and adaptability, particularly in psychological therapies. Cavalier King Charles Spaniels, as smaller dogs, are well-suited to hospital environments, providing a sense of closeness and security (Fine, 2019; Serpell, 2017).

Other breeds include German Shepherds, valued for loyalty and their capacity to instill a sense of safety; Beagles, noted for playfulness and friendly temperament; and Border Collies, employed in therapies involving active interaction and play. In institutional settings such as hospitals, schools, and nursing homes, Labrador Retrievers, Golden Retrievers, Poodles, and Beagles are most frequently utilized (Fine, 2019; Serpell, 2017).

The effectiveness of therapeutic interaction may also be influenced by the dog's visual characteristics. Lavan and Knesl (2015) observed that darker-coated dogs, particularly black, may evoke perceptions of threat in some individuals, thereby reducing their suitability in certain interactions.

Dog-assisted therapy is increasingly gaining recognition in clinical practice, with research highlighting its benefits across diverse patient populations as well as among healthcare professionals. Numerous studies underscore the positive effects of interaction with dogs in reducing stress, anxiety, and professional burnout, while enhancing feelings of safety, support, and emotional connectedness (Fine, 2019). Dogs contribute to a more relaxed work environment, foster social interaction, and facilitate the establishment of therapeutic relationships (Barker et al., 2005).

Stress assessment in therapy dogs often involves physiological indicators, particularly salivary cortisol measurement as a biomarker of hypothalamic–pituitary–adrenal axis activation (Cobb et al., 2016). While short-term cortisol fluctuations may reflect adaptive responses, prolonged elevations can negatively affect health and immune function (Chrousos, 2009). Interpretation of these findings requires caution, as cortisol may also reflect positive arousal, and high individual variability further complicates generalization (Starling et al., 2013; Cobb et al., 2016).

The welfare of therapy dogs represents a critical dimension for ensuring the quality and sustainability of interventions. Although adequately structured activities do not appear to pose significant risks to animals, the literature highlights a lack of validated and standardized methods for objective assessment of stress and long-term welfare, despite increasing research employing physiological and behavioral indicators (Gee et al., 2021; Kogan et al., 2019).

Behaviors such as lip licking, yawning, panting, avoidance of contact, or withdrawal may signal stress or discomfort, but require contextual interpretation as they may also be associated with positive arousal (Dreschel and Granger, 2005).

Recent literature on this subject predominantly originates from Western European and North American contexts, while publications from transitional countries remain relatively scarce. Dog-assisted interventions in healthcare settings have attracted increasing attention from researchers and clinicians in recent years.

This paper aims to analyze studies published between 2025 and 2026 on dog-assisted therapy, highlight its benefits for various patient groups, and assess the extent of such practices in Bosnia and Herzegovina.

MATERIALS AND METHODS

The period 2025–2026 was selected in order to include the most recent studies on dog-assisted therapy, with the aim of highlighting current trends and research progress in both international and regional contexts. Sources were chosen based on their relevance and contribution to understanding the therapeutic effects of dogs, with particular attention to the research gap in Bosnia and Herzegovina and the potential for future pioneering studies.

Search Strategy and Eligibility Criteria

The search strategy was defined using the following keywords: "dog-assisted therapy," "patients," "healthcare professionals," and "dog welfare," restricted to studies published between 2025 and 2026. Searches were limited to articles containing these terms in the title or abstract.

Inclusion criteria encompassed studies explicitly analyzing dog-assisted therapy, involving patient or healthcare professional populations, and employing empirical research designs such as randomized controlled trials (RCTs), systematic reviews, meta-analyses, national surveys, and pilot studies. These studies provided relevant empirical data on the effects of dog-assisted therapy in various clinical and social contexts.

Exclusion criteria applied to studies not published within 2025–2026, those not addressing dog-assisted therapy, those lacking relevant populations (patients or healthcare professionals), or those of a purely theoretical nature without empirical data. Additionally, studies focusing on other animal species or failing to meet the methodological standards defined for this review were excluded.

Data Sources

The literature search was conducted across multiple scientific databases, including PubMed, Google Scholar, ScienceDirect, and Web of Science, to ensure comprehensive coverage of clinical and research studies in this field.

Study Selection Process

Following the initial search, identified studies underwent a multi-phase selection process. In the first phase, titles and abstracts were screened, after which potentially relevant articles were subjected to full-text analysis in accordance with eligibility criteria. Ultimately, 20 studies (n = 20) were included in the qualitative synthesis.

Categorization and Characteristics of Included Studies

A total of 20 studies met all inclusion criteria: Hüsgen et al., 2025; Mulraney et al., 2025; Massouda et al., 2025; Çaksen , 2025; Moe et al., 2025; Gee et al., 2025; Kelker et al., 2025; Núñez et al., 2025; Fernández-Sánchez et al., 2025; Sim et al., 2025; Risberg et al., 2025; Marciniuk et al., 2025; Song et al., 2025;

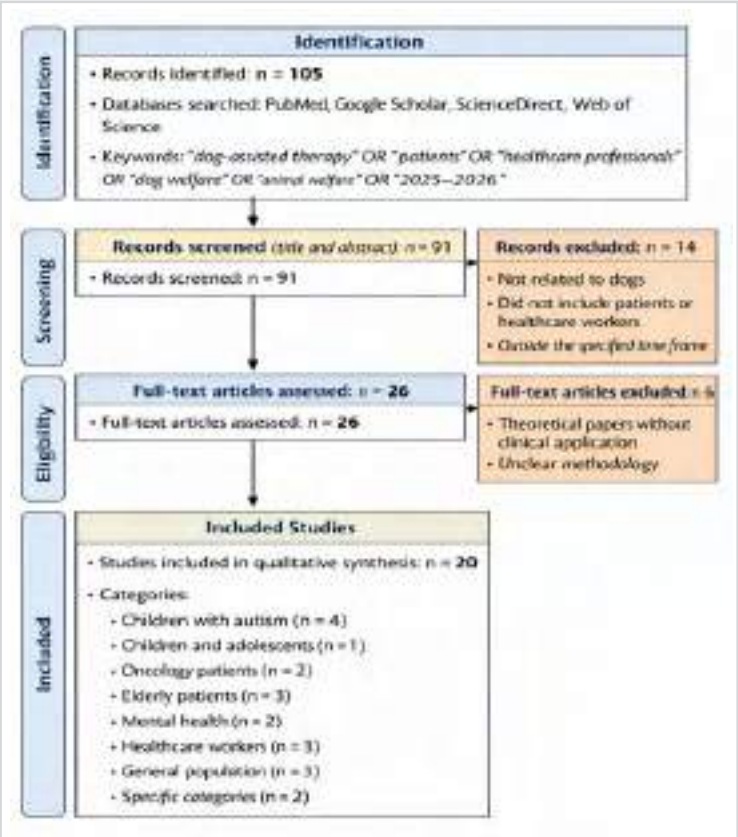

Figure 1 Flow of study selection
A total of 105 records were identified through database searches. After removing duplicates and irrelevant records, 91 were excluded prior to screening. Of the 26 studies assessed in full text, 20 met the inclusion criteria and were incorporated into the final synthesis.

Shoesmith et al., 2026; Wong et al., 2026; Hamdan et al., 2026; Shoesmith et al., 2026; Aguiar et al., 2025; Giuliano et al., 2025; Krause-Parello et al., 2025.

Most studies were conducted in the United States (n = 4), followed by the United Kingdom (n = 2) and Spain (n = 3). The remaining studies were conducted in the Netherlands, Australia, Sweden, Turkey, China, Jordan, Malaysia, Brazil, Italy, Poland, Sweden, and South Korea (each n = 1). The included studies were systematically classified according to the populations investigated, including children with autism spectrum disorder, hospitalized children and adolescents, oncology patients, older adults, patients undergoing rehabilitation, individuals with mental health disorders, healthcare professionals, the general population, and specific groups such as students, schoolchildren, and institutionalized individuals. This categorization enabled comparative analysis of the effects of dog-assisted therapy across diverse clinical and social contexts.

Validation of Sources and Data Collection

Validation of included studies was ensured through DOI identifiers or PubMed PMID numbers, thereby guaranteeing credibility and traceability. Data were systematically collected and organized into a table including authors, year of publication, country, study design, sample, population category, outcomes, key findings, and full APA references, thus enabling transparent and consistent analysis of the included works.

Data Synthesis

Data synthesis was conducted through qualitative analysis of the 20 included studies. Results were thematically organized according to populations and research outcomes, with the aim of identifying patterns and key findings regarding the effects of dog-assisted therapy. Particular emphasis was placed on comparing methodological approaches and identifying major research trends in this field. Risk of bias assessment was not performed, which represents a methodological limitation of this review.

RESULTS

The studies covered a range of clinical and population groups: children with autism (n = 4), children with autism (n = 4), children and adolescents (n = 1), oncology patients (n = 2), elderly patients (n = 3),

individuals with mental health disorders (n = 2), healthcare professionals (n = 3), the general population (n = 3), and specific categories such as palliative care, chronic pain, cardiovascular rehabilitation, and special education (n = 2). The majority of included studies (n ≈ 14/17) reported reductions in anxiety and stress levels, while randomized controlled trials (n = 4) consistently demonstrated statistically significant positive effects of dog-assisted interventions, confirming the consistency of findings in studies with higher methodological quality.

Table 1 Overview of studies conducted between 2025 and 2026

Authors Year Country	Study design	Sample (n)	Patient category	Main outcome	Key findings
Hüsgen et al. 2025 Netherlands	Observational study	n = 5 adolescents: two boys aged 12 and 15, and three girls aged 13, 18, and 18	Children with autism	Social interaction anxiety	Improved social interaction and reduced anxiety
Mulraney et al. 2025 Australia	Systematic review	n = 14 (meta-analysis) and n = 13 (meta-aggregation); mixed designs (RCTs, cohort, cross-sectional, longitudinal, single-group and case studies)	Children with autism	Social skills, emotional regulation	Improvement in social skills and emotional regulation
Massouda et al. 2025 USA	Pilot clinical trial	n = 39 (AAT: 18; control: 21), aged 7–14 years	Pediatric patients	Anxiety, pain	Reduction in anxiety and pain
Çaksen 2025 Türkey	Review / clinical report	n/a	Children with cancer	Anxiety, emotional distress	Reduction in anxiety and emotional distress
Moe et al. 2025 Sweden	Systematic review	n = 30 (from 2,380 initially identified studies)	Children and adolescents	Cognitive and socio-emotional outcomes	Improvements in cognitive and socio-emotional outcomes
Gee et al. 2025 USA	Randomized controlled trial (RCT)	n = 44 hospitalized patients	Older patients	Mood, anxiety	Improved mood and reduced anxiety
Kelker et al. 2025 USA	Randomized controlled trial (RCT)	n = 80 children	Pediatric patients	Mood, anxiety	Significant reduction in anxiety
Núñez et al. 2025 Spain	Controlled trial	n = 30 (intervention group: 15; control group: 15), matched by diagnosis and demographics	Adolescent females	Anxiety	Reduction in anxiety
Fernández-Sánchez et al. 2025 Spain	Controlled study	n = 25 adults with ASD	Adults with ASD	Functional outcomes	Improvement in functional outcomes
Sim et al. 2025 Malaysia	Meta-analysis	n = 15 included studies (from 290 identified); meta-analysis: n = 14 studies	Young adults	Stress, anxiety	Reduction in stress and anxiety
Shoesmith et al.	Survey study	n = 31 respondents out of	General population	Implementation	Widespread

Authors Year Country	Study design	Sample (n)	Patient category	Main outcome	Key findings
2025 UK		72 distributed surveys (response rate: 41.3%)		/application	implementation in healthcare settings
Aguiar et al. 2025 Brazil	Systematic review	n = 46; mixed designs (controlled trials, retrospective studies, historical records, systematic reviews)	Multiple populations	Therapeutic effects (overall)	Reduction in anxiety and depressive symptoms; improved socialization and cognitive stimulation; reduced perceived pain; increased treatment
Giuliano et al. 2025 Italy	Pilot study	n = 10 children and 4 therapy dogs; weekly AAS sessions (60 min) over 90 days	Children with ASD	Social functioning	Improved social functioning
Krause-Parello et al. 2025 USA	Interventional study	n = 28 female military veterans with PTSD	Veterans	Psychological well-being	Improvement in psychological well-being
Risberg and Edner 2025 Sweden	Case study	n = 1 (34-year-old patient)	Patient with atypical autism and depressive symptoms	Long-term effects on depression	Dog-assisted therapy associated with reduced depressive symptoms and improved emotional state over time
Marciniuk et al. 2025 Poland	Review article	~20 studies	Patients with depression and anxiety	Effectiveness of DAA on depression and anxiety	Positive effects on symptom reduction and emotional state; further empirical studies needed
Song et al. 2025 South Korea	Narrative/ systematic review	n/a	Various populations (stress and depression)	Stress and depression	Reduction in stress and depressive symptoms; improved psychological well-being
Wong et al. 2026 China	Randomized controlled trial (RCT)	n = 64 children (6–15 years) with ASD	Children with autism	Quality of life, psychosocial health	Improved quality of life and psychosocial health

Authors Year Country	Study design	Sample (n)	Patient category	Main outcome	Key findings
Hamdan et al. 2026 Jordan	Randomized controlled trial (RCT)	n = 49 patients	Children with autism	Cooperation, anxiety	Improved cooperation and reduced anxiety
Shoesmith et al. 2026 UK	Systematic review	n = 33 (29 RCTs; 5 high-quality); positive DAI effects: social skills 57%, symptoms 50%, depression 43%, agitation 33%; CONSORT adherence 48.6%	Children and adults	Social and behavioral outcomes	Positive social and behavioral outcomes

The analysis of the included studies indicates consistent positive effects of dog-assisted therapy across different populations, alongside notable methodological heterogeneity that limits the direct comparability of the results.

DISCUSSION

Despite consistent positive findings, notable differences were observed in the quality and design of the included studies. Randomized controlled trials (Kelker et al., 2025; Wong et al., 2026; Hamdan et al., 2026) represent the highest level of evidence and consistently demonstrate reductions in anxiety and improvements in psychological outcomes. However, the limited number of such studies and relatively small sample sizes reduce the generalizability of these findings. Observational and pilot studies (Hüsgen et al., 2025; Giuliano et al., 2025) confirm similar trends but do not allow for strong causal inferences. Systematic reviews and meta-analyses (Sim et al., 2025; Shoesmith et al., 2025) further corroborate the overall positive effect, while highlighting pronounced heterogeneity in study design, intervention duration, and measurement instruments.

The analysis also indicates variability in effect sizes across studies, which may be attributable to differences in participant characteristics, type of intervention, therapy intensity, and methodological limitations such as selection bias and lack of blinding. This heterogeneity complicates direct comparison of results and underscores the need for standardized research protocols.

Overall, the available evidence points to the promising therapeutic potential of dog-assisted interventions, particularly in reducing anxiety and improving psychosocial functioning. Nevertheless, more methodologically rigorous and longitudinal studies are required to draw firmer conclusions.

The studies identified several methodological limitations, including small sample sizes, limited standardization of interventions, lack of longitudinal follow-up, and challenges in objectively evaluating outcomes. Broader challenges were also noted, such as the need for specialized professional training, interdisciplinary coordination, appropriate regulatory frameworks, and validation of evidence-based protocols (Aguiar et al., 2025).

From a clinical perspective, findings suggest that AAT may serve as a valuable complementary intervention in hospitals, rehabilitation, and trauma programs, contributing to reduced anxiety and improved psychological well-being. Observed effects across diverse populations—including individuals with PTSD, hospitalized patients, and those with chronic illnesses—confirm the broad applicability of this intervention (Marchand, 2023).

Dog-assisted therapy in children with autism spectrum disorder has been associated with improvements in social behavior, communication, and reductions in anxiety (Sim et al., 2025). Similarly, Giuliano et al. (2025) highlight the complexity of physiological and hormonal responses during therapy, with findings suggesting enhanced social behavior without adverse effects on dogs, while emphasizing the need to monitor canine welfare. These results align with earlier research confirming the positive effects of AAT, while also noting methodological limitations such as small samples, protocol heterogeneity, and lack of standardized outcomes (Çetin and Çuhadar, 2021; Mulraney et al., 2025).

Comparable positive effects have been observed among oncology patients, where dog-assisted therapy has been linked to reductions in psychological distress, fear, and pain perception. These findings are consistent with earlier studies reporting improvements in mood and emotional support during treatment (Pinto et al., 2021; Holder et al., 2020).

The presence of therapy dogs in hospital settings has been associated with reduced anxiety and improved hospitalization experiences (Hernández-Espeso et al., 2026), including greater patient cooperation and reduced discomfort. These findings correspond with earlier research indicating higher patient satisfaction and improved postoperative recovery (Harper, 2015).

Although dog-assisted therapy is most often considered in terms of patient benefits, positive effects have also been observed among healthcare professionals, including reductions in stress and burnout (Acquadro Maran et al., 2022). These findings build on earlier studies reporting improvements in team cohesion, job satisfaction, and physiological stress parameters (Brooks et al., 2018).

Despite these encouraging results, the included studies exhibit significant methodological heterogeneity in terms of design, sample size, and measurement instruments. Observational studies (pre-post, cohort, and cross-sectional) predominate, while fewer randomized controlled trials are available (Acquadro Maran et al., 2022). Observational studies consistently indicate positive associations between dog-assisted interventions and reduced perceived stress, but do not permit causal conclusions. Conversely, available RCTs provide stronger evidence but are constrained by small samples and short intervention durations.

Moreover, findings regarding the duration of effects are inconsistent: some studies report long-term benefits, while others note only short-term improvements, further underscoring the need for longitudinal and methodologically robust research. Overall, the strength of evidence can be rated as moderate to low, due to the predominance of observational studies and limitations in experimental design.

Existing research suggests that therapy dogs under controlled conditions generally do not exhibit significant increases in stress; however, inadequate conditions-such as prolonged sessions, lack of rest, and excessive stimulation-may lead to elevated physiological stress indicators (Gee et al., 2021). The importance of animal selection, training, and experience has also been emphasized, with adequately prepared and experienced dogs demonstrating better adaptive responses (Kogan et al., 2019).

A crucial aspect is the relationship between the dog and its handler, which plays a key role in stress regulation. Secure attachment between dog and handler can act as a protective factor in stressful situations, enabling the dog to feel safer and adapt more easily to therapeutic environments (Payne et al., 2015). At the same time, the handler's ability to recognize subtle signs of stress in the dog is essential for timely intervention and safeguarding animal welfare (Mariti et al., 2012).

Within this framework, the application of the "One Welfare" approach emphasizes the inseparable link between human and animal welfare, underscoring that the quality of therapeutic outcomes directly depends on the welfare of the animals involved (WOAH 2022). Its implementation requires integrating the protection of therapy dogs' physical and psychological health into all stages of intervention planning and delivery.

Accordingly, it is necessary to develop and implement standardized guidelines encompassing animal welfare assessment, ethical oversight, and regulation of intervention duration and intensity. In this context, the importance of clearly defined protocols is emphasized, including session time limits, appropriate selection of therapy dogs, and professional supervision of interventions (Ng et al., 2015).

The welfare of therapy dogs must be a central element in the development and implementation of dog-assisted therapy. These animals should not be regarded merely as therapeutic resources, but as active participants whose well-being directly influences the quality, safety, and sustainability of therapeutic interventions.

Comparison with global trends indicates that dog-assisted therapy in Bosnia and Herzegovina remains in an early stage of development. While standardized protocols, accreditation systems, and institutionally integrated services have been established in developed countries (Shoesmith et al., 2025; Hernández-Espeso et al., 2026), in Bosnia and Herzegovina this intervention has not yet been systematically regulated or formally integrated into the healthcare and education systems.

This study has several limitations that must be considered when interpreting the results. The review was restricted to a relatively short time frame (2025–

2026), which may have excluded relevant earlier studies that could contribute to a broader understanding of dog-assisted therapy. However, this temporal restriction was deliberately chosen to highlight the most recent evidence and contemporary trends in the application of this intervention.

The total number of included studies (n = 20) reflects the application of strictly defined inclusion and exclusion criteria, encompassing only those studies that fully met the methodological requirements of this review. Consequently, a comprehensive meta-analysis was not feasible, and results were interpreted through qualitative synthesis without statistical aggregation.

Heterogeneity among the included studies in terms of design, populations, interventions, and outcomes may affect comparability and hinder the formulation of unified conclusions, a common challenge in similar research (Kamioka et al., 2014; Moe et al., 2025; Aguiar et al., 2025). Although the focus was on dog-assisted therapy, it is possible that some studies included interventions that were not strictly standardized, which may influence the consistency of interpretation.

CONCLUSION

Dog-assisted therapy represents a significant complementary intervention that demonstrates positive effects in reducing anxiety, improving emotional regulation, social skills, and quality of life across diverse populations, while also potentially contributing to stress reduction among healthcare professionals. The available literature reveals important methodological limitations, including study heterogeneity, small sample sizes, and lack of standardized interventions, which restrict the ability to draw firm and generalizable conclusions. There is a clear need for the standardization of dog-assisted therapy, encompassing the definition of intervention protocols, session duration and intensity, and outcome evaluation criteria, in order to ensure consistency, safety, and comparability of results across studies. Dog-assisted therapy constitutes a promising complementary intervention with potential for integration into modern, holistically oriented healthcare systems. However, its sustainable and widespread application depends on the development of standardized therapeutic protocols, the generation of methodologically rigorous scientific evidence, and consistent adherence to ethical principles. In Bosnia and Herzegovina, particular emphasis is placed on the need for a systemic approach to the introduction of dog-assisted therapy, including the development of national guidelines, strengthening of cross-sectoral collaboration, and the advancement of educational and research capacities.

CONFLICT OF INTEREST

The author declares no conflict of interest.

Abbreviations

AAT: Animal-Assisted Therapy
CAT: Canine-Assisted Therapy

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Klinička primjena terapije uz pomoć pasa – koristi za pacijente, zdravstvene radnike i pse: Pregledni rad

SAŽETAK

Značajan broj novijih istraživanja potvrđuje primjenu terapije uz pomoć pasa u zdravstvenim ustanovama. Terapija uz pomoć pasa, kao dio terapije uz pomoć životinja (AAT), sve više dobija na značaju u kliničkoj praksi, kako u radu sa pacijentima, tako i u pružanju podrške zdravstvenim profesionalcima. Ovaj sistematski pregled analizira 20 studija objavljenih između 2025. i 2026. godine, s fokusom na intervencije uz pomoć pasa u zdravstvenim ustanovama koje uključuju različite populacije. Pretraga je provedena u bazama podataka PubMed, Google Scholar i ScienceDirect. Proces selekcije pratio je PRISMA metodologiju: identifikacija (n = 105), pregled (n = 91), procjena podobnosti (n = 36) i konačno uključivanje (n = 20). Uključene studije obuhvatile su: djecu s autizmom (n = 4), djecu i adolescente (n = 1), onkološke pacijente (n = 2), starije osobe/pacijenti (n = 3), osobe s poremećajima mentalnog zdravlja (n = 2), zdravstvene profesionalce (n = 3), opću populaciju (n = 3) te specifične kategorije poput palijativne brige, hronične boli, kardiovaskularne rehabilitacije i specijalnog obrazovanja (n = 2). Rezultati pokazuju da terapija uz pomoć pasa doprinosi smanjenju stresa i anksioznosti, poboljšanju emocionalne regulacije, unapređenju socijalnih vještina i boljem kvalitetu života u različitim dobnim skupinama. Kod zdravstvenih profesionalaca, intervencije uz pomoć pasa povezane su sa smanjenjem sagorijevanja na poslu (eng. *burnout*) i povećanjem psihološke otpornosti. Terapija uz pomoć pasa ima značajan pozitivan učinak na pacijente i zdravstvene profesionalce, uz potrebu za daljnjim istraživanjima i integracijom u multidisciplinarne timove. U kontekstu Bosne i Hercegovine, ovaj oblik terapije je nedovoljno razvijen. U međunarodno indeksiranim bazama podataka nisu identificirana istraživanja na ovu temu, što ukazuje na istraživački jaz i potrebu za daljnjim razvojem i implementacijom ove metode u zdravstveni sistem.

Ključne riječi: Bosna i Hercegovina, dobrobit pasa, terapija uz pomoć pasa, zdravstveni radnici, zdravstveni profesionalci.

RESEARCH ARTICLE

Temporal alterations in plasma oxidative stress and antioxidant defence in experimentally induced hypothyroid and hyperthyroid rats

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ABSTRACT

The plasma oxidant-antioxidant response to chronic hypothyroidism and hyperthyroidism was evaluated in rats across three cross-sectional sampling points. Forty-nine male Wistar rats were used. Seven were sampled on day 0 to establish baseline values, and the remaining 42 received standard drinking water (control), 0.05% propylthiouracil (PTU), or 0.0012% L-thyroxine (L-T4) for six weeks (n = 14 per group). Blood was sampled on day 0 (baseline), week 3, and week 6 for serum thyroid hormones (TSH, TT3, TT4, fT3, fT4) and plasma TBARS, NO, 8-OHdG, SOD, catalase (CAT), GSH-Px, total glutathione (GSH), and total antioxidant status (TAS). Data were analysed using one-way ANOVA with Tukey's HSD post-hoc test. Hormone profiles confirmed model induction. Body weight decreased in both treatment groups by week 6, with hypophagia in hypothyroid and hyperphagia in hyperthyroid rats ($p < 0.001$). Plasma TBARS levels increased in both states and peaked in hypothyroid rats at week 6. Plasma NO levels decreased at week 3 and remained suppressed in hyperthyroid rats. 8-OHdG was unchanged. SOD increased in both treatment groups, while CAT showed a non-significant elevation trend in hypothyroid rats at week 6. GSH-Px and GSH were lowest in hypothyroid rats. TAS declined over time in both treatment groups. Both dysthyroid states drive sustained plasma lipid peroxidation with partial antioxidant compensation. The persistent NO reduction in hyperthyroidism suggests early vascular vulnerability warranting further study.

Keywords: 8-OHdG, antioxidant enzymes, hyperthyroidism, hypothyroidism, lipid peroxidation, nitric oxide, rat

INTRODUCTION

Thyroid hormones (THs) regulate energy metabolism, basal metabolic rate, growth, and tissue oxygen consumption (Mullur et al., 2014; Bianco et al., 2014). Iodine deficiency remains the most common cause of hypothyroidism worldwide, while iatrogenic and autoimmune forms of hyperthyroidism are increasingly recognised in iodine-replete regions (Vanderpump, 2011; Taylor et al., 2018). Both conditions are clinically important in veterinary practice. Hypothyroidism is one of the most common canine endocrinopathies, with a reported prevalence of 0.2 to 0.8% (Panciera, 1994; Scott-Moncrieff, 2007), whereas feline hyperthyroidism is among the most frequently diagnosed endocrine disorders in older cats (Carney et al., 2016; McLean et al., 2014). Beyond these well-known clinical entities, the systemic impact of thyroid dysfunction is closely linked to oxidative metabolism. Comparable thyroid-

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related shifts in serum biomarkers have also been described in poultry models such as post-moult and zinc-induced moulted laying hens (Anwar et al., 2018; Idris et al., 2023).

THs directly modulate mitochondrial function and oxygen consumption, which alters reactive oxygen species (ROS) generation at the respiratory chain (Venditti and Di Meo, 2006; Cano-Europa et al., 2012; Mancini et al., 2016). Hyperthyroidism accelerates basal metabolism and ROS production. Hypothyroidism slows metabolic rate but is also linked to oxidative damage through impaired antioxidant defences, altered lipid handling, and elevated oxidised LDL (Sarandöl et al., 2005; Zha et al., 2015; Hosseini et al., 2023; Fasciolo et al., 2023). Recent reports confirm that this oxidant-antioxidant imbalance occurs across thyroid disease states and that redox biomarkers carry diagnostic and prognostic value (Kochman et al., 2021; Macvanin et al., 2023). When sustained, the imbalance drives injury to lipids, proteins, and DNA, and contributes to cardiovascular, neurodegenerative, metabolic, and inflammatory disease (Hybertson et al., 2011; Kalyanaraman, 2013).

Experimental studies have shown that dysthyroid states alter tissue lipid peroxidation, nitric oxide (NO) signalling, DNA oxidation, and the activities of major antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Reported results depend strongly on the tissues, species, and protocol, and they remain partly contradictory (Messarah et al., 2010; Mukherjee et al., 2014; Torres-Manzo et al., 2018; Hosseini et al., 2023). The plasma compartment, which is the most accessible matrix in routine veterinary practice, has received comparatively little attention, and few studies report longitudinal changes during sustained dysthyroidism. We previously reported that six-week PTU and L-T4 treatments alter haematological parameters in rats (Kandır and Keskin, 2016), raising the question of whether parallel changes also occur in the plasma oxidant-antioxidant network.

Asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor, can accumulate during oxidative stress through inhibition of dimethylarginine dimethylaminohydrolase (DDAH). Several studies report elevated ADMA in hyperthyroid patients and rats, providing a mechanistic link between dysthyroidism and reduced endothelial NO availability (Hermenegildo et al., 2002; Arikan et al., 2007; Teerlink, 2005; Cetin et al., 2022). In parallel, thyroid hormone-driven oxidative stress activates Nrf2-mediated antioxidant transcription in lymphoid and peripheral tissues of hyperthyroid animals (Costilla et al., 2019). The temporal relationship between TH disturbance and the plasma NO-antioxidant network has not been fully resolved.

We used propylthiouracil (PTU)- and L-thyroxine (L-T4)-induced hypo- and hyperthyroid rat models, which are well-established oral protocols that avoid the daily fluctuations of injection-based dosing (Guerrero et al., 1999; Bianco et al., 2014). Our aim was to characterise plasma lipid peroxidation (TBARS), NO, DNA oxidation (8-OHdG), and the antioxidant components SOD, CAT, GSH-Px, total GSH, and total antioxidant status (TAS) over six weeks of sustained hypothyroidism or hyperthyroidism in rats.

MATERIALS AND METHODS

Animals and housing

Forty-nine clinically healthy male Wistar rats (12 weeks old, 300 to 350 g) were obtained from Kobay Experimental Animals Laboratory (Ankara, Türkiye) and housed at the Selçuk University Veterinary Faculty Experimental Animals Unit. Rats were kept at 22 ± 2 °C and 50 ± 10% relative humidity under a 12-hour light/dark cycle, with two animals housed per cage. Standard pelleted rat chow (Bil-Yem Gıda San. ve Tic. Ltd. Şti., Ankara, Türkiye; ≥23% crude protein, ≤7% crude fibre, ≥6% crude fat, 2,600 kcal/kg metabolisable energy, 1.3 mg/kg iodine) and drinking water were provided *ad libitum*. Daily water consumption averaged approximately 50 mL per rat.

Experimental design

After a 10-day acclimatisation period, seven randomly selected rats were sampled on day 0 to provide a common pre-treatment baseline. The remaining 42 animals were randomly allocated to three groups (Control, Hypothyroid, Hyperthyroid; n = 14 per group) using simple randomisation by a random number generator. From each group, seven animals were sampled at week 3 and seven at week 6 by terminal cardiac puncture. Because animals were terminally sampled, each sampling time comprised an independent cohort, the study therefore follows a parallel-group, independent-samples design with three cross-sectional sampling points rather than a repeated-measures (within-animal) design. Treatments were administered in drinking

water. The Control group received standard chow and water *ad libitum*. The hypothyroid group received 0.05% (w/v) propylthiouracil (PTU; P3755, Sigma-Aldrich, St. Louis, MO, USA). The hyperthyroid group received 0.0012% (w/v) L-thyroxine (L-T4; T2376, Sigma-Aldrich) (Moulakakis et al., 2007; Kandır and Keskin, 2016).

Based on mean daily water intake, the estimated daily doses were approximately 25 mg/rat for PTU and 0.6 mg/rat for L-T4. Drinking solutions were renewed daily. Body weight was recorded at two-day intervals throughout the experiment, measurements taken on day 0 and at weeks 3 and 6, immediately before blood sampling. Feed consumption was recorded per cage during the week preceding each sampling time and is reported as grams per cage/day, with two rats per cage, feed intake values therefore represent the cage as the experimental unit and not the individual animal.

Blood sampling and processing

On day 0 and at weeks 3 and 6, rats were anaesthetised with diethyl ether and approximately 10 mL of blood was collected by cardiac puncture, after which the animals were decapitated. Blood was distributed into EDTA-containing tubes and plain tubes for plasma and serum preparation. Plasma was separated by centrifugation at 3,500 rpm for 10 minutes at +4 °C (Hettich Rotina 35 R, Tuttlingen, Germany). Plasma and serum aliquots were stored at −80 °C until analysis. All samples were coded numerically at the time of collection, and downstream biochemical and hormone analyses were performed by laboratory personnel blinded to group identity.

Serum thyroid hormone determination

Serum TSH, TT3, TT4, fT3, and fT4 concentrations were measured by chemiluminescent immunoassay using commercial kits and an ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics, USA), following the manufacturer's instructions (Sarandöl et al., 2005; Kandır and Keskin, 2016). All animals (n = 7 per group per sampling time) provided sufficient serum for these analyses.

Plasma oxidative stress and antioxidant parameters

Plasma TBARS (Cat. No. 10009055), NO (780001), 8-OHdG (589320), GSH (703002), GSH-Px (703102), CAT (707002), and SOD (706002) were measured spectrophotometrically using commercial kits (Cayman Chemical Co., Ann Arbor, MI, USA), and plasma TAS with a Rel Assay Diagnostics® kit (Mega Tıp, Gaziantep, Türkiye). All assays were performed in duplicate on a BioTek ELx800 microplate reader according to the manufacturers' protocols.

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). The normality of distributions was assessed by the Shapiro-Wilk test and the homogeneity of variances by the median-based Levene's test. Between-group differences at each sampling time were analysed by one-way ANOVA followed by Tukey's honestly significant difference (HSD) post-hoc test. When Levene's test indicated unequal variances ($p < 0.05$), the Welch-corrected F statistic and the Games-Howell post-hoc test were used instead. Between-timepoint comparisons within each treatment group were performed by one-way ANOVA followed by Tukey's HSD on independent cohorts. Within-group comparisons across day 0, week 3, and week 6 were performed primarily to confirm the absence of age-related drift in Control animals over the six-week experimental period, thereby ensuring that any changes observed in the treatment groups reflect treatment effects rather than natural maturation. All analyses were performed in IBM SPSS Statistics 19.0 (IBM Corp., USA), and a two-tailed p-value below 0.05 was considered statistically significant.

Ethics statement

All experimental procedures complied with the relevant national legislation governing the use of laboratory animals and were approved by the Necmettin Erbakan University Experimental Medicine Research and Application Center Animal Experiments Ethics Committee (decision no. 2012-083, dated 31 October 2012) and was conducted in line with the PREPARE (Smith et al., 2018) and ARRIVE 2.0 (Percie du Sert et al., 2020) guidelines for reporting animal research.

RESULTS

Group means for body weight and feed intake (n = 7 per group per time point), serum thyroid hormones (n = 7), and plasma oxidative-stress and antioxidant parameters (n = 6) are summarised in Tables 1–4.

Body weight and feed intake

At week 3, body weight did not differ significantly among the three groups (one-way ANOVA $F(2,18) = 2.89$, $p = 0.081$; Tukey HSD: all pairwise $p > 0.05$). By week 6, both treatment groups had significantly lower body weight than controls (Hypothyroid: 367.3 ± 7.3 g; Hyperthyroid: 347.0 ± 9.3 g vs Control: 443.1 ± 12.6 g; $F(2,18) = 25.87$, $p < 0.001$; Tukey HSD $p < 0.001$ for both comparisons; Hypothyroid vs Hyperthyroid $p > 0.05$). Between-timepoint comparisons within each treatment group, performed on independent animals sampled at each time point, showed significant body-weight gain from day 0 to weeks 3 and 6 in the Control group ($p < 0.05$), no significant gain in the Hyperthyroid group (one-way ANOVA $p > 0.05$ across time points), and an intermediate pattern in the Hypothyroid group. Feed intake, recorded per cage (two rats per cage, expressed as g per cage/day), differed significantly among groups at both week 3 ($F(2,18) = 52.13$, $p < 0.001$) and week 6 ($F(2,18) = 45.21$, $p < 0.001$): hypophagia in hypothyroid (44.1 ± 2.2 at week 3 and 39.1 ± 1.7 at week 6 g per cage/day) and hyperphagia in hyperthyroid rats (70.9 ± 2.0 at week 3 and 72.3 ± 2.9 at week 6 g per cage/day) versus control (62.7–56.6g per cage/day). All pairwise Tukey HSD comparisons were significant at week 6 ($p < 0.01$ for each), and at week 3 the hypothyroid group differed significantly from both other groups ($p < 0.001$), while the hyperthyroid–control contrast only approached significance ($p = 0.052$) (Table 1; Figure 1A, B). Relative to the contemporaneous control, the hypothyroid group consumed approximately 30% less feed at both sampling times, while the hyperthyroid group consumed 13% more at week 3 (borderline) and 28% more at week 6, reflecting an emerging hypermetabolic drive that became firmly significant by week 6.

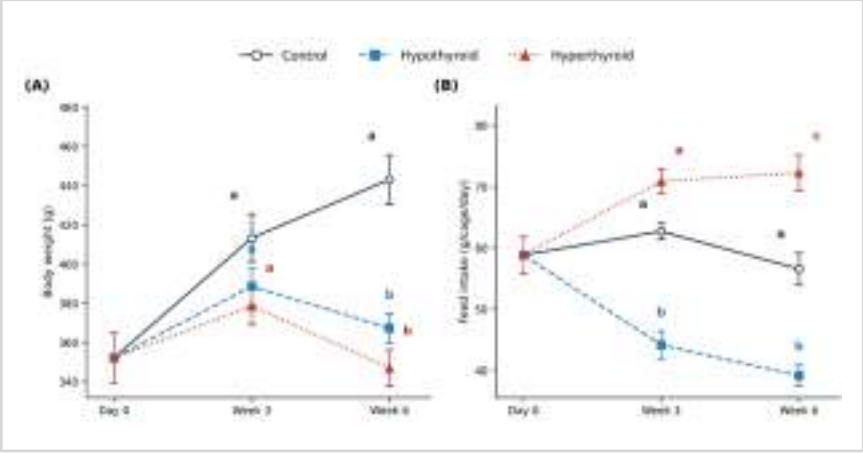

Figure 1 Body weight and feed intake across the study. (A) Body weight (g) on day 0, week 3, and week 6. (B) Feed intake (g per cage/day, two rats per cage). Values are mean ± SEM (n = 7 per group per time point). Different letters at each time point indicate significant between-group differences by Tukey's HSD post-hoc test ($p < 0.05$)

Table 1 Body weight and feed intake (mean ± SEM, n = 7 per group per timepoint)

Parameter / Group	Day 0 *	Week 3	Week 6
Body weight (g)			
Control	352.14 ± 12.74	413.29 ± 12.21	443.14 ± 12.56 a
Hypothyroid		388.57 ± 9.45	367.29 ± 7.34 b
Hyperthyroid		378.57 ± 9.62	347.00 ± 9.28 b
Feed intake (g/cage/day) §			
Control	58.83 ± 2.98	62.71 ± 1.32 a	56.57 ± 2.62 a
Hypothyroid		44.14 ± 2.24 b	39.14 ± 1.71 b
Hyperthyroid		70.86 ± 2.01 a	72.29 ± 2.91 c

** Day-0 value from a common baseline cohort of seven rats sampled prior to treatment. Lowercase letters (a, b, c) within columns indicate significant between-group differences at the same sampling time ($p < 0.05$). § Per cage (2 rats).*

Serum thyroid hormones

The induced thyroid states were confirmed by serum hormone profiles (Table 2; Figure 2). At week 3, between-group differences were highly significant for TSH ($F(2,18) = 68.82$, $p < 0.001$; Welch $F(2,8.0) = 61.42$, $p < 0.001$ because Levene's test indicated unequal variances), TT3 ($p < 0.001$) and TT4 ($p < 0.001$). Games-Howell or Tukey HSD post-hoc tests separated all three groups for each hormone at week 3 (all $p < 0.01$). The same pattern persisted at week 6, with all pairwise comparisons remaining significant (all $p < 0.01$). Free hormone fractions paralleled the total hormones. Free T3 (fT3) showed highly significant three-group differences at both week 3 ($p < 0.001$) and week 6 ($p < 0.001$). At week 3, the hypothyroid group did not yet differ significantly from control for fT3 ($p = 0.173$), while both groups differed from hyperthyroid ($p < 0.001$), and by week 6 all three groups were separated ($p \leq 0.001$ for all pairs). Free T4 (fT4) separated all three groups at both time points (week 3 and 6: $p < 0.001$). Within-group comparisons against the common day-0 baseline ($n = 7$) showed that Control hormone values did not differ significantly from baseline at either time point (across day 0, week 3, and week 6: TSH $p = 0.40$, TT3 $p = 0.21$, TT4 $p = 0.31$, fT3 $p = 0.11$, fT4 $p = 0.76$), confirming the stability of euthyroid hormone status across the six-week period. In contrast, both treatment groups deviated significantly from baseline at both time points for all hormones ($p < 0.01$). The progressive accumulation of TT4 in hyperthyroid rats between weeks 3 and 6 (8.28 ± 0.78 to 10.40 ± 0.52 µg/dL; $p = 0.033$) and the further rise in fT3 in the same group (5.49 ± 0.39 to 8.92 ± 0.78 pg/mL; $p < 0.001$) are consistent with the cumulative effect of ongoing oral L-T4 administration.

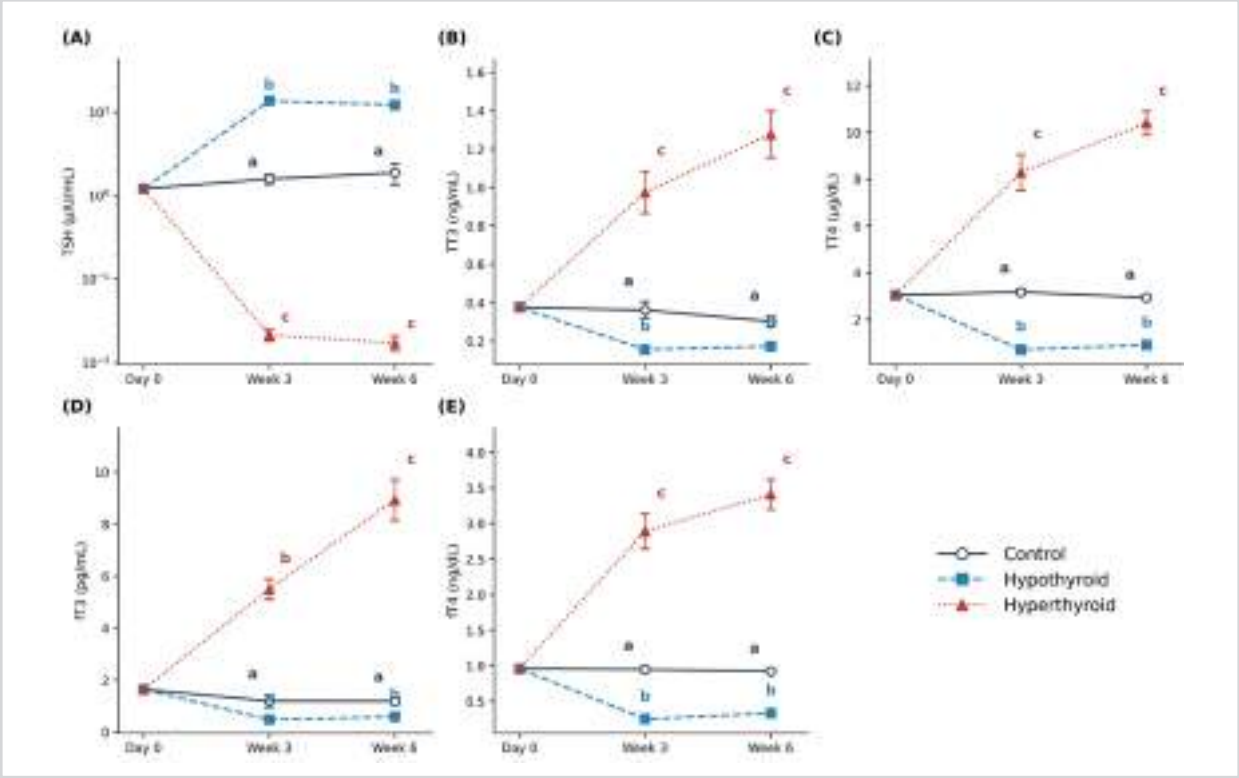

Figure 2 Serum thyroid hormone profiles confirming model induction across the study. (A) Thyroid-stimulating hormone (TSH, µIU/mL) shown on a logarithmic scale to accommodate the wide range between treatment groups. (B) Total triiodothyronine (TT3, ng/mL). (C) Total thyroxine (TT4, µg/dL). (D) Free triiodothyronine (fT3, pg/mL). (E) Free thyroxine (fT4, ng/dL). Values are mean ± SEM ($n = 7$ per group per time point). Different letters at each time point indicate significant between-group ($p < 0.05$)

Table 2 Serum thyroid hormones (mean ± SEM, n = 7 per group per time point)

Parameter / Group	Day 0 *	Week 3	Week 6
TSH (µIU/mL)			
Control	1.21 ± 0.13	1.58 ± 0.21 a	1.88 ± 0.54 a
Hypothyroid		13.65 ± 1.54 b	12.22 ± 1.49 b
Hyperthyroid		0.021 ± 0.004 c	0.017 ± 0.004 c
TT3 (ng/mL)			
Control	0.38 ± 0.01	0.36 ± 0.04 a	0.30 ± 0.03 a
Hypothyroid		0.156 ± 0.014 b	0.173 ± 0.010 b
Hyperthyroid		0.974 ± 0.110 c	1.277 ± 0.122 c
TT4 (µg/dL)			
Control	3.05 ± 0.08	3.17 ± 0.13 a	2.94 ± 0.09 a
Hypothyroid		0.72 ± 0.11 b	0.91 ± 0.08 b
Hyperthyroid		8.28 ± 0.78 c	10.40 ± 0.52 c
fT3 (pg/mL)			
Control	1.64 ± 0.05	1.20 ± 0.25 a	1.19 ± 0.14 a
Hypothyroid		0.48 ± 0.05 a	0.59 ± 0.06 b
Hyperthyroid		5.49 ± 0.39 b	8.92 ± 0.78 c
fT4 (ng/dL)			
Control	0.96 ± 0.03	0.95 ± 0.04 a	0.93 ± 0.03 a
Hypothyroid		0.25 ± 0.03 b	0.33 ± 0.03 b
Hyperthyroid		2.89 ± 0.25 c	3.41 ± 0.21 c

** Day-0 value from common baseline cohort (n = 7). Lowercase letters (a, b, c) within columns indicate significant between-group differences at the same sampling time (p < 0.05). TSH, thyroid-stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; fT3, free triiodothyronine; fT4, free thyroxine.*

Plasma oxidative stress parameters

Plasma TBARS increased significantly in both treatment groups at weeks 3 and 6 compared with the contemporaneous control ($F(2,15) \geq 32.09$, all $p < 0.001$), and pairwise Tukey HSD comparisons separated all three groups at each time point: TBARS peaked in hypothyroid rats at week 6 (22.3 ± 1.2 µM vs Control 9.0 ± 0.8 µM; $p < 0.001$) (Table 3; Figure 3A). Plasma NO decreased significantly in both treatment groups at week 3 ($F(2,15) = 26.96$, $p < 0.001$) and the three groups were all separated ($p < 0.05$) (Table 3; Figure 3B). By week 6, the hyperthyroid group remained suppressed ($p = 0.007$) but the contrast with the Control group did not reach significance ($p = 0.075$). Plasma 8-OHdG did not differ significantly between groups at either sampling time (week 3: $F(2,15) = 0.67$, $p = 0.53$; week 6: $F(2,15) = 1.08$, $p = 0.36$) (Table 3; Figure 3C). The Shapiro-Wilk test indicated non-normality for the 8-OHdG and GPx distributions at week 3 ($p < 0.05$); Welch and Games-Howell results yielded the same qualitative conclusions. In Control animals, plasma TBARS, NO, and 8-OHdG values at week 3 and week 6 did not differ significantly from the day-0 baseline ($p > 0.05$ for all three parameters), confirming the absence of age-related drift across the six-week period.

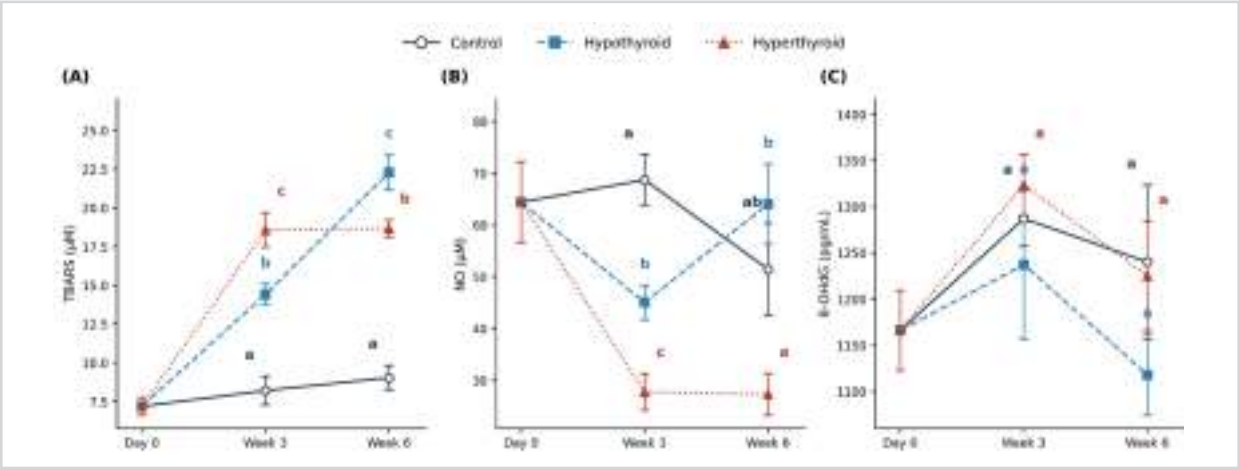

Figure 3 Plasma oxidative stress markers across the study. (A) Thiobarbituric acid reactive substances (TBARS, µM). (B) Nitric oxide (NO, µM). (C) 8-hydroxy-2′-deoxyguanosine (8-OHdG, pg/mL). Values are mean ± SEM (n = 6). Different letters at each time point indicate significant between-group differences ($p < 0.05$)

Table 3 Plasma oxidative-stress parameters (mean ± SEM, n = 6)

Parameter / Group	Day 0 *	Week 3	Week 6
TBARS (µM)			
Control	7.18 ± 0.58	8.20 ± 0.93 a	9.03 ± 0.78 a
Hypothyroid		14.41 ± 0.66 b	22.28 ± 1.15 c
Hyperthyroid		18.57 ± 1.12 c	18.67 ± 0.55 b
NO (µM)			
Control	64.41 ± 7.82	68.73 ± 4.85 a	51.45 ± 8.88 ab
Hypothyroid		45.04 ± 3.34 b	64.07 ± 7.73 b
Hyperthyroid		27.75 ± 3.53 c	27.27 ± 4.05 a
8-OHdG (pg/mL)			
Control	1166 ± 43	1287 ± 30	1240 ± 83
Hypothyroid		1237 ± 80	1118 ± 44
Hyperthyroid		1324 ± 33	1225 ± 59

** Day-0 baseline values (n = 6) common to all groups. Within columns, different lowercase letters (a, b, c) indicate significant between-group differences at the same sampling time ($p < 0.05$).TBARS, thiobarbituric acid reactive substances; NO, nitric oxide; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.*

Plasma antioxidant system

Plasma SOD activity increased significantly in both treatment groups (Table 4; Figure 4A). At week 3, the hyperthyroid group exhibited higher SOD activity than the other two groups ($F(2,15) = 21.04$, $p < 0.001$), while the hypothyroid and control groups did not differ. By week 6, both treatment groups exceeded the control ($F(2,15) = 24.35$, $p < 0.001$ for both comparisons). Plasma CAT activity showed a numerical increase in hypothyroid rats at week 6 (170.1 ± 9.2 nmol/min/mL vs Control 135.9 ± 12.1), but this trend did not reach statistical significance ($F(2,15) = 2.32$, $p = 0.13$) (Table 4; Figure 4B). Plasma GSH-Px did not differ between groups at week 3 but at week 6 the hypothyroid group was significantly lower than the hyperthyroid group ($F(2,15) = 6.42$, $p = 0.010$); the difference between hypothyroid and control approached but did not reach significance ($p = 0.051$) (Table 4; Figure 4C). Plasma total GSH was lower in the hypothyroid than in the

control group at week 3 ($F(2,15) = 4.28$, $p < 0.05$); no significant between-group differences were detected at week 6. Plasma TAS at week 3 showed marked variance heterogeneity (Levene's $p < 0.001$), so the Welch-corrected ANOVA and Games-Howell post-hoc were applied: the hypothyroid group was higher than the control ($F(2,15) = 4.65$, $p = 0.027$; Games-Howell $p = 0.036$), while the hyperthyroid group was numerically lower but did not differ significantly from either of the other groups (Games-Howell $p = 0.44$ vs control; $p = 0.093$ vs hypothyroid) (Table 4; Figure 4D). As with the oxidative-stress markers, plasma antioxidant parameters in Control animals remained stable across day 0, week 3, and week 6 (Table 4), supporting the interpretation that the changes observed in hypothyroid and hyperthyroid groups are treatment-driven rather than age-driven.

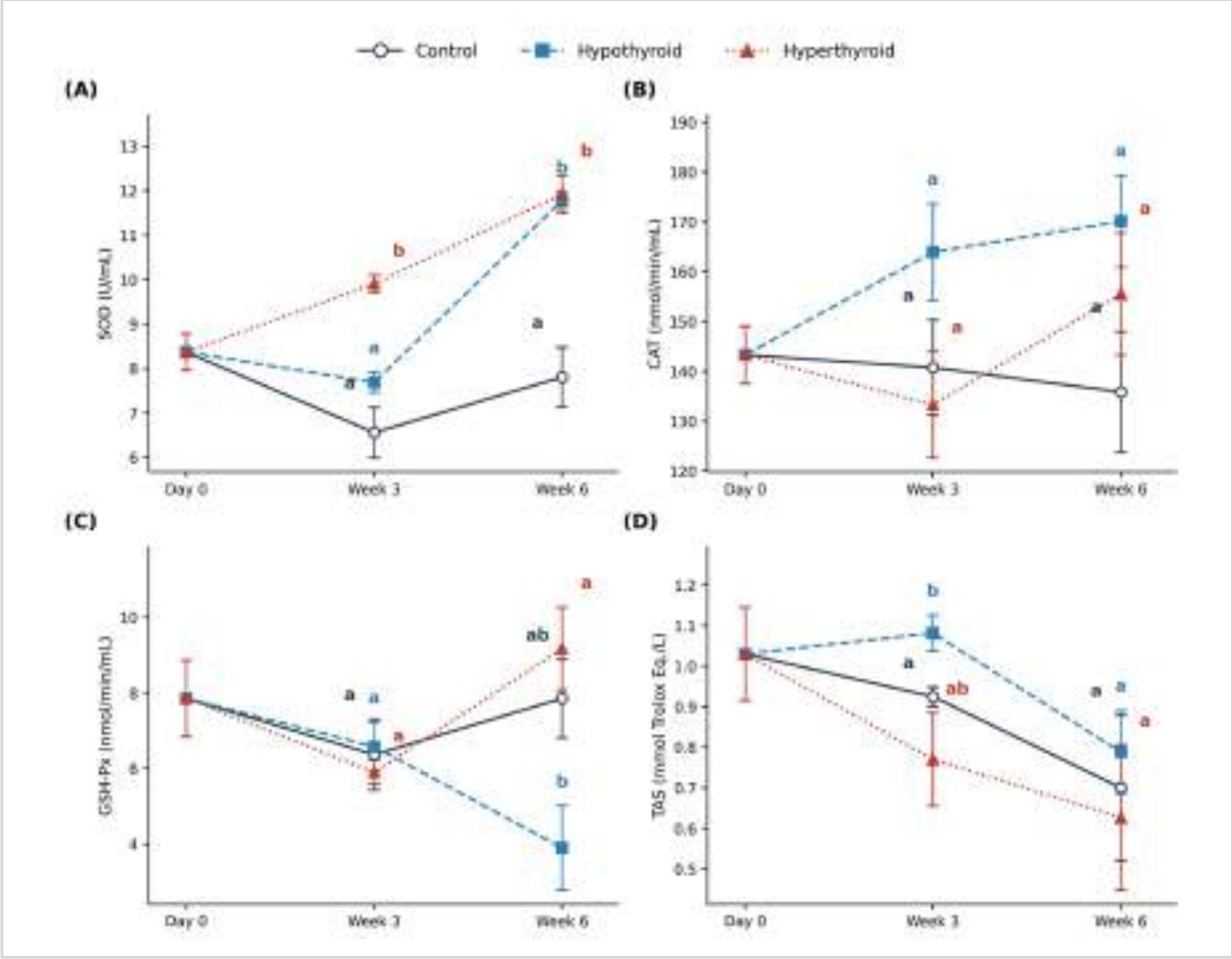

Figure 4 Plasma antioxidant defence parameters across the study. (A) Superoxide dismutase (SOD, U/mL). (B) Catalase (CAT, nmol/min/mL). (C) Glutathione peroxidase (GSH-Px, nmol/min/mL). (D) Total antioxidant status (TAS, mmol Trolox equivalent per L). Values are mean ± SEM (n = 7 per group). Different letters at each time point indicate significant between-group differences ($p < 0.05$)

Table 4 Plasma antioxidant system parameters (mean ± SEM, n = 6)

Parameter / Group	Day 0 *	Week 3	Week 6
SOD (U/mL)			
Control	8.37 ± 0.41	6.56 ± 0.57 a	7.81 ± 0.67 a
Hypothyroid		7.69 ± 0.23 a	11.78 ± 0.20 b
Hyperthyroid		9.91 ± 0.20 b	11.92 ± 0.42 b
CAT (nmol/min/mL)			
Control	143.3 ± 5.8	140.8 ± 9.6	135.9 ± 12.1
Hypothyroid		163.9 ± 9.7	170.1 ± 9.2
Hyperthyroid		133.3 ± 10.7	155.5 ± 12.3
GSH-Px (nmol/min/mL)			
Control	7.86 ± 1.01	6.37 ± 0.94	7.86 ± 1.04 ab
Hypothyroid		6.58 ± 0.65	3.91 ± 1.12 b
Hyperthyroid		5.90 ± 0.32	9.17 ± 1.09 a
Total GSH (µM)			
Control	8.98 ± 1.12	11.12 ± 0.91 a	6.24 ± 2.06
Hypothyroid		8.12 ± 0.76 b	7.33 ± 0.52
Hyperthyroid		9.95 ± 0.44 ab	5.94 ± 0.58
TAS (mmol Trolox Eq./L)			
Control	1.03 ± 0.12	0.93 ± 0.02 a	0.70 ± 0.18
Hypothyroid		1.08 ± 0.04 b	0.79 ± 0.10
Hyperthyroid		0.77 ± 0.12 ab	0.63 ± 0.18

** Day-0 baseline values (n = 6) common to all groups. Within columns, different lowercase letters (a, b, c) indicate significant between-group differences at the same sampling time ($p < 0.05$). SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; GSH, glutathione; TAS, total antioxidant status.*

DISCUSSION AND CONCLUSIONS

The present study examined the temporal alterations in plasma response of the oxidant–antioxidant system to sustained hypothyroidism and hyperthyroidism induced by oral PTU and L-T4. The significant, directionally appropriate changes in serum TSH, TT3, TT4, fT3, and fT4 in both treatment groups relative to the contemporaneous control confirmed that the intended thyroid states were achieved (Rondeel et al., 1992; Messarah et al., 2011; Bianco et al., 2014). The continued increase in TT4 between weeks 3 and 6 in the hyperthyroid group is consistent with the cumulative effect of ongoing oral L-T4 administration (Guerrero et al., 1999; Bianco et al., 2014). An informative dissociation was observed between total and free triiodothyronine in the hypothyroid group: at week 3, fT3 did not yet differ significantly from control (Tukey HSD $p = 0.173$) even though TT3 was already markedly reduced, and clear three-way separation only emerged by week 6. This pattern is consistent with slower equilibration of the unbound hormone fraction relative to the total pool and indicates that, in PTU-induced hypothyroidism, free thyroid hormone deficiency follows total hormone depletion with a measurable lag. In the hyperthyroid group, by contrast, fT3 rose progressively from 5.49 ± 0.39 pg/mL at week 3 to 8.92 ± 0.78 pg/mL at week 6, mirroring the further accumulation of TT4 and reflecting the cumulative effect of ongoing oral L-T4 exposure. The stability of all five hormones in the Control group across day 0, week 3, and week 6 ($p > 0.05$) further indicates that the six-week sampling window did not introduce confounding age-related drift, in agreement with reports that age-dependent shifts in thyroid hormone levels become measurable only over longer intervals (Rao-Rupanagudi et al., 1992). Coordinated, time-dependent shifts in serum T3 and T4 have also been reported in nutritionally and physiologically modulated laying-hen models (Anwar et al., 2018; Idris et al., 2023), supporting the broader principle that thyroid hormone profiles respond rapidly and progressively to chronic metabolic perturbations across species.

The reduction in body weight in both treatment groups by week 6 is in line with earlier reports that body weight

gain is impaired in both states, despite hyperphagia in hyperthyroidism and hypophagia in hypothyroidism (Pamplona et al., 1999; López-Torres et al., 2000; Iossa et al., 2001; Biondi, 2010; Klieverik et al., 2009; Mullur et al., 2014). Body weight at week 3 did not yet differ statistically among the groups, demonstrating that the metabolic consequences of dysthyroidism on body mass require sustained exposure. Although hypothyroidism has clinically been associated with obesity, careful metabolic studies show that hypothyroid rodents reduce total energy intake and gain less body weight than euthyroid controls, in line with our observations (Iossa et al., 2001; Mullur et al., 2014). Comparable thyroid-state-dependent shifts in body weight and feed intake have been reported in other veterinary species, including significant body-weight reduction in zinc-induced moulted laying hens accompanied by altered T3/T4 ratios (Idris et al., 2023). The magnitude and direction of the feed-intake shifts observed here, with approximately 30% hypophagia in hypothyroid rats and a progressively widening hyperphagia of 13% to 28% in hyperthyroid rats from week 3 to week 6, are consistent with established rodent and avian dysthyroid models (Iossa et al., 2001; Mullur et al., 2014; Anwar et al., 2018) and with central thyroid-hormone modulation of hypothalamic NPY/AgRP and POMC appetite circuits (Amin et al., 2011; Fekete and Lechan, 2014). Dysregulation of adipocytokines and altered central appetite regulation contribute to this phenotype (Iglesias and Diez, 2007; Çınar and Gürlek, 2013; Fekete and Lechan, 2014; Amin et al., 2011).

A central finding of this study is the elevation in plasma TBARS in both dysthyroid states at weeks 3 and 6, with the highest values reached in hypothyroid rats at week 6. Hyperthyroidism is classically associated with accelerated mitochondrial ROS production and lipid peroxidation (Venditti and Di Meo, 2006; Fasciolo et al., 2023). Reports in hypothyroidism are more heterogeneous, with both increases and decreases described depending on tissue, model, and assay (Das and Chainy, 2001; Messarah et al., 2010, 2011; Cano-Europa et al., 2012; Torres-Manzo et al., 2018; Hosseini et al., 2023; Kochman et al., 2021). The significant TBARS elevation in our PTU-treated rats is most likely driven by altered lipoprotein metabolism. Hypothyroidism is associated with raised total cholesterol and LDL (Abrams and Grundy, 1981; Asvold et al., 2007; Kandır, 2015), with increased LDL oxidisability and elevated lipid peroxidation products even in subclinical disease (Diekman et al., 1998; Zha et al., 2015), and with reduced paraoxonase-1 (PON-1) activity (Sarandöl et al., 2005). LDL is highly susceptible to oxidation (Slotte and Grönberg, 1990). The combination of greater substrate availability and reduced lipid-peroxide hydrolysing capacity provides a plausible mechanism for the elevated plasma TBARS we observed.

The hyperthyroid response was different in shape. TBARS increased by week 3 and then stabilised between weeks 3 and 6, despite continued L-T4 exposure. This pattern suggests partial antioxidant adaptation. SOD activity increased significantly in the hyperthyroid group at both sampling times. Activation of the Nrf2/Keap1 axis is increasingly recognised as a central mediator of this adaptive response, transcribing several antioxidant enzymes in lymphoid and peripheral tissues of hyperthyroid animals (Costilla et al., 2019). In our hypothyroid group, plasma CAT showed an elevation trend by week 6, however that did not reach significance level. This is consistent with previous reports of CAT upregulation in tissues of hypothyroid rodents (Venditti et al., 1997; Messarah et al., 2010). The pronounced upregulation of SOD activity, without comparable induction of CAT or GSH-Px and coupled with reduced GSH-Px activity in hypothyroid rats at week 6, points to a kinetic mismatch within the enzymatic antioxidant cascade. Superoxide is efficiently dismuted, but the subsequent decomposition of hydrogen peroxide and reduction of lipid hydroperoxides remain inadequate. These observations support the view that increased mitochondrial electron flow in hyperthyroidism can generate ROS at rates that exceed the antioxidant capacity and lead to net oxidative injury (Venditti and Di Meo, 2006; Mancini et al., 2016). It should also be noted that SOD, CAT, and GSH-Px are predominantly intracellular enzymes, so the plasma activities reported here are comparatively low and are best interpreted as a circulating signal rather than as direct evidence of tissue enzyme regulation. The progressive decline of plasma TAS in both treatment groups by week 6 deserves separate consideration. Plasma albumin is the principal protein contributor to circulating antioxidant capacity, with redox-active free thiols and substantial metal-ion binding (Halliwell, 1988; Anraku et al., 2013). Chronic hyperthyroidism accelerates whole-body protein catabolism (Mullur et al., 2014; Kandır, 2015), and a reduction in plasma albumin could therefore lower the antioxidant buffer of plasma even without changes in

low-molecular-weight antioxidants. The TAS decline in our hyperthyroid group is plausibly multifactorial, with reduced albumin contribution compounding the depletion of total glutathione and the increased oxidant load.

The plasma oxidative changes reported here align with the haematological alterations documented in our previous study (Kandır and Keskin, 2016). At week 6, hypothyroid rats showed reduced red blood cell count, haemoglobin concentration, haematocrit, and red cell distribution width, with an elevated plateletcrit. Hyperthyroid rats at the same time point had lower mean corpuscular haemoglobin concentration and platelet count, with a shift in the leukocyte differential from lymphocytes toward granulocytes. The pronounced elevation in plasma TBARS in hypothyroid rats at week 6 is biologically consistent with these red cell indices. Erythrocyte membranes are particularly susceptible to lipid peroxidation because of their high polyunsaturated fatty acid content and continuous oxygen exposure (Yücel et al., 2009; Messarah et al., 2011). Sustained plasma lipid peroxidation, together with an unmet hydrolytic antioxidant capacity reflected in the lower GSH-Px we observed, would shorten erythrocyte survival and contribute to the anaemic phenotype. In hyperthyroid rats, the lymphocyte-to-granulocyte shift coincides temporally with the persistent suppression of plasma NO, in line with the broader picture of an immune-redox-vascular axis disturbed by thyroid hormone excess (Costilla et al., 2019; Cetin et al., 2022). Parallel observations in moulted laying hens, where serum aminotransferases and the lipid profile shift in concert with thyroid hormone and cortisol changes (Anwar et al., 2018; Idris et al., 2023), reinforce the view that thyroid status influences a coordinated multi-tissue redox and metabolic signature. The haematological values in our previous study remained within physiological reference ranges, suggesting that the oxidative stress signatures described here may precede overt haematological pathology and could offer earlier diagnostic value. Disturbed iron homeostasis is a subsequent consequence of chronic dysthyroidism (Zimmermann and Köhrle, 2002; Kandır, 2015). Redox-active iron pools can potentiate Fenton-driven hydroxyl radical generation that accelerates lipid peroxidation at biological membranes (Halliwell and Gutteridge, 1986), adding a complementary mechanistic layer to the parallel between dysthyroid plasma lipid peroxidation and the haematological phenotype.

Plasma NO was decreased in both treatment groups at week 3 and remained suppressed in hyperthyroid rats at week 6 relative to the hypothyroid group. Tissue NOS activity in dysthyroid states is heterogeneous. It is increased in most cardiac and renal tissues of hyperthyroid rats and is more variable in hypothyroidism (Quesada et al., 2002; McAllister et al., 2005). Circulating NO availability is determined by both NOS-driven synthesis and ADMA-mediated inhibition (Teerlink, 2005). Plasma ADMA has been reported as elevated in hyperthyroid humans and rats, alongside reduced DDAH activity in oxidative environments (Hermenegildo et al., 2002; Arikan et al., 2007; Karabağ and Sözbilir, 2011; Böger et al., 2000). Recent clinical evidence further correlates thyroid hormone profiles with circulating ADMA and ischemia-modified albumin in euthyroid adults, irrespective of underlying autoimmune thyroiditis (Cetin et al., 2022). The persistent NO suppression in our hyperthyroid rats fits this mechanism. ADMA was not measured in the present study, which is a limitation, and future work should pair plasma NO with ADMA and DDAH activity to clarify the L-arginine/NO pathway in dysthyroid states. The recovery of plasma NO alongside elevated TBARS by week 6 in hypothyroid rats suggests a complex temporal interplay between NO availability and lipid peroxidation, a finding that warrants comprehensive mechanistic elucidation.

DNA oxidation, assessed via plasma 8-OHdG, did not differ between groups at any time point. Plasma 8-OHdG is a sensitive but compartment-dependent biomarker (Dizdaroglu and Jaruga, 2012). Circulating levels reflect a balance between cellular oxidative damage and excretion or repair (Cooke et al., 2003). The assay used here is an immunoassay, and the manufacturer notes that it is not fully validated for plasma and that the antibody recognises several structurally related oxidised guanine species; more generally, immunoassays are less sensitive and specific than chromatographic methods (HPLC, mass spectrometry) and yield 8-OHdG values that are not directly comparable across techniques (Graille et al., 2020). Studies in tissues such as heart, liver, and skeletal muscle of hyper- and hypothyroid rodents have reported increased nuclear and mitochondrial DNA oxidation (Gredilla et al., 2001a, 2001b; Moulakakis et al., 2007, 2008). Plasma 8-OHdG has been less consistently reported. Our findings suggest that at the doses and durations used here, systemic plasma 8-OHdG is a relatively insensitive marker of dysthyroid

oxidative stress, and that lipid peroxidation may precede measurable plasma DNA-oxidation responses.

The stability of all measured parameters in the Control group across the six-week experimental period (Tables 1–4, $p > 0.05$) indicates that the age range of the rats used (12–18 weeks) does not introduce confounding natural changes in plasma oxidant-antioxidant parameters over this window, and supports attribution of the observed group differences to the induced thyroid states rather than to maturation.

The primary limitation of this study is its reliance on circulating biomarkers, which may not always mirror redox dynamics at organ level. Systemic concentrations integrate inputs from multiple sources and reflect a balance among cellular release, excretion, and repair. Therefore, the absence of alterations in the blood (as seen with 8-OHdG) does not preclude localized tissue damage. The systemic oxidative profile reported here is likely paralleled by intracellular shifts in metabolically active organs such as the liver, kidneys, and skeletal muscle (Marcocci et al., 2012), which warrant direct examination in future investigations. Furthermore, the lack of ADMA and DDAH measurements, along with the exclusive use of male animals, constitute additional limitations.

In male Wistar rats, both PTU-induced hypothyroidism and L-T4-induced hyperthyroidism caused sustained increases in plasma lipid peroxidation, suppression of nitric oxide (particularly in hyperthyroidism), and compensatory up-regulation of SOD in both states. The numerical but non-significant elevation in CAT activity in hypothyroid rats by week 6 suggests an early enzymatic adaptation that may require longer exposure or larger sample sizes to confirm. Plasma TAS and total glutathione declined over time, which indicates that antioxidant reserves are not fully sustained against chronic thyroid hormone imbalance. These findings support the evaluation of plasma oxidative-stress and antioxidant biomarkers as candidate early markers of dysthyroid redox imbalance in future studies and point to vascular NO availability as a potentially relevant target in hyperthyroidism. To elucidate the underlying mechanisms, tissue-level analyses and ADMA/DDAH-resolved studies are necessary. Although these results were obtained in a rat model under controlled experimental conditions, their translation to clinical veterinary or human practice requires validation in target species, including assessment of biomarker performance in spontaneous dysthyroid disease and during long-term clinical follow-up.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualisation: S.K., T.K.; methodology: S.K.; investigation and data acquisition: S.K.; formal analysis: S.K.; writing—original draft: S.K.; writing—review and editing: S.K., T.K.; supervision: T.K. Both authors approved the final version of the manuscript.

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Vremenska dinamika promjena oksidativnog stresa i antioksidativne odbrane u plazmi kod eksperimentalno induciranih hipotireoidnih i hipertireoidnih štakora

SAŽETAK

Odgovor plazme na oksidativni i antioksidativni status kod hronične hipotireoze i hipertireoze procijenjen je kod štakora u tri presječna uzorkovanja. Korišteno je 49 mužjaka Wistar štakora. Sedam životinja uzorkovano je na nulti dan radi određivanja bazalnih vrijednosti, dok je preostalih 42 dobivalo standardnu pitku vodu (kontrola), 0,05% propiltiouracil (PTU) ili 0,0012% L-tiroksin (L-T4) tokom šest sedmica (n = 14 po grupi). Krv je uzorkovana na nulti dan (bazalno stanje), u 3. sedmici i u 6. sedmici za analizu serumskih hormona štitne žlijezde (TSH, TT3, TT4, fT3, fT4) i plazmatskih parametara TBARS, NO, 8-OHdG, SOD, katalaza (CAT), GSH-Px, ukupni glutation (GSH) i ukupni antioksidativni status (TAS). Podaci su analizirani jednofaktorskom ANOVA-om uz Tukey HSD post-hoc test. Hormonski profili potvrdili su uspješnu indukciju modela. Tjelesna masa se smanjila u obje tretirane grupe do 6. sedmice, uz hipofagiju kod hipotireoidnih i hiperfagiju kod hipertireoidnih štakora ($p < 0,001$). Nivoi TBARS u plazmi porasli su u oba stanja i dostigli maksimum kod hipotireoidnih štakora u 6. sedmici. Nivoi NO u plazmi smanjili su se u 3. sedmici i ostali sniženi kod hipertireoidnih štakora. 8-OHdG nije pokazao promjene. Aktivnost SOD porasla je u obje tretirane grupe, dok je katalaza pokazala nesignifikantan trend porasta kod hipotireoidnih štakora u 6. sedmici. GSH-Px i GSH bili su najniži kod hipotireoidnih štakora. TAS se smanjivao tokom vremena u obje tretirane grupe. Oba distireoidna stanja dovode do trajne povišene lipidne peroksidacije u plazmi uz djelimičnu antioksidativnu kompenzaciju. Trajno smanjenje NO u hipertireozi ukazuje na ranu vaskularnu osjetljivost koja zahtijeva daljnja istraživanja.

Ključne riječi: 8-OHdG, antioksidativni enzimi, hipertireoza, hipotireoza, lipidna peroksidacija, dušikov oksid.

RESEARCH ARTICLE

The AST to platelet ratio index is a predictor of pleural effusion development in acute pancreatitis

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ABSTRACT

Pleural effusion is a common extra pancreatic complication of acute pancreatitis and is associated with a more severe clinical course and poorer outcomes. Early identification of patients at risk remains clinically important. The aim of this study was to evaluate the predictive value of non-invasive liver fibrosis indices for the development of pleural effusion in patients with acute pancreatitis. This retrospective single-centre observational study included 97 patients hospitalised with acute pancreatitis. Laboratory parameters obtained at admission were used to calculate several liver fibrosis indices, including APRI, AARPRI, FIB-4, ALBI, ABAI, GPR, APP, and FIS. The presence of pleural effusion was assessed using chest radiography. Comparative analysis demonstrated that ABAI, AARPRI, ALBI, APRI, FIS, and FIB-4 were significantly associated with pleural effusion. Receiver operating characteristic analysis showed the highest discriminative ability for ALBI (AUC 0.707), followed by ABAI (AUC 0.695) and APRI (AUC 0.650). In univariate logistic regression, ALBI, FIS, and APRI were significant predictors of pleural effusion, whereas in multivariate analysis only APRI remained an independent predictor (OR 3.677, p=0.047). These findings indicate that non-invasive liver fibrosis indices, particularly APRI, may serve as simple and accessible biomarkers for early prediction of pleural effusion in patients with acute pancreatitis.

Keywords: Biomarkers, disease severity, liver function tests, prognosis, risk assessment

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory condition of the exocrine pancreas characterised by acinar cell injury and a cascade of local and systemic inflammatory responses, with clinical severity ranging from mild, self-limited pancreatic oedema to fulminant disease complicated by necrosis, organ failure, and death (Bejjani et al., 2024; Tenner et al., 2024). In clinical practice, gallstone disease and alcohol use remain the most common aetiological factors, while hypertriglyceridaemia, drug-induced pancreatitis, malignant obstruction, and infectious triggers represent less frequent but clinically relevant causes (Tenner et al., 2024; Walkowska et al., 2022). The diagnostic work-up is typically grounded in characteristic abdominal pain—often epigastric, occasionally radiating to the shoulder and exacerbated by oral intake—together with biochemical and imaging confirmation when indicated (Walkowska et al., 2022; Tenner et al., 2024).

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Although serum amylase is widely used as a biochemical marker, its diagnostic sensitivity may be reduced in late presentations and in hypertriglyceridaemia, underscoring the need for a broader laboratory context when evaluating suspected AP (Walkowska et al., 2022). In this setting, hepatobiliary parameters such as bilirubin, gamma-glutamyl transferase, and transaminases may provide useful additional signals, reflecting either shared biliary pathology or systemic involvement, and potentially contributing to early risk stratification (Tenner et al., 2024; Xu et al., 2020). At the same time, the pathophysiology of AP is driven by a complex inflammatory network, with prominent cytokine activation—including interleukin-1β, interleukin-6, interleukin-8, and tumour necrosis factor-α—contributing to systemic inflammatory response syndrome and the progression toward multiorgan dysfunction in severe cases (Bejjani et al., 2024; Metri et al., 2024).

Given the clinical need to anticipate deterioration, several severity scores have been developed and used to estimate disease course and the risk of organ failure, including radiology-based indices and clinical scoring systems such as Ranson and APACHE (Raghuwanshi et al., 2016). Nevertheless, thoracic complications frequently emerge as early systemic manifestations of AP and remain among the most clinically consequential. Pleural effusion (PE), in particular, represents one of the most common extra-pancreatic radiological findings, often preceding pulmonary oedema and infiltrates and, in many patients, signalling a more severe disease phenotype requiring closer monitoring and occasionally ventilatory support (Kumar et al., 2018; Shah and Rana, 2020). Contemporary evidence further supports PE as an early marker of severe pancreatitis, with left-sided effusions being reported most frequently, followed by bilateral and right-sided distributions, and with clinically meaningful associations with adverse outcomes (Luiken et al., 2022).

Mechanistically, PE in AP may develop through several pathways, including pseudocyst formation, trans-diaphragmatic lymphatic obstruction, and pancreaticopleural fistulae that allow enzyme-rich fluid to track into the pleural cavity, potentially compromising respiratory mechanics when effusions are large or progressive (Kumar et al., 2018; Luiken et al., 2022). Importantly, PE has also been linked to broader systemic involvement, including hepatic impairment, which may manifest through derangements in albumin and bilirubin levels during the acute inflammatory phase (Xu et al., 2020; Luiken et al., 2022).

In parallel with these clinical observations, non-invasive indices originally developed to estimate liver fibrosis—constructed from routine laboratory parameters such as transaminases, platelets, bilirubin, and albumin—have increasingly been explored beyond chronic liver disease contexts. However, the predictive role of such indices for PE development during AP remains insufficiently studied. Notably, Kirdok et al. (2024) evaluated Fibrosis-4 (FIB-4) in relation to AP severity using traditional clinical scores but did not assess PE as a distinct complication despite its recognised value as a severity signal . Likewise, studies focusing on single hepatobiliary markers have suggested prognostic roles for bilirubin or albumin in assessing AP severity, yet without specifically addressing PE as an early event in the clinical trajectory (Xu et al., 2020).

Accordingly, the present study aimed to determine whether non-invasive liver fibrosis indices calculated from admission laboratory parameters are associated with, and can predict, the development of PE in patients hospitalised with AP, irrespective of underlying aetiology and baseline severity status.

MATERIAL AND METHODS

The present study was conducted as a retrospective single-centre observational study at the Department of Gastroenterohepatology, General Hospital "Primarius Abdulah Nakaš", Sarajevo, Bosnia and Herzegovina. The study included patients hospitalised with a diagnosis of AP between 2016 and 2021. A total of 97 adult patients of both sexes were analysed, comprising 41 women and 56 men. The study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the General Hospital "Prim. dr. Abdulah Nakaš".

The diagnosis of AP was established using standard clinical criteria, requiring at least two of the following: characteristic abdominal pain consistent with pancreatitis, serum amylase levels at least three times above the upper reference limit, and radiological findings compatible with pancreatitis on abdominal ultrasonography (Walkowska et al., 2022). Ultrasonographic examinations were performed using a Toshiba Aplio 300 system equipped with a convex probe (PVT-375BT).

Patients with already known medical history of clinically established chronic liver disease, chronic pancreatitis, chronic heart failure, chronic kidney disease, shock requiring mechanical ventilation, recent respiratory infection within the previous three months, or those who did not provide informed consent were excluded from the study. All patients received standard supportive therapy for AP, including intravenous fluid resuscitation, analgesia, and electrolyte correction. Antibiotic therapy was administered only when clinically indicated.

Blood samples were obtained from the cubital vein at hospital admission and processed according to standard laboratory procedures. Serum was separated by centrifugation within 30 minutes and stored at −20°C until analysis. Laboratory assessments included platelet count, serum amylase, and hepatobiliary parameters, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, and albumin. Biochemical analyses were performed using standard enzymatic colorimetric methods on automated analysers, while platelet counts were determined using an automated haematology analyser.

PE was assessed during hospitalisation using standard posteroanterior and lateral chest radiography. Chest radiography was performed within the first 48 hours of admission or earlier if respiratory symptoms were present. Radiographic signs consistent with pleural fluid, such as costophrenic angle blunting, were considered diagnostic for PE (Karkhanis and Joshi, 2012).

Based on admission laboratory values, several non-invasive liver fibrosis indices were calculated. These indices were derived from routinely measured biochemical and haematological parameters and have previously been applied in the non-invasive assessment of liver fibrosis and systemic disease states (Deng et al., 2015; Chou et al., 2023). The following formulas were used:

APRI (AST to Platelet Ratio Index):
$APRI = [(AST / ULN) / PLT] \times 100$
AARPRI (AST/ALT ratio to Platelet Ratio Index):
$AARPRI = (AST / ALT) / PLT \times 100$
FIB-4 (Fibrosis-4 Index):
$FIB\text{-}4 = (Age \times AST) / [PLT \times \sqrt{ALT}]$
GPR (GGT to Platelet Ratio):
$GPR = (GGT / ULN) / PLT \times 100$
APP (Albumin–Platelet Product):
$APP = (Albumin \times PLT) / 1000$
ALBI (Albumin–Bilirubin Index):
$ALBI^* = (0.66 \times \log10\ Bilirubin) - (0.085 \times Albumin)$
*Based on the ALBI score, patients were stratified into prognostic classes: grade 1 (≤ -2.60), grade 2 (> -2.60 to ≤ -1.39), and grade 3 (> -1.39).
ABAI (Age–Bilirubin–Albumin Index):
$ABAI = 1.5 + (0.065 \times Age) + (1.85 \times Bilirubin) - (1.65 \times Albumin)$
FIS (Fibrosis Index Score):
$FIS = 8 - (0.01 \times PLT) - Albumin$

In these formulas, PLT represents platelet count expressed in $\times 10^9$/L, while ULN denotes the upper limit of normal for AST (40 U/L) and GGT (73 U/L). AST indicates aspartate aminotransferase, ALT alanine aminotransferase, and GGT gamma-glutamyl transferase. Albumin and bilirubin represent their respective serum concentrations according to standard laboratory units.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0. The distribution of variables was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range. Between-group comparisons were performed using the Student's t-test or the Mann–Whitney U test, as appropriate. The diagnostic performance of non-invasive indices for PE was evaluated using receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve and corresponding 95% confidence intervals. Binary logistic regression analysis was used to identify independent predictors of PE. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 97 patients with AP were included in the study, comprising 41 women (42.3%) and 56 men (57.7%), with a mean age of 57.6 ± 14.3 years. PE was observed in 24 patients (24.7%), while 73 patients (75.3%) had no radiographic evidence of PE. Baseline demographic, laboratory, and index-derived parameters are presented in Table 1.

Table 1 Demographic and clinical characteristics of acute pancreatitis patients

Parameters	Value
Gender	
Female	41 (42.3%)
Male	56 (57.7%)
Pleural Effusion	
No	73 (75.3%)
Yes	24 (24.7%)
Age	57.59 ± 14.25
Amylase	540 (301.50 – 1572.50)
AST (U/L)	37.0 (24.0 – 107.0)
ALT (U/L)	57.0 (33.5 – 129.0)
GGT (U/L)	54.0 (27.0 – 144.50)
Platelets (10*9)	221.0 (180.50 – 281.50)
APRI	0.488 (0.234 – 1.209)
AARPRI	0.312 (0.165– 0.756)
FIB4	1.393 (0.866 – 2.314)
GPR	38.074 (11.553 – 61.222)
Total Bilirubin (μmol/L)	12.800 (7.950 – 26.700)
Albumin (g/L)	33.0 (29.0 – 37.0)
ALBI	-2.03 ± 0.506
APP	7.182 (5.514 – 9.553)
ABAI	-20.290 (-34.077 – -0.1150)
FIS	-27.35 ± 5.567

Data expressed as mean (±SD) and median (interquartile range (IQR)).

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; APRI: AST to platelet ratio index; AARPRI: aspartate aminotransferase to alanine aminotransferase ratio to platelet ratio index; FIB4: Fibrosis-4; GPR: gamma-glutamyl transferase to platelet ratio; ALBI: albumin-bilirubin score, APP: albumin-platelet product; ABAI: age, bilirubin, albumin index; FIS: Fibrosis Score

Comparison between patients with and without PE revealed statistically significant differences in several non-invasive liver fibrosis indices (Table 2). Patients with PE had significantly higher values of ABAI, AARPRI, APRI, FIS, and FIB-4, as well as less favourable ALBI scores. In contrast, APP and GPR did not differ significantly between the groups. No statistically significant difference was observed in the distribution of ALBI grades between the groups.

Table 2 Comparison of non-invasive liver fibrosis indices between patients with and without pleural effusion

Parameter	AP with PE (n=24)	AP without PE (n=73)	p-value
ABAI	−4.250 (−22.211–16.196)	−27.325 (−38.415 to −6.617)	0.004*
AARPRI	0.472 (0.254–2.952)	0.271 (0.120–0.688)	0.014*
ALBI	−1.747 ± 0.488	−2.119 ± 0.479	0.001**
ALBI grade 1	4 (16.7%)	2 (2.7%)	
ALBI grade 2	20 (83.3%)	71 (97.3%)	0.221
APP	6.943 ± 2.591	8.025 ± 3.141	0.131

Parameter	AP with PE (n=24)	AP without PE (n=73)	p-value
APRI	0.727 (0.357–2.281)	0.421 (0.211–1.077)	0.028*
FIS	−24.927 ± 6.594	−28.146 ± 4.982	0.013*
FIB-4	1.860 (1.065–3.962)	1.208 (0.828–1.944)	0.018*
GPR	34.371 (14.423–55.406)	21.673 (10.847–76.069)	0.570

Data expressed as mean (±SD) and median (the interquartile range-IQR). The student's t-test assessed differences in normally distributed variables, while the Mann-Whitney U test was applied for non-normally distributed variables.

AP: acute pancreatitis; PE: pleural effusion; ABAI: age, bilirubin, albumin index; AARPRI: aspartate aminotransferase to alanine aminotransferase ratio to platelet ratio index; ALBI: albumin-bilirubin score, APP: albumin-platelet product; APRI: aspartate aminotransferase to platelet ratio index; FIS: Fibrosis Score; FIB4: Fibrosis-4; GPR: gamma-glutamyl transferase to platelet ratio

*p<0.05; **p<0.001

Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of the non-invasive indices to discriminate patients with PE (Table 3, Figure 1). Among the evaluated indices, the ALBI score demonstrated the highest discriminatory performance (AUC 0.707; p=0.001) at a cut-off value of −1.890, with a sensitivity of 66.7% and specificity of 68.5%. The ABAI index showed similar performance (AUC 0.695; p<0.001) at a cut-off value of −32.085, yielding a sensitivity of 91.7% and specificity of 61.6%. Other indices, including APRI, FIS, AARPRI, and FIB-4, showed modest but statistically significant discriminatory ability, with AUC values ranging from 0.650 to 0.667.

Table 3 ROC analysis of non-invasive liver fibrosis indices for prediction of pleural effusion

Test Result Variables	AUC	p-value	95% CI		Cut-off Value	Sensitivity	Specificity
			Lower Bound	Upper Bound			
APRI	0.650	0.019*	0.525	0.774	0.241	87.8%	30.1%
ALBI	0.707	0.001**	0.583	0.831	-1.890	66.7%	68.5%
ABAI	0.695	<0.001**	0.587	0.803	-32.085	91.7%	61.6%
FIS	0.658	0.037*	0.510	0.807	-26.685	70.8%	61.6%
AARPRI	0.667	0.004*	0.552	0.782	0.212	84.5%	45.2%
FIB-4	0.662	0.013*	0.534	0.791	1.412	70.8%	58.9%

AUC – area under curve; CI – confidence interval; ABAI: age, bilirubin, albumin index; AARPRI: aspartate aminotransferase to alanine aminotransferase ratio to platelet ratio index; ALBI: albumin-bilirubin score; APRI: AST to platelet ratio index; FIS: Fibrosis Score; FIB4: Fibrosis-4

*p<0.05 ** p≤0.001

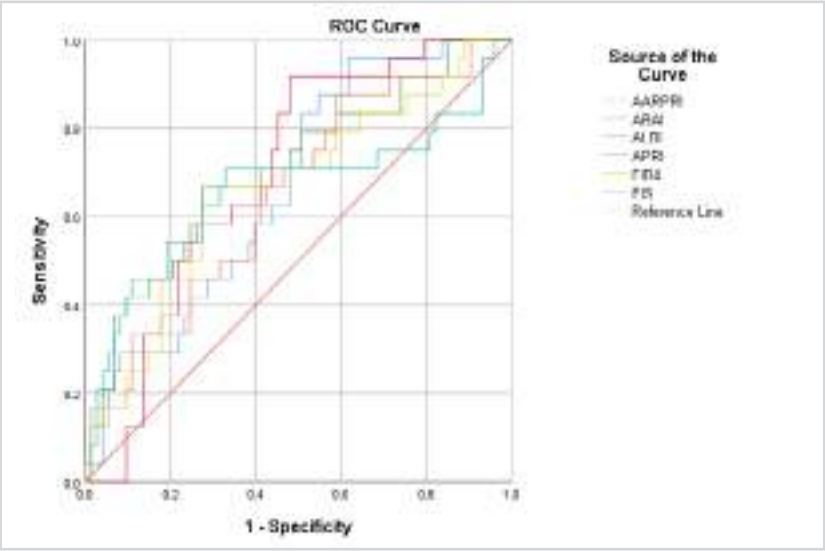

Figure 1 ROC curve analysis for differentiating pleural effusion using noninvasive liver fibrosis indices in acute pancreatitis patients

Data was expressed using ROC (receiver operating characteristic) analysis.

ABAindex: age, bilirubin, albumin index; AARPRI: aspartate aminotransferase to alanine aminotransferase ratio to platelet ratio index; ALBI: albumin-bilirubin score; APRI: AST to platelet ratio index; FIS: Fibrosis Score; FIB4: Fibrosis-4 Univariate binary logistic regression analysis identified ALBI, FIS, and APRI as significant predictors of PE in patients with AP (Table 4). Higher ALBI (OR 5.080; 95% CI 1.734–14.882; p=0.003), higher FIS (OR 1.115; 95% CI 1.019–1.219; p=0.017), and higher APRI values (OR 1.436; 95% CI 1.024–2.013; p=0.036) were associated with the presence of PE. However, in the multivariable logistic regression model, only APRI remained an independent predictor of PE (OR 3.677; 95% CI 1.020–13.255; p=0.047).

Table 4 Logistic regression analysis of non-invasive liver indices as predictors of pleural effusion

Variables	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
ALBI	5.080	(1.734-14.882)	0.003*	4.186	0.398-14.490	0.235
ALBI Grade 2	0.420	(0.088-2.010)	0.277			
ABAI	1.007	(0.997-1.018)	0.180			
FIS	1.115	(1.019-1.219)	0.017*	0.689	(0.444-1.071)	0.098
APRI	**1.436**	**(1.024-2.013)**	**0.036***	**3.677***	**(1.020-13.255)**	**0.047***
AARPRI	1.261	(0.972-1.634)	0.080			
FIB4	1.264	(0.998-1.601)	0.052			

Dependent variable: Pleural Effusion

CI – confidence interval; ABAI: age, bilirubin, albumin index; AARPRI: aspartate aminotransferase to alanine aminotransferase ratio to platelet ratio index; ALBI: albumin-bilirubin score; APRI: AST to platelet ratio index; FIS: Fibrosis Score; FIB4: Fibrosis-4

*p<0.05 ** p≤0.001

DISCUSSION AND CONCLUSION

The investigation of early predictors of complications in AP is of major clinical importance, as the disease course may deteriorate rapidly and lead to respiratory complications, systemic inflammatory response, and multiorgan failure. Among extrapancreatic manifestations, PE is recognised as a marker of more severe disease and poorer clinical outcomes (Luiken et al., 2022). Therefore, identifying laboratory-derived indices capable of predicting PE at admission may contribute to earlier risk stratification and improved patient management.

Previous studies have investigated the prognostic role of hepatobiliary parameters and liver-related indices in AP. In the study by Kirdok et al. (2024), the predictive value of the FIB-4 index for AP severity was evaluated. The authors reported that higher FIB-4 values were associated with more severe disease, particularly in patients with underlying non-alcoholic fatty liver disease. However, PE was not assessed as a specific outcome parameter. Similarly, Shi et al. (2020) examined the association between the ALBI score and in-hospital mortality in critically ill patients with AP. They found that higher ALBI values were significantly associated with increased mortality, suggesting that liver-related indices may serve as useful prognostic tools, although PE was not analysed separately. Our findings are in line with emerging evidence suggesting that non-invasive liver-related indices may have prognostic value in AP. Although previous studies primarily focused on outcomes such as disease severity and mortality, they support the concept that composite liver-related indices reflect systemic inflammatory burden and organ involvement. In this context, our results extend these observations by demonstrating a potential role of APRI in predicting PE as an early extrapancreatic complication.

In the present study, several non-invasive liver fibrosis indices differed significantly between patients with and without PE, including APRI, ALBI, ABAI, FIS, AARPRI, and FIB-4. Among them, ALBI demonstrated the highest discriminatory ability in ROC analysis, while APRI emerged as the only independent predictor of PE in the multivariable model. These findings suggest that indices incorporating transaminases, platelet count, albumin, and bilirubin may reflect systemic inflammatory and perfusion-related disturbances occurring in more severe forms of AP.

The pathophysiological mechanisms underlying these associations are likely multifactorial. AP is characterised by a systemic inflammatory response involving cytokine activation, oxidative stress, and microcirculatory disturbances (Komara et al., 2020; Shah and Rana, 2020). These processes may impair hepatic perfusion and function, leading to elevations in transaminases, alterations in bilirubin metabolism, and reductions in serum albumin concentrations (Zhang et al., 2024). Since several of the investigated indices combine these parameters, they may act as indirect markers of systemic disease severity rather than isolated hepatic injury.

Platelet activation and consumption are also recognised features of systemic inflammation and microvascular dysfunction in AP. Thrombocytopenia and altered platelet dynamics have been associated with the development of multiorgan failure and poorer outcomes (Metri et al., 2024). Because platelet count represents a key component of indices such as APRI and FIB-4, these scores may partially reflect the severity of systemic inflammatory and microcirculatory changes.

Experimental and clinical studies have demonstrated significant alterations in hepatic perfusion during AP, including reductions in portal venous flow during the inflammatory phase and partial recovery after adequate fluid resuscitation (Tutcu et al., 2010). Such haemodynamic changes may influence liver-related biochemical parameters and contribute to the observed associations between fibrosis indices and PE.

Serum albumin and bilirubin are widely used, inexpensive biochemical markers that reflect hepatic synthetic and excretory function. Previous studies have shown that decreased albumin and altered bilirubin levels are associated with increased severity and mortality in AP (Xu et al., 2020; Shi et al., 2020). Because indices such as ALBI and ABAI incorporate these parameters, they may capture systemic metabolic and inflammatory disturbances associated with more severe disease.

Elderly patients are particularly vulnerable to severe forms of AP, and the presence of PE in this population is often associated with worse outcomes. Previous research has demonstrated that PE may serve as an independent predictor of disease severity in older patients, particularly when combined with other risk factors (He et al., 2021).

From a clinical perspective, the early prediction of PE using simple and widely available indices such as APRI may enable closer monitoring and earlier therapeutic interventions. Such an approach may help prevent disease progression, respiratory complications, and multiorgan failure.

This study has several limitations. First, the relatively small sample size limits the generalisability of the findings. Second, the single-centre design may introduce selection bias. Third, the limited number of comparable studies in the literature restricts direct comparisons with previous research. Therefore, larger prospective multicentre studies are needed to confirm the prognostic value of these indices. Although patients with clinically established chronic kidney disease were excluded, renal function was not systematically assessed beyond available clinical data. Condition such as acute kidney injury may influence fluid balance and contribute to the development of PE. Therefore, a potential confounding effect cannot be excluded and should be considered when interpreting the results. However, despite this potential limitation, APRI remained independently associated with PE, suggesting a degree of robustness of the observed relationship.

The persistence of APRI as an independent predictor in the multivariable model may be explained by intercorrelations among the evaluated indices. Many of the analysed parameters share common components, including transaminases, bilirubin, albumin, and platelet count, which may lead to collinearity and reduce their independent contribution in adjusted models. Therefore, simpler composite indices such as APRI may demonstrate greater stability in multivariable analysis.

In conclusion, the present study demonstrated that several non-invasive liver fibrosis indices are associated with the development of PE in patients with AP. Among them, APRI emerged as an independent predictor in the multivariable model. These findings highlight the relationship between liver-related laboratory parameters and the severity of AP and suggest that simple, low-cost indices may assist in early risk stratification. However, external validation in larger, prospective, and multicentre cohorts is required before routine clinical implementation. Such validation is necessary to confirm the reproducibility and generalisability of these findings across different patient populations and healthcare settings.

CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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Indeks omjera AST i trombocita je prediktor razvoja pleuralne efuzije kod akutnog pankreatitisa

SAŽETAK

Pleuralna efuzija predstavlja čestu ekstrapankreasnu komplikaciju akutnog pankreatitisa te je povezana s težom kliničkom slikom i lošijim ishodima liječenja. Rano prepoznavanje pacijenata s povećanim rizikom od razvoja pleuralne efuzije i dalje ima značajan klinički značaj. Cilj ovog istraživanja bio je procijeniti prediktivnu vrijednost neinvazivnih indeksa fibroze jetre za razvoj pleuralne efuzije kod pacijenata s akutnim pankreatitisom.

Ova retrospektivna opservaciona studija provedena u jednom centru obuhvatila je 97 pacijenata hospitaliziranih zbog akutnog pankreatitisa. Laboratorijski parametri prikupljeni pri prijemu korišteni su za izračunavanje više indeksa fibroze jetre, uključujući APRI, AARPRI, FIB-4, ALBI, ABAI, GPR, APP i FIS. Prisustvo pleuralne efuzije procijenjeno je radiografijom grudnog koša. Komparativna analiza pokazala je da su ABAI, AARPRI, ALBI, APRI, FIS i FIB-4 značajno povezani s prisustvom pleuralne efuzije. Analiza ROC krivulje pokazala je najveću diskriminacijsku sposobnost za ALBI (AUC 0,707), zatim za ABAI (AUC 0,695) i APRI (AUC 0,650). U univarijantnoj logističkoj regresijskoj analizi, ALBI, FIS i APRI bili su značajni prediktori razvoja pleuralne efuzije, dok je u multivarijantnoj analizi samo APRI ostao nezavisni prediktor (OR 3,677; p=0,047).

Dobijeni rezultati ukazuju da neinvazivni indeksi fibroze jetre, naročito APRI, mogu predstavljati jednostavne i lako dostupne biomarkere za rano predviđanje razvoja pleuralne efuzije kod pacijenata s akutnim pankreatitisom.

Ključne riječi: Biomarkeri, težina bolesti, testovi funkcije jetre, prognoza, procjena rizika

RESEARCH ARTICLE

Haematological and cytokine responses of Arbor Acre broilers and two Nigerian indigenous chicken genotypes to experimental *Eimeria tenella* infection

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ABSTRACT

Genetic background influences host responses to avian coccidiosis; however, comparative pathological and immune-haematological data for Nigerian indigenous chickens remain limited. This study investigated mortality, haematological alterations, and systemic interferon-gamma (IFN-γ) and interleukin-10 (IL-10) responses following experimental *Eimeria tenella* infection in Arbor Acre broiler, frizzle-feathered, and normal-feathered chickens. Ninety-day-old chicks (n = 30 per genotype) were reared under controlled conditions and confirmed coccidia-free at 19 days of age. Birds were allocated to infected (n = 15 per genotype) and uninfected control groups (n = 15 per genotype). Clinical signs and mortality were monitored, while haematological indices and serum cytokine levels were assessed at 5, 7, and 10 days post-infection (dpi). Mortality was highest in Arbor Acre broilers (40.0%), intermediate in the Normal feathered (26.67%) and lowest in the Frizzle-feathered (20.0%) chickens. Infection induced significant reductions in packed cell volume, haemoglobin concentration, and red blood cell counts, most pronounced at 7 dpi, consistent with haemorrhagic anaemia, with the most severe changes observed in broilers. Total white blood cell and heterophil counts increased across genotypes, indicating a systemic inflammatory response. Serum IFN-γ and IL-10 concentrations were significantly elevated in infected birds at all sampling points but did not differ among genotypes. These findings suggest that genotype-dependent differences in *E. tenella* infection are expressed primarily through mortality and haematological pathology rather than systemic IFN-γ or IL-10 responses. The lower mortality and less pronounced haematological alterations observed in Nigerian indigenous chickens may indicate a greater degree of tolerance to caecal coccidiosis, although further studies are required to confirm the mechanisms underlying this response. Further studies incorporating caecal histopathology, local cytokine expression, and genetic analyses are recommended to clarify mechanisms underlying genotype-related variation in disease outcome.

Keywords: *Eimeria tenella*, coccidiosis, chicken genotype, haematology, cytokine response, tolerance, resilience, genetic resistance

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INTRODUCTION

Avian coccidiosis is one of the most economically important parasitic diseases affecting the poultry industry globally, causing huge losses through mortality, impaired growth, poor feed efficiency, and costs associated with prophylaxis and treatment (Blake and Tomley, 2014; Blake et al., 2020). Coccidiosis in chickens is caused by intracellular protozoan parasites of the genus *Eimeria* (Chapman et al., 2013). *Eimeria tenella,* which has its predilection site in the caeca, is regarded as one of the most pathogenic species due to its association with severe haemorrhagic enteritis, anaemia, and high mortality, particularly in young chickens (Mesa-Pineda et al., 2021). Despite advances in chemoprophylaxis and vaccination, the emergence of drug resistance and variable vaccine efficacy continue to challenge sustainable coccidiosis control (Shivaramaiah et al., 2014; Chapman and Rathinam, 2022).

The genetic background of a host is an important factor which determines susceptibility, disease severity, and outcomes following *Eimeria* infection. Previous studies have demonstrated marked differences among chicken lines and breeds in mortality rates, lesion severity, oocyst output, and immune responses following experimental *E. tenella* infection (Bumstead and Millard, 1987; Lillehoj et al., 2007; Boulton et al., 2018). Commercial broiler chickens, which have been intensively selected for rapid growth and feed efficiency, are often reported to exhibit increased susceptibility to enteric diseases, including coccidiosis, compared with indigenous or unimproved chicken populations (Pinard-Van Der Laan et al., 1998; Broadwater et al., 2025). Nigerian indigenous chickens, such as frizzle-feathered and normal-feathered ecotypes, are widely considered to possess enhanced resilience to infectious diseases, although the immunopathological mechanisms underlying this apparent tolerance remain poorly characterised.

Haematological parameters are valuable indicators of systemic responses to coccidial infection and reflect the degree of anaemia, inflammatory response, and physiological stress associated with caecal damage (Oguntade et al., 2021). *Eimeria tenella* infection is commonly associated with reductions in packed cell volume, haemoglobin concentration, and erythrocyte count, consistent with haemorrhagic anaemia, alongside alterations in leukocyte profiles indicative of inflammatory and immune activation (Fatoba and Adeleke, 2018). However, the magnitude and pattern of these haematological changes may vary substantially between chicken genotypes, reflecting differences in host-parasite interactions and disease tolerance.

Protective immunity against *E. tenella* is predominantly cell mediated, with interferon gamma (IFN-γ) playing a central role in limiting parasite replication through macrophage activation and modulation of T-cell responses (Lillehoj and Lillehoj, 2000; Dalloul and Lillehoj, 2006). On the other hand, interleukin-10 (IL-10) functions as a key regulatory cytokine that constrains excessive inflammation but may also facilitate parasite persistence when overexpressed (Rothwell et al., 2004; Arendt et al., 2019). The balance between pro-inflammatory and regulatory cytokine responses is therefore critical in determining disease outcome, tissue damage, and survival following *E. tenella* infection. Evidence suggests that genetic differences among chicken populations influence cytokine expression profiles, yet comparative data linking IFN-γ and IL-10 responses to mortality and haematological changes across commercial and indigenous genotypes remain limited.

The present study investigated genotype-dependent differences in mortality, haematological indices, and serum IFN-γ and IL-10 responses in Arbor Acre broiler chickens and two Nigerian indigenous chicken genotypes (frizzle-feathered and normal-feathered) following experimental *E. tenella* infection. By integrating clinical outcome measures with haematological and immunological parameters, this study aimed to provide insight into host genotype influences on susceptibility and immune regulation during caecal coccidiosis.

MATERIALS AND METHODS

Ethical Approval

Ethical approval for this study was granted by the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC), with approval number ABUCAUC/2024/025.

Location of the Study

The study was conducted at the Poultry Research Pen of the Veterinary Teaching Hospital, Ahmadu Bello University, Zaria.

Experimental Chickens and Management

Unsexed day-old chicks (DOCs) of two (2) genotypes of Nigerian indigenous chickens (Frizzle feathered [FF]

and Normal feathered [NF]) and one (1) exotic breed of broiler (Arbor Acre [AA]) were obtained from the breeder stock of NF and FF indigenous chickens in the Poultry Breeding Unit of the Directorate Farm, Federal University of Agriculture, Abeokuta, Ogun State, Nigeria and a reputable hatchery in Nigeria (CHI Hatchery, Ibadan) respectively.

The pens were cleaned, washed with detergent and water, and disinfected 7 days before the arrival of the birds. Coccidiostat-free and drug-free starter feed (ME = 2,926.38 kcal/kg, CP = 21.16%) was composed, milled, and fed to the birds *ad libitum*. Clean borehole water (coccidiostat-free and drug-free) was also administered *ad libitum*. The chicks were brooded for 19 days, screened, and confirmed negative for *E. tenella* oocysts and transferred to well-disinfected deep litter pens measuring 2m x 2m each.

Source of *Eimeria tenella* Used for the Experimental Study

Eimeria tenella, previously isolated and characterized by Jatau et al. (2016), was obtained from the Protozoology Laboratory, Department of Veterinary Parasitology and Entomology Laboratory, ABU Zaria, Nigeria.

Experimental Design

A total of 90 chicks (Arbor Acre [AA], Frizzle-feathered [FF], and Normal-feathered [NF] – n=30 each) were obtained for the experiment. The birds were screened (at day 19 of age) and confirmed healthy and free from coccidiosis. Six (6) groups; 3 control groups – C1, C2, and C3 (n=15 each) consisting of AA, FF, and NF, respectively, and 3 treatment groups – T1, T2, and T3 (n=15 each) consisting of AA, FF, and NF, respectively, were designed for the experiment. Each bird in all groups was wing-tagged for proper identification and data collection. At the third week of age (day 21, day 0 post-infection [pi]), each bird in the treatment groups was inoculated orally with 40,000 sporulated *E. tenella* oocysts. Birds of the control group were not infected. At days 5, 7, and 10 pi, three (3) birds from each group were randomly selected for blood collection. The experiment was terminated at day 10 pi (Day 31 of the experiment).

Parasite Inoculation

A suspension containing 40,000 sporulated *E. tenella* oocysts per mL was prepared under standard conditions following the method of Holdsworth et al. (2004). Each bird in the infected groups received 1 mL of suspension (40,000 sporulated *E. tenella* oocysts) by oral gavage. Control birds received an equivalent volume of phosphate-buffered saline (PBS).

Clinical Signs and Determination of Mortality Rate

Clinical signs were observed and recorded daily. The mortality rate for each group was determined by dividing the number of dead chickens by the number of initial chickens at the time of challenge, multiplied by one hundred (Wang et al. 2020).

Blood Sample Collection and Haematological Examination

Two millilitres (2 mL) of blood were collected from the wing vein of each bird using sterile 2 mL syringes. One millilitre (1 mL) of the blood sample was immediately placed into a sample bottle containing EDTA (Ethylenediaminetetraacetic acid) for haematological analyses and the remaining 1 ml of blood was placed in plain sample bottles without EDTA for serological studies (ELISA). The uncoagulated blood was used to determine packed cell volume (PCV) using a microhaematocrit capillary tube and a haematocrit reader as described by Feldmann et al. (2000). Red blood cell count (RBC count) and total white blood cell count (TWBC) were determined using the haemocytometer method (Feldmann et al., 2000), while haemoglobin concentration (HbC) was determined using the cyanomethhaemoglobin method (Campbell, 2015). Other haematological indices, including mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were calculated according to Esievo (2017) as follows:

$$\text{MCV } (f\text{L}) = \frac{\text{PCV (\%)}}{\text{RBC (x10}^{12}\text{/L)}} \times 10$$

$$\text{MCH (pg)} = \frac{\text{Hb (g/dL)}}{\text{RBC (x10}^{12}\text{/L)}} \times 10$$

$$\text{MCHC (g/dL)} = \frac{\text{Hb (g/dL)}}{\text{PCV (\%)}} \times 100$$

Determination of Serum Interleukin-10 and Interferon Gamma

The blood samples collected from the birds were allowed to clot for two hours at room temperature before centrifugation for 20 minutes at approximately

1000 x *g* to harvest the serum, which was stored at -2^{0}C. The serum concentrations of IL-10 and IFN-γ were detected using an indirect ELISA with the "Chicken IL-10 ELISA Kit" and "Chicken IFN-γ ELISA Kit" of Abbkine, Inc – China in duplicate according to the manufacturer's instructions.

Data Analyses

Descriptive statistics were used to describe mortality rates. Data for haematological parameters and cytokines (IL-10 and IFN-γ) were expressed as means and standard error of means (± SEM), and they were statistically analysed using a one-way analysis of variance (ANOVA), complimented by post hoc analysis using the Tukey's multiple comparison. All statistical analyses were processed by GraphPad Prism® software version 6.07. Values of $P \leq 0.05$ were considered significant.

RESULTS

Clinical Signs and Mortality

Birds experimentally infected with *Eimeria tenella* (T1, T2 and T3) developed clinical signs typical of caecal coccidiosis, including depression, reduced feed intake, somnolence, bloody diarrhoea, emaciation and mortality. No clinical signs or mortalities were observed in the control groups.

Mortality occurred only in infected birds and varied among genotypes (Table 1). Arbor Acre broilers (T1) exhibited the highest mortality rate (40.0%), followed by normal-feathered chickens (T3; 26.67%) and frizzle-feathered chickens (T2; 20.0%).

Haematological Parameters

Infection with *E. tenella* resulted in reductions in packed cell volume (PCV), red blood cell (RBC) count and haemoglobin concentration (HbC) in all infected groups compared with their respective controls (Table 2). These changes were most pronounced at 7 dpi, coinciding with the peak phase of infection. Among infected birds, Arbor Acre broilers generally exhibited the greatest reductions in erythrocytic parameters, particularly RBC count and HbC at 7 dpi ($p < 0.05$) compared to the Frizzle-feathered and Normal feathered chickens.

Alterations in erythrocyte indices were observed during infection. Mean corpuscular volume (MCV) increased markedly in infected Arbor Acre broilers at 7 dpi and was significantly higher than that of frizzle-feathered chickens, while mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) showed relatively minor variations. MCHC did not differ significantly ($p > 0.05$) among infected and control groups throughout the study period.

Total white blood cell (TWBC) counts were generally higher in all infected birds than in controls at all sampling periods, indicating activation of systemic inflammatory responses. However, the increases were only significant ($p < 0.05$) in the Frizzle-feathered and Normal-feathered chickens when compared with their respective controls at 5 and 7 dpi. Significant differences among infected genotypes were not observed.

Serum Cytokine Responses

Serum concentrations of both interleukin-10 (IL-10) and interferon-gamma (IFN-γ) were significantly ($p < 0.05$) elevated in infected birds compared with their respective controls at 5, 7 and 10 dpi (Table 3). Despite these infection-induced increases, no significant differences ($p > 0.05$) were detected among the infected genotypes at any sampling point.

Overall, the cytokine results indicate that *E. tenella* infection elicited strong systemic pro-inflammatory and regulatory immune responses across all chicken genotypes, while genotype-related differences were more evident in mortality and haematological outcomes than in circulating IFN-γ or IL-10 concentrations.

Table 1 Mortality rate of Arbor acre, frizzle feathered, and normal feathered chickens infected with *E. tenella* and their controls

Groups	Mortality	Population	Mortality rate (%)
C1	0	15	0.00
C2	0	15	0.00
C3	0	15	0.00
T1	6	15	40.00

Groups	Mortality	Population	Mortality rate (%)
T2	3	15	20.00
T3	4	15	26.67

C1 – Arbor acre control; **C2** – Frizzle feathered control; **C3** – Normal feathered control; **T1** – Arbor acre infected; **T2** – Frizzle feathered infected; **T3** – Normal feathered infected

Table 2 Haematological parameters of Arbor acre, frizzle feathered, and normal feathered chickens infected with *E. tenella* and their controls at 5-, 7- and 10-days post infection (dpi)

Parameters	Experimental groups						
	C1	C2	C3	T1	T2	T3	P-value
5 dpi							
PCV (%)	36.0±2.65^{ab}	32.5±0.50^{ab}	38.0±1.41^{a}	32.3±1.45^{ab}	31.0±1.53^{ab}	29.5±1.04^{b}	0.0093
RBC (x10^{12}/L)	4.10±0.15	3.70±0.10	3.82±0.09	3.80±0.21	3.57±0.20	3.73±0.23	0.4943
HbC (g/dL)	12.03±0.90	10.90±0.20	12.66±0.47	11.60±0.64	10.63±0.67	9.83±0.95	0.0923
MCV (fL)	87.63±3.87^{b}	87.87±1.02^{ab}	99.38±1.90^{a}	85.22±1.79^{b}	87.05±2.11^{b}	79.62±2.88^{b}	0.0007
MCH (pg)	29.28±1.20^{ab}	29.47±0.26^{ab}	33.11±0.63^{a}	30.53±0.40^{ab}	29.81±0.79^{ab}	26.47±2.53^{b}	0.0541
MCHC (g/dL)	33.42±0.44	33.54 ± 0.10	33.31 ± 0.03	35.85 ± 0.42	34.32±1.71	33.13±2.44	0.7593
TWBC (x10^{9}/L)	4.50 ± 0.30^{ab}	3.93 ± 0.30^{b}	3.84 ± 0.21^{b}	5.53 ± 0.34^{ab}	6.63 ± 0.86^{a}	6.53 ± 0.48^{a}	0.0008
7 dpi							
PCV (%)	32.67±1.45^{a}	33.33±0.88^{a}	32.00±0.84^{a}	21.00±1.00^{b}	28.00±1.14^{ab}	26.00±1.79^{b}	0.0003
RBC (x10^{12}/L)	3.30±0.26^{a}	3.40±0.26^{a}	3.38±0.17^{a}	1.50±0.10^{b}	2.90±0.09^{a}	2.34±0.34^{a}	0.0010
HbC (g/dL)	10.77±0.38^{a}	11.07±0.23^{a}	10.60±0.19^{a}	7.00±0.30^{c}	9.34±0.39^{ab}	8.50±0.56^{b}	0.0001
MCV (fL)	99.56±3.73^{b}	98.91±5.75^{b}	95.22±3.19^{b}	140.18±2.68^{a}	96.81±4.57^{b}	116.56±9.53^{ab}	0.0046
MCH (pg)	46.74±1.12^{a}	32.86±2.04^{b}	38.21±3.36^{ab}	32.88±1.70^{b}	32.28±1.50^{b}	31.57±1.13^{b}	0.0088
MCHC (g/dL)	32.99 ± 0.51	33.21 ± 0.18	33.15 ± 0.30	33.34 ± 0.16	33.35 ± 0.09	32.75 ± 0.60	0.8705
TWBC (x10^{9}/L)	3.83 ± 0.26^{bc}	3.57 ± 0.29^{c}	4.02 ± 0.29^{bc}	5.24 ± 0.32^{ab}	6.30 ± 0.20^{a}	5.60 ± 0.34^{a}	0.0002
10 dpi							
PCV (%)	36.67±0.88^{ab}	40.00±3.00^{a}	37.00±0.95^{a}	33.00±0.00^{ab}	32.00±1.30^{ab}	28.00±3.19^{b}	0.0093
RBC (x10^{12}/L)	3.80±0.17^{a}	4.00±0.20^{a}	3.82±0.18^{a}	2.90±0.00^{ab}	3.00±0.16^{ab}	2.45±0.40^{b}	0.0056
HbC (g/dL)	12.00±0.38	13.10±1.20	11.10±1.11	10.50±0.00	10.34±0.32	9.03±0.98	0.1253
MCV (fL)	96.75±3.25	99.87±2.51	97.57±4.19	113.79±0.00	107.38±4.75	118.79±9.41	0.1000
MCH (pg)	36.21±0.00	34.73±1.48	38.56±3.68	31.67±1.35	32.68±1.37	29.30±3.12	0.2171
MCHC (g/dL)	32.72 ± 0.37	32.71 ± 0.55	29.97 ± 2.78	31.82 ± 0.00	32.40 ± 0.81	32.35 ± 0.89	0.8399
TWBC (x10^{9}/L)	4.35 ± 0.15^{c}	5.13 ± 0.48^{bc}	4.40 ± 0.47^{c}	6.26 ± 0.19^{ab}	7.20 ± 0.00^{a}	6.70 ± 0.17^{ab}	0.0002

Data expressed as Mean ± Standard Error of Mean (SEM) (n = 3 blood samples per group)

Values with different superscript letters within the same row are statistically significant ($P \leq 0.05$)

C1 – Arbor acre control; C2 – Frizzle feathered control; C3 – Normal feathered control; T1 – Arbor acre infected; T2 – Frizzle feathered infected; T3 – Normal feathered infected

Table 3 Mean (± SEM) serum interleukin-10 and interferon gamma of Arbor acre, Frizzle feathered, and Normal feathered chickens infected with *E. tenella* and their controls at 5-, 7- and 10-days post infection (dpi)

Serum cytokines	Experimental groups						P-value
	C1	C2	C3	T1	T2	T3	
5 dpi							
IL-10 (pg/ml)	54.55±5.68^{b}	60.86±2.43^{b}	60.87±4.79^{b}	94.88±4.38^{a}	86.02±2.53^{a}	88.19±5.73^{a}	<0.0001
IFN-γ **(pg/ml)**	77.64±3.99^{bc}	66.99±3.78^{bd}	79.34±6.80^{bc}	111.0±2.70^{a}	94.07±7.85^{ac}	102.1±1.86^{a}	0.0005
7 dpi							
IL-10 (pg/ml)	50.36±5.88^{c}	66.03±7.52^{bc}	63.10±2.38^{c}	87.96±5.50^{ab}	93.05±3.32^{a}	94.19±2.69^{a}	<0.0001
IFN-γ **(pg/ml)**	52.23±2.12^{ae}	67.65±1.97^{def}	77.64±3.80^{bce}	82.91±6.31^{ae}	91.45±4.69^{ac}	98.10±2.56^{a}	<0.0001
10 dpi							
IL-10 (pg/ml)	60.28±2.68^{bce}	57.29±5.57^{bde}	49.18±3.29^{b}	89.28±0.92^{a}	78.66±3.03^{ac}	77.39±7.45^{ae}	0.0002
IFN-γ **(pg/ml)**	77.21±4.81^{b}	70.15±3.10^{b}	64.64±2.95^{b}	97.11±1.22^{a}	96.49±3.99^{a}	98.80±4.19^{a}	<0.0001

Data expressed as Mean ± Standard Error of Mean (SEM) (n = 3 blood samples per group)

Values with different superscript letters within the same row are statistically significant ($P \leq 0.05$)

C1 – Arbor acre control; C2 – Frizzle feathered control; C3 – Normal feathered control; T1 – Arbor acre infected; T2 – Frizzle feathered infected; T3 – Normal feathered infected

DISCUSSION AND CONCLUSION

The present study demonstrated clear genotype-dependent differences in mortality, haematological responses, and cytokine profiles following experimental *Eimeria tenella* infection, despite all infected groups being exposed to the same parasite dose. These findings reinforce the importance of host genetic background in shaping disease outcome and immunopathology during caecal coccidiosis.

Mortality occurred exclusively in infected birds, confirming the pathogenicity of *E. tenella* under the experimental conditions. The highest mortality was observed in Arbor Acre broilers, followed by Normal-feathered and Frizzle-feathered Nigerian indigenous chickens. This pattern is consistent with previous reports indicating that intensively selected commercial broilers may exhibit increased susceptibility to enteric diseases compared with indigenous or unimproved chicken populations (Boulton et al., 2018; Broadwater et al., 2025). The lower mortality observed in indigenous genotypes suggests a greater degree of tolerance to *E. tenella*-induced pathology, rather than complete resistance, as evidenced by the presence of clinical disease and measurable haematological and immunological alterations.

The progressive reductions in packed cell volume (PCV), haemoglobin concentration (Hb), and red blood cell (RBC) count in infected birds, particularly at 7 dpi, reflect the haemorrhagic nature of caecal coccidiosis. *Eimeria tenella* causes extensive destruction of caecal epithelium and submucosal vasculature, leading to blood loss, anaemia, and hypoxia (Chapman et al., 2013; Mesa-Pineda et al., 2021). The more pronounced reductions in PCV, Hb, and RBC counts observed in Arbor Acre broilers at peak infection (7 dpi) agree with earlier studies reporting more severe anaemia in improved and genetically susceptible chicken lines compared to unimproved indigenous chickens (Pinard-Van Der Laan et al., 1998; Ekezie et al., 2023). In contrast, the relatively moderate haematological depression and earlier recovery observed in indigenous chickens suggest improved capacity to withstand blood loss or more efficient regenerative erythropoiesis.

Alterations in erythrocyte indices further support this interpretation. The transient increase in mean corpuscular volume observed in broilers at 7 dpi, accompanied by reductions in RBC count and haemoglobin concentration, is indicative of a regenerative macrocytic response to acute blood loss (Campbell, 2015). The absence of persistent differences in MCHC across genotypes and time points suggests

that hypochromia was not a dominant feature, and that anaemia was primarily attributable to haemorrhage rather than impaired haemoglobin synthesis. Similar erythrocytic responses have been described in experimental *E. tenella* infections and are considered characteristic of acute caecal coccidiosis (Esievo, 2017; Umar et al., 2022).

Leucocytosis was observed across all infected groups. This finding is consistent with an active inflammatory and immune response to coccidial infection (Esievo et al., 2017; Oguntade et al., 2024). Although mean total white blood cell (TWBC) counts increased across all infected groups, the rise was statistically significant only in Frizzle-feathered and Normal-feathered chickens at 5 and 7 dpi, relative to their respective controls. This suggests that the indigenous genotypes mounted a stronger systemic leucocytic response to infection compared with Arbor Acre broilers. Notably, no significant differences were observed in TWBC counts among the three infected groups, indicating that the variation was more evident in comparison with controls rather than between genotypes. The enhanced leucocytic response in the Frizzle-feathered and Normal-feathered chickens may partly explain their lower mortality rates compared to Arbor Acre broilers, as a more robust leucocytic response in the indigenous chickens likely contributed to a better control of the infection. These results are supported by the findings of Oguntade et al. (2024), who also reported significantly higher TWBC counts in Nigerian indigenous chickens than in Arbor Acre broilers at 7 dpi.

Serum cytokine analysis revealed sustained elevations of both IFN-γ and IL-10 in infected birds across all genotypes and time points, confirming the activation of cell-mediated immunity alongside regulatory mechanisms. Interferon gamma (IFN-γ) is a key effector cytokine in protection against *Eimeria*, mediating macrophage activation, inhibition of intracellular parasite development, and enhancement of antigen presentation (Lillehoj and Lillehoj, 2000; Dalloul and Lillehoj, 2006). The consistent increase in IFN-γ levels in infected birds supports its central role in host defence during *E. tenella* infection.

The concurrent marked elevation of IL-10 highlights the importance of immunoregulation during caecal coccidiosis. Interleukin 10 (IL-10) functions to limit excessive inflammation and tissue damage but may also permit parasite survival when expressed at high levels (Rothwell et al., 2004; Arendt et al., 2019).

The lack of significant differences in systemic IFN-γ and IL-10 concentrations among infected genotypes may reflect compartmentalization of immune responses during *E. tenella* infection. Cytokine production within the caecal mucosa can differ substantially from circulating serum concentrations, and local tissue responses may be more relevant determinants of parasite control and tissue damage (Yun et al., 2000; Brown and Esterházy 2021). As a result, serum cytokine measurements alone as carried out in this study, may underestimate genotype-related differences in immune regulation. The findings of Thakur et al. (2019) confirm this fact. In their report they observed significant genotype-related differences in intestinal gene expression of IFN-γ, IL-17 and IL-1β between coccidiosis infected indigenous chickens (Kadaknath, Cari Vishal) and exotic (Cobb broilers) chickens.

The findings of this study indicate that the Nigerian indigenous chickens (Frizzle feathered and Normal feathered chickens) exhibited greater tolerance to *E. tenella* infection than commercial broilers (Arbor Acre broilers), characterised by lower mortality and less severe haematological disruption despite comparable systemic cytokine responses. This supports the concept that tolerance, rather than resistance, is a key feature of indigenous chicken genotypes and may be advantageous under endemic disease pressure (Råberg et al., 2009; Broadwater et al., 2025). Such traits may represent valuable genetic resources for breeding programmes aimed at improving resilience to coccidiosis without compromising immune regulation.

In conclusion, the present study demonstrates that host genotype significantly influences mortality and haematological responses to *E. tenella* infection, whereas systemic IFN-γ and IL-10 responses remain broadly comparable across genotypes. These results contribute to a better understanding of host-parasite interactions in avian coccidiosis and highlight the potential value of indigenous chicken genotypes in sustainable poultry production systems.

However, some limitations should be considered when interpreting the findings of this study. First, the sample size was relatively modest, which may have reduced the ability to detect subtle genotype-related differences in some haematological and cytokine parameters. Second, only systemic concentrations of IFN-γ and IL-10 were evaluated; local immune responses within the caecal tissue, where *E. tenella* infection occurs, were not assessed. Third, the study focused on a

limited number of immune mediators and therefore may not fully reflect the complexity of host immune regulation during coccidiosis. Furthermore, genetic markers associated with disease resistance or tolerance were not investigated. Future studies should integrate histopathological lesion scoring, tissue cytokine profiling, immunohistochemistry, transcriptomic analyses, and genetic characterization of indigenous chicken populations to better elucidate the mechanisms underlying resilience to *E. tenella* infection.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

CONTRIBUTIONS

Conception: GA; Design: SBO, IDJ; Supervision: SBO, IDJ; Fundings: GA; Data Collection and/or Processing: GA; Analysis and/or Interpretation of the Data: JES; Literature Review: JES; Writing: GA; Critical Review: SBO, IDJ.

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Hematološki i citokinski odgovori Arbor Acre brojlera i dva nigerijska autohtona genotipa kokoši na eksperimentalnu infekciju *Eimeria tenella*

SAŽETAK

Genetska pozadina utiče na odgovore domaćina na avijarnu kokcidiozu; međutim, komparativni patološki i imuno-hematološki podaci za nigerijske autohtone kokoši i dalje su ograničeni. Ova studija je istraživala mortalitet, hematološke promjene i sistemske odgovore interferona-gama (IFN-γ) i interleukina-10 (IL-10) nakon eksperimentalne infekcije *Eimeria tenella* kod Arbor Acre brojlera, kovrdžavo pernatih i normalno pernatih kokoši. Pilići starosti 90 dana (n = 30 po genotipu) uzgajani su u kontrolisanim uslovima i potvrđeno je da su slobodni od kokcidija u dobi od 19 dana. Ptice su raspoređene u inficirane (n = 15 po genotipu) i neinficirane kontrolne grupe (n = 15 po genotipu). Klinički znakovi i mortalitet su praćeni, dok su hematološki parametri i nivoi serumskih citokina analizirani 5., 7. i 10. dana nakon infekcije (dpi). Mortalitet je bio najviši kod Arbor Acre brojlera (40,0%), srednji kod normalno pernatih (26,67%) i najniži kod kovrdžavo pernatih kokoši (20,0%). Infekcija je izazvala značajno smanjenje hematokrita (PCV), koncentracije hemoglobina i broja eritrocita, najizraženije 7. dana nakon infekcije, što je bilo u skladu sa hemoragičnom anemijom, pri čemu su najteže promjene zabilježene kod brojlera. Ukupan broj leukocita i heterofila je porastao kod svih genotipova, što ukazuje na sistemski inflamatorni odgovor. Serumske koncentracije IFN-γ i IL-10 bile su značajno povišene kod inficiranih ptica u svim vremenskim tačkama, ali se nisu razlikovale između genotipova. Ovi rezultati sugerišu da se genotipske razlike u infekciji *E. tenella* prvenstveno manifestuju kroz mortalitet i hematološke promjene, a ne kroz sistemske IFN-γ ili IL-10 odgovore. Niži mortalitet i blaže hematološke promjene kod nigerijskih autohtonih kokoši mogu ukazivati na veću toleranciju na cekalnu kokcidiozu, iako su potrebna dodatna istraživanja za potvrdu mehanizama ovog odgovora. Dalja istraživanja koja uključuju histopatologiju slijepog crijeva, lokalnu ekspresiju citokina i genetske analize preporučuju se radi razjašnjavanja mehanizama genotipski uslovljenih razlika u ishodu bolesti.

Ključne riječi: *Eimeria tenella*, kokcidioza, genotip kokoši, hematologija, citokinski odgovor, tolerancija, otpornost, genetska otpornost

SHORT COMMUNICATION

First record of the pipefish *Syngnathus typhle* (Linnaeus, 1758) (Teleostei: Syngnathidae) in Bosnia and Herzegovina

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ABSTRACT

The present study reports the first record of the broadnosed pipefish, *Syngnathus typhle* (Linnaeus, 1758), in Bosnia and Herzegovina. The specimen was observed at a depth of approximately 40 cm within a *Cymodocea nodosa* meadow over a muddy–sandy substrate in Neum Bay. The individual exhibited pronounced cryptic behavior, showing crypsis through morphological and behavioral mimicry of seagrass leaves, maintaining an inverted posture and closely aligning with surrounding vegetation. The specimen was documented using photography and was briefly handled in situ without being removed from the water. The observed individual was a brooding male, carrying eggs within the ventral brood pouch. This finding extends the known distribution of *S. typhle* in the Adriatic Sea and highlights the importance of continued field surveys in the relatively understudied coastal waters of Bosnia and Herzegovina.

Keywords: Adriatic Sea, Bosnia and Herzegovina, pipefish

INTRODUCTION

Pipefishes (family Syngnathidae) represent a diverse group of marine fishes widely distributed in coastal and estuarine habitats of the Mediterranean Sea (Dawson, 1986). Six species of the genus *Syngnathus* have been recorded throughout the Adriatic Sea along the coasts of Croatia, Italy, Montenegro, Albania, and Slovenia (Jardas, 1996; Lipej et al., 2010).

Syngnathus typhle (Linnaeus, 1758) is distributed throughout the eastern Atlantic from Norway to southern Spain, including the Baltic Sea and the British Isles. It can be considered endemic to pan-Europe. Within the Mediterranean Sea, the species has been recorded from the Iberian Peninsula, the Gulf of Lion, the Ligurian Sea, Venice Lagoon, western Sicily, Croatian estuarine systems, as well as the Black Sea and the Sea of Azov (Pollom, 2014) (Figure 1).

Recent studies based on updated marine species checklists and consolidated survey data confirmed the presence of 106 fish species in the territorial waters of Bosnia and Herzegovina, providing the first structured preliminary inventory of the country's marine ichthyofauna. Representatives of the family Syngnathidae, including *Syngnathus tenuirostris*, *Hippocampus hippocampus*, and *Hippocampus guttulatus*, had previously been documented, whereas *Syngnathus typhle* had not been recorded (Kahrić and Gajić, 2016; Čelebičić et al., 2025).

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Figure 1 Distribution of *Syngnathus typhle*. Reproduced from Pollom (2014) with permission for non-commercial use

The present study reports the first occurrence of *S. typhle* in Bosnia and Herzegovina and demonstrates the applicability of non-destructive photographic and morphometric methods for documenting rare, endangered or poorly studied marine species.

MATERIALS AND METHODS

The specimen was observed during a field survey conducted in Neum Bay, Bosnia and Herzegovina, at a depth of approximately 0.4 m within a *Cymodocea nodosa* meadow on muddy–sandy substrate (42.913339°N, 17.625523°E). The individual was photographed underwater and briefly handled in situ, without removal from the water.

Species identification was based on external morphological characteristics and taxonomic keys provided in *Ribe Jadrana* (Šoljan, 1965). Diagnostic identification followed determination points 52, 54, 55, 57, 61, 65, and 66 of the key. Morphological features used for identification included body symmetry, non-protruding eyes, an elongated rigid oral tube with terminal mouth opening, a single soft dorsal fin,

Figure 2 *Syngnathus typhle* L. recorded in Neum Bay

body axis alignment, presence of pectoral fins, and proportional head morphology.

Taxonomic nomenclature was verified using WoRMS – World Register of Marine Species (2026), confirming *Syngnathus typhle* (Linnaeus, 1758) as the accepted species name.

Morphometric analysis was performed using ImageJ software on photographic material. After calibration using a known scale, morphometric characters were measured from the images. This methodology minimized specimen handling and avoided destructive sampling. The approach follows recent recommendations emphasizing the use of image-based morphometric techniques and non-invasive documentation in marine biological research (Rizzo et al., 2017; Andrialovanirina et al., 2020).

RESULTS

One specimen of *Syngnathus typhle* was recorded in Neum Bay, Bosnia and Herzegovina, at a depth of approximately 0.4 m within a *Cymodocea nodosa* meadow on muddy–sandy substrate (Figure 2). The specimen morphologically corresponded to *S. typhle*, possessing a robust cylindrical body, relatively

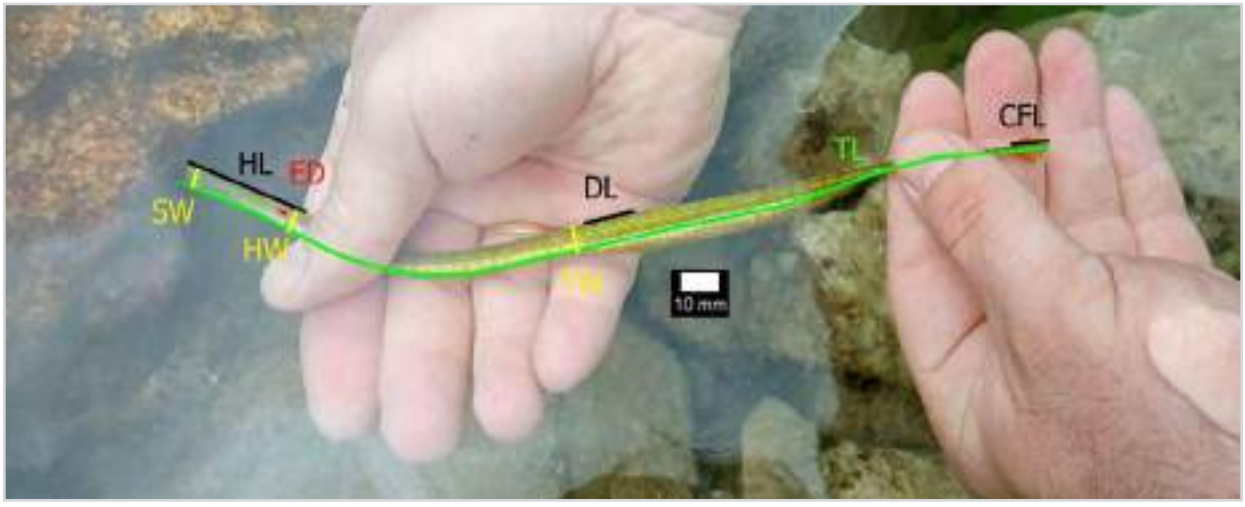

Figure 3 Morphometric measurements of *Syngnathus typhle* L.

short and broad snout, and a distinct ventral brood pouch enlargement characteristic of gravid males. Identification based on the determination key of Šoljan (1965) initially corresponded to *Siphonostoma typhle* KP.

However, verification through WoRMS confirmed *Syngnathus typhle* (Linnaeus, 1758) as the currently accepted name. The specimen was identified as a male due to the presence of a developed ventral brood pouch used for embryo incubation.

Morphometric measurements obtained using ImageJ are presented in Table 1 and Figure 3. The specimen had a total length of 234.97 mm. The use of digital image analysis enabled accurate morphometric characterization without removing the organism from its habitat or causing unnecessary stress. Such approaches are increasingly important in studies involving potentially rare, poorly known, or conservation-sensitive marine species.

Table 1 Morphometric measurements (mm) of the examined specimen including total length (TL), snout width (SW), head width (HW), trunk width (TW), head length (HL), caudal fin length (CFL), dorsal fin length (DL), and eye diameter (ED)

Characteristic	(mm)
TL – Total length	234.97
SW – Snout width	5.57
HW – Head width	5.81
TW – Trunk width	6.00
HL – Head length	32.65
CFL – Caudal fin length	9.30
DL – Dorsal fin length	12.80
ED – Eye diameter	1.12

The individual exhibited pronounced cryptic behavior, showing crypsis through morphological and behavioral mimicry of seagrass leaves, maintaining an inverted posture and closely aligning with surrounding vegetation. Such camouflage behavior is characteristic of syngnathid fishes inhabiting seagrass meadows and represents an important adaptation (Kendrick and Hyndes, 2005; Shokri et al., 2009).

DISCUSSION AND CONCLUSION

Syngnathus typhle is widely distributed throughout the Mediterranean Sea and has frequently been recorded along the Adriatic coasts of neighboring countries (Jardas, 1996; Lipej et al., 2010). Its occurrence in Bosnia and Herzegovina was therefore expected, although previously undocumented. The present record extends the known distribution of the species within the Adriatic Sea and contributes to the knowledge of the marine ichthyofauna of Bosnia and Herzegovina.

This finding represents a new species record within the family Syngnathidae and the second recorded species of the genus Syngnathus for the country (Čelebičić et al., 2025). The observation of the species within a *Cymodocea nodosa* meadow further emphasizes the ecological importance of seagrass habitats for syngnathid fishes. Syngnathids are often an important component of seagrass ecosystems, where they mimic macrophytes through cryptic coloration and body shape adaptations.

Species associated with seagrass habitats are considered important indicator organisms that can be used to assess the conservation value and ecological condition of estuarine and coastal seagrass beds. Consequently, the conservation of syngnathids may also provide broader ecological benefits for other species sharing the same habitats, as significant correlations in density and spatial assemblage structure with other fish species have been documented (Shokri et al., 2009).

The study additionally demonstrates the usefulness of non-destructive photographic documentation and digital morphometric analysis in marine biodiversity research. The applied methodology enabled accurate species identification and morphometric characterization without removing the specimen from its habitat, thereby minimizing stress and potential disturbance to the organism. Such approaches are increasingly important for studying rare, poorly known, or potentially vulnerable marine species and support ethical and precautionary research practices.

Further systematic investigations are necessary to better assess the diversity, distribution, ecological role, and conservation status of syngnathid fishes in Bosnia and Herzegovina and the wider Adriatic region.

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Prvi nalaz šila tupokljunog *Syngnathus typhle* (Linnaeus, 1758) (Teleostei: Syngnathidae) u Bosni i Hercegovini

SAŽETAK

U ovom radu se izvještava o prvom nalazu šila tupokljunog *Syngnathus typhle* (Linnaeus, 1758) u Bosni i Hercegovini. Jedinka je zabilježena na dubini od približno 40 cm unutar livade *Cymodocea nodosa* na muljevito-pjeskovitom dnu u Neumskom zaljevu. Uočena jedinka pokazivala je izraženo kriptično ponašanje, ostvarujući kriptičnost putem morfološke i bihevioralne mimikrije listova morske cvjetnice, zadržavajući inverzan položaj i usklađujući se s okolnom vegetacijom. Jedinka je dokumentovana in-situ fotografijom uz kratkotrajno rukovanje bez vađenja iz vode i analizirana ImageJ softverom. Uočeni primjerak bio je 23,5 cm dug, gravidni mužjak, s jajima u ventralnoj inkubacionoj vreći. Ovaj nalaz proširuje poznatu rasprostranjenost vrste *S. typhle* u Jadranskom moru i naglašava značaj daljnjih terenskih istraživanja u relativno nedovoljno istraženim obalnim vodama Bosne i Hercegovine.

Ključne riječi: Bosna i Hercegovina, Jadransko more, šilo tupokljuno

PROFESSIONAL PAPER

The dog as a patient rather than an experimental animal in cancer treatment: Implications for comparative oncology and translational medicine

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ABSTRACT

Comparative oncology leverages spontaneously occurring canine malignancies as robust bidirectional models to bridge the translational gap between preclinical laboratory discoveries and human clinical applications. Unlike conventional genetically uniform rodent models, which often fail to capture natural tumor dynamics, companion dogs develop cancers within an intact, co-evolved immune system and a shared anthropogenic environment. This comprehensive review examines the deep histopathological, genomic, and molecular homologies shared between canine and human neoplasms, with particular emphasis on aggressive entities such as osteosarcoma, malignant melanoma, mammary carcinoma, and non-Hodgkin lymphoma. High-throughput sequencing confirms mutual somatic driver mutations and identical signaling pathway aberrations (e.g., TP53, HER2, and PTEN), substantially increasing translational predictability. Furthermore, companion dogs act as important environmental sentinels for shared ecological carcinogens and provide an accelerated clinical timeline due to their compressed lifespans. Integrating veterinary clinical trials into drug development timelines enables the realistic evaluation of therapeutic efficacy, systemic toxicities, and immune-mediated resistances without compromising animal welfare. Recent advancements in experimental therapeutics, particularly Newcastle Disease Virus (NDV)-based oncolytic virotherapy using the ZG1999HDS strain, underscore the immense clinical and immunological potential of comparative frameworks. Although challenges regarding international trial standardization and cross-species regulatory frameworks persist, the companion canine model represents an irreplaceable, ethically sound foundation within the modern "One Health" paradigm, driving parallel medical breakthroughs that directly benefit both human and veterinary oncology.

Keywords: Comparative oncology, One Health, translational models, canine tumors, oncolytic virotherapy

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INTRODUCTION

Comparative oncology represents a critical interface between veterinary and human medicine, offering a robust bidirectional framework that aligns with the contemporary "One Health" paradigm (Khanna et al., 2006; Vail and Mac Ewen, 2000). Dogs (*Canis lupus familiaris*) living in close anthropogenic environments are naturally exposed to identical environmental risk factors, including chemical carcinogens, air pollutants, and dietary shifts, making them invaluable, highly sensitive biological sentinels for shared ecological carcinogenesis (Schiffman and Breene, 2015; Reif, 2011). Consequently, companion dogs develop spontaneous malignancies that closely parallel human cancers in their biological behavior, clinical presentation, histological appearance, and response to therapeutic interventions (Vail and Mac Ewen, 2000; Gardner et al., 2016). High-throughput genomic analyses have demonstrated a profound degree of sequence homology and evolutionary conservation between the canine and human genomes (Lindblad-Toh et al., 2005). These molecular studies have revealed shared somatic driver mutations, copy number variations, and identical aberrations in critical oncogenic signaling pathways, such as the PI3K/AKT/mTOR and MAPK pathways (Lindblad-Toh et al., 2005; Simpson et al., 2017). Notably, highly aggressive malignancies such as osteosarcoma, malignant melanoma, urothelial (bladder) carcinoma, and non-Hodgkin lymphoma in dogs exhibit striking molecular and clinical redundancies with their human counterparts, presenting ideal target-rich environments for translational oncological research (Gardner et al., 2016; Simpson et al., 2017; LeBlanc et al., 2021).

Traditional preclinical paradigms in drug development heavily rely on syngeneic, genetically engineered, or patient-derived xenograft (PDX) rodent models. However, these murine systems consistently fail to fully recapitulate macroscopic tumor heterogeneity, complex immune macroenvironments, clonal evolution, and natural disease dynamics over an extended timeline, contributing significantly to the high failure and attrition rates (>90%) of novel anticancer therapies during human phase I/II clinical trials (Hansen and Khanna, 2004; Mak et al., 2014). In contrast, tumors in companion dogs arise spontaneously within an intact, co-evolved immune system and a shared natural environment, providing a superior, highly predictive translational matrix (Vail and MacEwen, 2000; Somarelli et al., 2020). The canine immune apparatus shares profound structural and functional similarities with human immunology, particularly regarding tumor-infiltrating lymphocyte (TIL) architecture, myeloid-derived suppressor cell (MDSC) dynamics, and the expression profiles of immune checkpoint molecules such as PD-1 and PD-L1 (Somarelli et al., 2020; Maekawa et al., 2021). Utilizing the canine model facilitates the rigorous, ethical study of complex tumor-host interactions, the validation of novel small-molecule inhibitors and immunotherapies, and the optimization of multi-modal combination protocols (Khanna et al., 2006; LeBlanc et al., 2021). Crucially, these insights can be generated in a compressed timeframe driven by the naturally accelerated progression of canine diseases compared to humans, benefiting both veterinary and human oncology (Vail and Mac Ewen, 2000; Gordon et al., 2009).

Comparative Oncology and Translational Value

Spontaneously occurring canine tumors provide an invaluable translational model for human oncology due to deep histopathological, genetic, and clinical homologies. Unlike induced rodent models, canine malignancies develop naturally within an intact immune system, capturing the complex tumor heterogeneity and metastatic patterns seen in humans (Vail and Mac Ewen, 2000; Gardner et al., 2016). Comparative transcriptomics confirm shared driver mutations in key oncogenes and tumor suppressor genes such as TP53, RB1, PTEN, and HER2, which is particularly evident in osteosarcoma, lymphoma, melanoma, and mammary carcinoma (Gardner et al., 2016; Lindblad-Toh et al., 2005). Canine osteosarcoma exhibits identical skeletal localization, histological features, gene expression profiles, and a high propensity for early pulmonary metastasis, effectively mirroring human pediatric osteosarcoma (Simpson et al., 2017). Similarly, canine non-Hodgkin lymphoma shares clinical progression, pathophysiology, and therapeutic response to standard CHOP regimens with human counterparts (Somarelli et al., 2020). Furthermore, canine oral melanoma closely models rare and aggressive human mucosal melanoma, serving as an ideal platform for evaluating novel immunotherapies, while canine mammary tumors exhibit strong genetic and hormonal concordance with human breast cancer, including triple-negative breast cancer subtypes (Gardner et al., 2016; LeBlanc et al., 2021).

These tumors develop in complex biological conditions involving broad genetic diversity and environmental exposure (Reif, 2011; Rowell et al., 2011). While the canine species displays vast overall genetic diversity, individual breeds exhibit extreme genomic homogeneity due to selective breeding and founder effects (Lindblad-Toh et al., 2005). Specific breeds demonstrate high predispositions to distinct malignancies, such as lymphoma in Golden Retrievers or histiocytic sarcoma in Bernese Mountain Dogs (Rowell et al., 2011). This unique population architecture simplifies the mapping of heritable cancer-associated risk loci, thereby accelerating the discovery of oncogenic pathways relevant to both species. Furthermore, by sharing the human exposome, companion dogs act as effective sentinels for environmental carcinogens (Reif, 2011). They are exposed to identical household chemicals, passive smoke, pesticides, and air pollutants. The detection of matching bioaccumulated endocrine disruptors and organic pollutants in canine and human biospecimens underscores their utility as early warning systems for shared environmental oncogenic risks before clinical manifestation in humans. Finally, the shorter lifespan of dogs allows for accelerated clinical evaluation compared to human medicine (Vail and Mac Ewen, 2000; Gordon et al., 2009). Canine clinical trials offer condensed timelines to evaluate long-term efficacy, safety, resistance mechanisms, and pharmacokinetic profiles of novel therapies. These veterinary outcomes directly optimize human clinical trial designs, mitigate late-stage translational failures, and speed up the approval of innovative targeted molecules and immunotherapies.

Dogs in Drug Development

Spontaneously occurring canine tumors represent a vital translational bridge between conventional experimental rodent models and human clinical trials (Gordon et al., 2009). While traditional murine models often fail to predict human outcomes due to artificial tumor induction and immunodeficiency (Hansen and Khanna, 2004; Mak et al., 2014), pet dogs develop malignancies naturally within an intact, fully functional immune system (Somarelli et al., 2020). This allows for a rigorous and realistic evaluation of therapeutic efficacy, systemic toxicity, and the evolution of drug resistance pathways under real-world biological conditions. Integrating canine clinical trials into the early phases of drug discovery helps establish critical pharmacokinetic and pharmacodynamic profiles, enabling researchers to optimize drug dosing and schedules while identifying target toxicities that standard rodent assays frequently miss (LeBlanc and Mazcko, 2020).

Furthermore, the outbred nature and extensive genetic diversity of the companion dog population significantly enhance translational predictability compared to genetically homogenous laboratory strains (Mak et al., 2014). This genomic variation, combined with shared lifestyle and environmental exposures with human owners (Schiffman and Breene, 2015; Reif, 2011), closely mirrors the heterogeneous patient populations encountered in human medicine. Concurrently, enrolling client-owned dogs in veterinary clinical trials provides these patients with direct access to cutting-edge, novel anticancer interventions that would otherwise be unavailable. This parallel benefit supports a highly ethical research framework where veterinary patients receive advanced medical care, while the generated data directly mitigate the risk of late-stage failure in human clinical pipelines, advancing the core principles of the One Health initiative.

Experimental Therapeutics

Oncolytic Virotherapy

Oncolytic virotherapy has emerged as a compelling immunotherapy paradigm that utilizes either replication-competent, naturally occurring, or genetically engineered viruses to selectively target and destroy malignant populations while leaving healthy tissues undamaged. Oncolytic viruses preferentially replicate within neoplastic cells primarily due to the severe impairment of innate antiviral signaling pathways, such as the interferon-mediated antiviral response and translational suppression mechanisms, which are characteristically downregulated during tumor immunoediting and transformation (Russell et al., 2012; Kaufman et al., 2015). Upon entering the permissive intracellular milieu of a cancer cell, the virus hijacks the host metabolic machinery to undergo rapid replication, ultimately inducing direct tumor cell lysis through immunogenic cell death. This lytic event triggers a profound systemic immune activation by releasing a cascade of tumor-associated antigens, pathogen-associated molecular patterns, and danger-associated molecular patterns directly into the tumor microenvironment (Lichty et al., 2014). Consequently, this converts an immunologically "cold" tumor into a "hot" zone, recruiting innate effector cells and priming tumor-specific T lymphocytes to search and eliminate distal, non-infected metastatic deposits.

Newcastle Disease Virus (ZG1999HDS)

The Newcastle disease virus, an avian paramyxovirus, stands out as a highly promising agent within this therapeutic class, demonstrating intrinsic, selective replication capabilities in mammalian tumor cells while inducing robust, multi-faceted immune responses (Russell et al., 2012; Kaufman et al., 2015; Lichty et al., 2014). A particularly notable candidate is the specific ZG1999HDS strain, which has demonstrated pronounced, simultaneous cytolytic and immunomodulatory effects in preclinical models (Mazija et al., 2021). The oncolytic selectivity of the ZG1999HDS strain relies on its exploitation of defective interferon pathways inherent to malignant cells, allowing for unhindered viral transcription and syncytium formation that precipitates cell death, all while healthy host tissues easily restrict viral propagation. Crucially, this strain exhibits an exceptionally high safety profile with negligible off-target toxicity, making it a well-tolerated biological intervention in veterinary medicine. Recent clinical evaluations of the ZG1999HDS strain in canine cancer therapy have yielded highly promising results, demonstrating noticeable tumor regression, prolonged survival times, and an enhanced quality of life in veterinary patients diagnosed with advanced or chemoresistant malignancies (Ivanković et al., 2022).

Dogs vs Small Animal Models

Conventional rodent models, despite their utility in fundamental biological research, lack the physiological complexity and genetic diversity required to accurately predict human clinical outcomes (Hansen and Khanna, 2004; Mak et al., 2014). Induced or xenografted tumors in mice fail to replicate the sophisticated evolutionary pressure of an intact immune system, often leading to misleading data regarding therapeutic efficacy and systemic toxicity. Conversely, companion dogs develop malignancies spontaneously, better reflecting human physiology, functional immunity, and realistic tumor heterogeneity (Vail and MacEwen, 2000; Gardner et al., 2016). Canine cancers arise within a complex microenvironment that mimics human disease architecture, including intact stromal interactions, natural immune editing, and spontaneous metastatic cascades. Furthermore, the outbred nature of the canine population mirrors human genetic diversity far more accurately than syngeneic, inbred rodent strains, thereby enhancing the translational predictability of oncology pipelines (Lindblad-Toh et al., 2005; Somarelli et al., 2020).

Advanced *In Vitro* Systems

Modern *in vitro* platforms, including patient-derived organoids, microfluidic organs-on-a-chip, and multicellular three-dimensional cultures, have advanced pre-clinical drug screening while supporting the ethical 3Rs principles of replacement, reduction, and refinement in animal experimentation. These advanced systems excel at modeling early cell-to-cell signaling, specific metabolic pathways, and initial cytolytic responses in a controlled environment. However, they remain fundamentally limited by their inability to replicate systemic physiological complexity, such as functional macro-circulation, systemic immune-mediated toxicities, and multi-organ drug clearance mechanisms. Consequently, while high-throughput *in vitro* systems serve as excellent initial selection filters for therapeutic candidates, companion dogs provide an irreplaceable translational bridge between initial laboratory discovery and human clinical research (LeBlanc and Mazcko, 2020).

DISCUSSION AND CONCLUSION

The integration of companion dogs with spontaneously occurring tumors into preclinical research pipelines helps address a critical bottleneck in translational oncology. Dogs represent a highly relevant translational model due to their unique capability to mimic key clinical and biological features of human malignancies, including complex intratumor heterogeneity, dynamic immune system interactions, and natural, un-induced disease progression. By embedding these outbred animal patients into the therapeutic development timeline, researchers can successfully overcome the profound physiological and genomic limitations inherent to traditional, highly inbred experimental rodent models, thereby substantially improving the predictive value and safety margins of preclinical oncology research.

Furthermore, conducting clinical studies in companion dogs enables rigorous longitudinal monitoring of novel therapeutics under realistic, heterogeneous conditions. Unlike laboratory environments, the veterinary clinical setting naturally incorporates diverse environmental exposures, variable lifestyles, and age-related comorbidities that closely reflect the actual complexity of human oncology. This realistic backdrop allows for a far more accurate and stringent assessment of therapeutic efficacy, systemic toxicity, and the real-time emergence of cellular drug resistance mechanisms.

From an ethical standpoint, the modern paradigm shift toward treating companion animals as genuine patients—rather than mere experimental subjects—ensures the highest possible animal welfare standards while simultaneously providing veterinary patients with compassionate access to advanced, otherwise inaccessible anticancer therapies. This approach aligns seamlessly with contemporary biomedical ethics, fostering broader public and institutional acceptance of comparative oncology initiatives.

Within the broader "One Medicine" framework, canine oncology serves as a bidirectional catalyst that accelerates drug development pipelines and ultimately improves clinical outcomes in both human and veterinary medicine. The successful evaluation of novel therapeutic modalities, such as Newcastle Disease Virus (NDV)-based oncolytic virotherapy, underscores the immense value of integrating advanced immunological and translational perspectives into comparative protocols (LeBlanc and Mazcko, 2020; Ivanković et al., 2022). These biological interventions demonstrate that leveraging the dog's intact immune microenvironment can yield critical data regarding systemic anti-tumor immunity and bystander effects. Despite persistent operational challenges, including the standardization of veterinary clinical trial protocols and cross-species regulatory variability, companion canine models remain one of the most powerful, biologically accurate, and ethically sound approaches in modern translational oncology (Khanna et al., 2006).

In conclusion, companion dogs diagnosed with spontaneous tumors provide a highly relevant, biologically faithful, and ethically justified translational model that effectively bridges the gap between laboratory benches and human clinical trials. Their utilization enhances the clinical relevance of preclinical data, mitigates late-stage translational failures, and actively supports the development of innovative, multi-modal cancer therapies. Future progress in this field will fundamentally depend on strengthening interdisciplinary collaborations between human and veterinary oncologists, standardizing international comparative trial networks, and continuously integrating advanced therapeutic technologies to benefit both human and animal patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Pas kao pacijent, a ne eksperimentalna životinja u liječenju raka: Implikacije za komparativnu onkologiju i translacijsku medicinu

SAŽETAK

Komparativna onkologija koristi spontano nastale malignitete kod pasa kao pouzdane, dvosmjerne modele za premoštavanje translacijskog jaza između pretkliničkih laboratorijskih otkrića i humane kliničke primjene. Za razliku od konvencionalnih, genetski uniformnih modela glodara koji ne uspijevaju obuhvatiti prirodnu dinamiku tumora, psi kućni ljubimci razvijaju karcinome unutar netaknutog, koevoluiranog imunološkog sistema i zajedničkog antropogenog okruženja. Ovaj sveobuhvatni pregled istražuje duboke patohistološke, genomske i molekularne homologije koje dijele neoplazme pasa i ljudi, s posebnim naglaskom na agresivne entitete kao što su osteosarkom, maligni melanom, karcinom mliječne žlijezde i ne-Hodgkinov limfom. Visokopropusno sekvenciranje potvrđuje zajedničke somatske driver mutacije i identične aberacije signalnih puteva (npr. TP53, HER2 i PTEN), što značajno povećava translacijsku predvidljivost. Osim toga, psi kućni ljubimci djeluju kao ključne ekološke sentinelne vrste za zajedničke karcinogene iz okoliša i omogućavaju ubrzani klinički vremenski okvir zbog svog skraćenog životnog vijeka. Integracija veterinarskih kliničkih ispitivanja u vremenske okvire razvoja lijekova omogućava realnu procjenu terapijske efikasnosti, sistemske toksičnosti i imuno-posredovane rezistencije bez ugrožavanja dobrobiti životinja. Nedavni napredak u eksperimentalnoj terapeutici, posebno onkolitička viroterapija zasnovana na virusu Newcastle bolesti (NDV) uz korištenje soja ZG1999HDS, naglašava ogroman klinički i imunološki potencijal komparativnih protokola. Iako i dalje postoje izazovi u pogledu međunarodne standardizacije ispitivanja i međuvrsnih regulatornih okvira, model pasa kućnih ljubimaca predstavlja nezamjenjivu, etički utemeljenu osnovu unutar moderne paradigme "Jedno zdravlje" (One Health), podstičući paralelna medicinska otkrića koja direktno koriste humanoj i veterinarskoj onkologiji.

Ključne riječi: Jedno zdravlje, komparativna onkologija, onkolitička viroterapija, translacijski modeli, tumori pasa

STRUČNI RAD • PROFESSIONAL PAPER

Antimikrobna rezistencija u veterinarskoj medicini: uloga prakse i strategije kontrole

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SAŽETAK

Antimikrobna rezistencija (AMR) predstavlja sposobnost mikroorganizama (bakterija, virusa, gljivica i parazita) da prežive ili se razmnožavaju u prisustvu antimikrobnog lijeka koji bi ih inače inhibirao ili uništio. AMR je danas ozbiljan globalni javnozdravstveni i ekonomski problem u humanoj i veterinarskoj medicini. Nastaje usljed nepravilne, dugotrajne i intenzivne primjene antimikrobnih lijekova, uključujući profilaktičku primjenu, kao i primjenu subterapijskih doza, što omogućava selekciju bakterija otpornih na ove lijekove.

Patogeni od kliničkog značaja u veterinarskoj medicini uključuju Gram-negativne (*Salmonella* spp., *Campylobacter* spp. i *Pseudomonas aeruginosa*) i Gram-pozitivne bakterije (*Staphylococcus* spp. i *Enterococcus* spp.), koje izazivaju infekcije kod životinja i predstavljaju zoonotski rizik.

Rezistencija može biti prirodna ili stečena. Stečena rezistencija razvija se pod selekcijskim pritiskom antibakterijskih lijekova i širi se horizontalnim ili vertikalnim prenosom gena. Ključni mehanizmi uključuju enzimsku inaktivaciju, modifikaciju ciljnog mjesta, promjene propusnosti membrane, efluksne pumpe i zaobilaženje metaboličkih puteva. Horizontalni prenos je glavni mehanizam širenja multirezistentnosti (MDR, XDR, PDR), često uz unakrsnu rezistenciju.

Prevencija i kontrola AMR temelji se na racionalnoj upotrebi antibakterijskih lijekova, mikrobiološkoj dijagnostici i antibiogramu, ograničenju kritično važnih lijekova, edukaciji i primjeni "Jedno zdravlje (One Health)" pristupa te nadzoru potrošnje kroz DDDvet i ESVAC sisteme. Dodatno, poštivanje MDK i karence u hrani životinjskog porijekla predstavlja važan segment zaštite javnog zdravlja i kontrole izloženosti ostacima lijekova.

Alternativne metode, uključujući vakcinaciju, probiotike, bakteriofage i molekularne dijagnostičke metode, doprinose smanjenju upotrebe antibakterijskih lijekova i širenja AMR.

Efikasna implementacija ovih strategija omogućava očuvanje terapijske efikasnosti i smanjenje prenosa rezistentnih bakterija sa životinja na ljude.

Ključne riječi: Antimikrobna rezistencija, veterinarska medicina, multirezistentne bakterije, racionalna upotreba antimikrobnih lijekova, strategije kontrole.

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Antibakterijski lijekovi su prirodne, polusintetske ili sintetske supstance koje djeluju baktericidno ili bakteriostatski, odnosno uništavaju bakterije ili zaustavljaju njihov rast i razmnožavanje. Njihova primjena seže još prije perioda razvoja moderne medicine kada su se empirijski koristili različiti prirodni izvori s antibakterijskim svojstvima.

U ovom radu termin "antibakterijski lijekovi" obuhvata antibiotike, polusintetska i sintetska sredstva s antibakterijskim djelovanjem i koristi se kao jedinstveni termin za sve navedene grupe.

Još u doba starog Egipta utvrđeno je da nitaste plijesni koje su rasle na hljebu mogu služiti za liječenje rana i opekotina. Također su ljekari u drevnoj Kini i antičkoj Grčkoj koristili preparate na bazi plijesni u liječenju različitih bolesti (Durand i sar., 2019). U 19. vijeku zabilježena su prva sistematska opažanja antagonizma između mikroorganizama, uključujući inhibiciju rasta bakterija u prisustvu određenih plijesni i drugih mikroorganizama. Ovo su opisali pojedini naučnici (Burdon-Sanderson, Lister, Pasteur i Joubert), koji su postavili temelje koncepta antibioze. Međutim, iako je antibakterijsko djelovanje plijesni bilo prepoznato, aktivne supstance tada nisu bile izolovane. Prvi selektivno djelujući antibakterijski lijek arsfenamin otkrio je Paul Ehrlich 1909. godine, koji je imao selektivno toksično djelovanje protiv *Treponema pallidum* (Aminov, 2017; Durand i sar., 2019).

Gerhard Domagk je 1930. godine utvrdio antibakterijske efekte sulfanilamida, kojeg je dvije decenije ranije sintetizirao Paul Gelmo. Ovo je bio prvi efikasan antibakterijski lijek koji je stavljen na tržište 1935. godine pod nazivom Prontozil (Durand i sar., 2019).

Penicilin je otkrio Alexander Fleming 1928. godine kada je primijetio da plijesan *Penicillium notatum* proizvodi supstancu koja ubija bakterije. To je bilo revolucionarno otkriće za modernu medicinu, budući da su antibakterijski lijekovi tada smatrani "čudotvornim" terapijskim sredstvima. Njihov rad su kasnije unaprijedili Howard Florey i Ernst Chain 1940. godine, kada je i počela njegova masovna primjena. Fleming je također izolovao lizozim, antibakterijski enzim. Rene Dubos je tridesetih godina prošlog vijeka iz uzoraka zemljišta ekstrahovao enzim koji je razgrađivao kapsularni polisaharid *Streptococcus pneumoniae.* Nešto kasnije izolovao je i gramicidin iz *Bacillus brevis,* koji je inhibirao rast Gram-pozitivnih bakterija, ali je utvrđeno da je bio toksičan za sistemsku primjenu (Caneschi i sar., 2023; Durand i sar., 2019). Ova rana otkrića činila su važnu osnovu za razvoj modernih antibakterijskih lijekova i njihov dalji razvoj u kliničkoj praksi.

Selman Waksman detaljno je proučavao antibakterijsko djelovanje bakterija koje je izolovao iz tla, a naročito rod *Streptomyces*. Tokom 1940-ih godina uspio je razviti metode i strategije uzgoja poznate kao Waksmanov pristup, koje su služile za identifikaciju mikrobioloških antagonizama. Kroz ovaj pristup otkriveni su aktinomicin, streptomicin, neomicin te antifungalni lijekovi poput fumigacina i klavacina. Streptomicin je bio revolucionarni lijek za liječenje tuberkuloze (Durand i sar., 2019). Waksmanov pristup pokrenuo je "zlatno doba", tokom kojeg je otkriven veliki broj antibakterijskih lijekova, što je značajno smanjilo smrtnost od bakterijskih infekcija. Ovaj period bio je posebno značajan do 1960-ih godina prošlog vijeka, nakon čega su otkriveni novi, pretežno sintetski antibakterijski lijekovi (Hutchings i sar., 2019; Lawani-Luwaji, 2024).

Antibakterijski lijekovi su jedno od najznačajnijih revolucionarnih otkrića u medicini, ali je njihova prekomjerna i neracionalna upotreba dovela do porasta broja bakterija otpornih na liječenje. Bakterije su jednoćelijski i adaptivni mikroorganizmi sposobni da se prilagode kada uslovi njihove okoline više nisu povoljni, kao što je to na primjer prisutnost antibakterijskih lijekova (Caneschi i sar., 2023; Varela i sar., 2021). Bakterije nastavljaju rasti i razmnožavati se u prisustvu lijekova na koje su prethodno bile osjetljive (Yoo, 2025). Stoga se antimikrobna rezistencija (AMR) mora smatrati prirodnim fenomenom kojem doprinosi svaki antimikrobni lijek (Caneschi i sar., 2023).

Bakterije su prve razvile otpornost, dok je kasnije rezistencija utvrđena i na lijekove protiv virusa, gljivica i parazita. Pojava i širenje rezistentnih mikroorganizama doveli su do smanjenja terapijske efikasnosti velikog broja antibakterijskih lijekova, dužeg trajanja bolesti, povećanja mortaliteta te značajnih ekonomskih gubitaka povezanih sa zdravljem životinja i proizvodnjom hrane životinjskog porijekla (Dadgostar, 2018; Naylor i sar., 2024; O'Neill, 2016; WHO, 2014, 2016, 2018).

U ranim istraživanjima razvoja rezistencije, uključujući radove Florey i Chain, prepoznat je značaj bakterijskih enzima poput penicilinaza (beta-laktamaza) pri čemu je njihovo prisustvo prvo opisano kod *Staphylococcus aureus*. Nakon toga, rezistencija se sve češće javlja na

različite grupe antibakterijskih lijekova, ukazujući na to da otpornost može nastati prirodno, ali i kao posljedica njihove primjene (Durand i sar., 2019; Lobanovska i Pilla, 2017).

Vlada Ujedinjenog Kraljevstva zatražila je izradu pregleda AMR, pri čemu je procijenjeno da bi AMR mogla uzrokovati smrt oko 10 miliona ljudi godišnje do 2050. godine (Murray i sar., 2022). Iako postoje određene kritike ovih prognoza, Svjetska zdravstvena organizacija (WHO), Svjetska organizacija za zdravlje životinja (WOAH) te Organizacija za hranu i poljoprivredu Ujedinjenih nacija (FAO) smatraju da antibiotska rezistencija čini jednu od vodećih prijetnji javnom zdravlju u 21. vijeku. Efikasno smanjenje i suzbijanje širenja AMR zahtijeva koordinisan, multisektorski i globalno usklađen pristup (Ahmad i sar., 2023; Ahmad i Khan, 2019; FAO, 2021; WHO, 2015; Zinsstag i sar., 2017).

Ukoliko se ne stavi pod kontrolu, širenje AMR moglo bi dovesti do toga da mnoge patogene bakterije budu znatno smrtonosnije u budućnosti nego što su danas. Dosadašnja istraživanja identifikovala su šest vodećih bakterijskih patogena povezanih sa smrtnošću usljed AMR u 2019. godini, a to su: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii* i *Pseudomonas aeruginosa* (Murray i sar., 2022). Ovi mikroorganizmi ne samo da su dio normalne mikrobne populacije životinja, već rezistentni sojevi predstavljaju rizik za prenos na ljude, direktnim kontaktom ili putem hrane animalnog porijekla. Stoga, veterinarska medicina ima značajnu ulogu ne samo u nastanku, već i u kontroli AMR (Bengtsson i Greko, 2014; Holmes i sar., 2016; Landers i sar., 2012; McEwen i Collignon, 2018).

Antibakterijski lijekovi se u veterinarskoj medicini primjenjuju u svrhu liječenja, metafilakse te u određenim okolnostima, u cilju profilakse, kako u intenzivnoj stočarskoj proizvodnji, tako i kod kućnih ljubimaca (Prescott, 2008; McEwen i Collignon, 2018). Njihova neadekvatna primjena, uključujući pokretanje terapije akutnih stanja prije dobijanja rezultata mikrobiološke dijagnostike, nepravilno doziranje, neodgovarajuće trajanje terapije, kao i primjena lijekova izvan odobrenih indikacija (off-label primjena), označava ključne faktore koji doprinose selekciji i održavanju rezistentnih bakterijskih sojeva (Caneschi i sar., 2023; Guardabassi i Prescott, 2015; Landers i sar., 2012).

Rezistencija ugrožava efikasnost standardnih terapijskih postupaka, otežava liječenje, a u pojedinim slučajevima čini ga nemogućim, što može dovesti do tzv. postantibiotske ere (Arnold i Straus, 2005; Mohammadzadeh i sar., 2005). Smith i Coast (2013) opisuju scenarij bez antibakterijskih lijekova u kojem bi u postoperativnoj profilaksi totalne artroplastike mortalitet porastao na 40-50%, dok bi među inficiranim pacijentima mortalitet iznosio oko 30% uz značajno smanjenje kvaliteta i očekivanog trajanja života.

Danas se industrija antimikrobnih lijekova, općenito, suočava s ekonomskim izazovima zbog čega su mnoge farmaceutske kompanije napustile ili smanjile istraživanja i razvoj novih preparata usljed ograničene profitabilnosti. Naime, kratko trajanje terapije i niski povrat ulaganja čine antibakterijske lijekove manje atraktivnim u poređenju s lijekovima za dugotrajnu terapiju hroničnih bolesti koji donose veće prihode (Ardal, 2020; McDonell i sar., 2024).

Međutim, savremena istraživanja sve više uključuju primjenu vještačke inteligencije (AI) u cilju brže identifikacije novih antibakterijskih supstanci, posebno protiv bakterija za koje već decenijama ne postoje adekvatna terapijska rješenja, poput onih uzrokovanih tzv. "superbakterijama". Najnovija literatura ističe da metode temeljene na AI omogućavaju virtuelno pretraživanje velikih biblioteka molekula, generativne mreže za dizajn novih antibakterijskih lijekova, kao i predviđanje njihove biološke aktivnosti. Ovim se značajno skraćuje vrijeme i smanjuju troškovi razvoja novih antibakterijskih lijekova (Bagdad i Miteva, 2024; Boudza i sar., 2026; de la Fuente-Nunez i Collins, 2025; Melo i sar., 2021; Mulati i sar., 2025).

Infekcije uzrokovane rezistentnim bakterijama čine dodatni finansijski teret zdravstvenim sistemima i društvu u cjelini, usljed komplikacija tokom liječenja i produženog boravka pacijenata u bolnicama. Ovo je povezano s dodatnim troškovima i resursima potrebnim za zbrinjavanje bolesnika (Lee i sar., 2021; Nelson i sar., 2022).

Povećane stope mortaliteta i morbiditeta dodatno smanjuju produktivnost, narušavaju povjerenje u zdravstveni sistem te mogu potaknuti pribjegavanje alternativnim metodama liječenja, što indirektno može doprinijeti daljem širenju infekcija (Smith i Coast, 2013; Stewardson i sar., 2023).

Posljednjih godina sve veća pažnja usmjerena je na koncept racionalne upotrebe antibakterijskih lijekova

(antimikrobno upravljanje; engl. antimicrobial stewardship) u veterinarskoj praksi. Ovaj koncept podrazumijeva njihovu odgovornu i racionalnu primjenu zasnovanu na naučnim dokazima, rezultatima mikrobiološke dijagnostike i antibiograma, kao i na poštovanju važećih stručnih i regulatornih smjernica (Guadarabassi i Prescott, 2015; EMA, 2021).

Pored profesionalne odgovornosti veterinara, značajnu ulogu imaju i regulatorne mjere koje se provode na nacionalnom i međunarodnom nivou. One uključuju ograničavanje ili zabranu primjene pojedinih kritično važnih antibakterijskih lijekova u veterinarskoj medicini s ciljem očuvanja njihove efikasnosti i smanjenja rizika za javno zdravlje (Dimuccio i sar., 2026; WHO, 2018).

U tom kontekstu, Evropska agencija za lijekove (EMA) razvila je AMEG klasifikaciju (Antimicrobial Advice ad hoc Expert Group), kojom se antibakterijski lijekovi razvrstavaju u četiri kategorije (A–D) prema riziku od razvoja AMR i njihovom značaju za humanu medicinu. Ova klasifikacija ne predstavlja samo rangiranje antibakterijskih lijekova, već pruža preporuke o nivou njihove prihvatljivosti u veterinarskoj medicini, u skladu s rizikom po javno zdravlje i dostupnošću terapijskih alternativa (EMA, 2023).

Sve navedene mjere čine integralni dio koncepta "Jedno zdravlje" (One Health), prema kojem racionalna upotreba antibakterijskih lijekova u veterinarskoj medicini ima direktan utjecaj na očuvanje javnozdravstvenog sektora, uzimajući u obzir mogućnost prenosa rezistentnih bakterija i gena rezistencije između životinja, ljudi i okoline (Larsson i sar., 2023; Velasquez-Meza i sar., 2022; Woolhouse, 2024)**.**

Cilj ovog rada je prikazati osnovne mehanizme razvoja AMR, analizirati ulogu veterinarske prakse u njenom nastanku i širenju te istaknuti savremene strategije prevencije i kontrole antibakterijske rezistencije u veterinarskoj medicini, s posebnim naglaskom na značaj One Health pristupa.

Antibakterijski lijekovi u veterinarskoj medicini

Antibakterijski lijekovi čine osnovni terapijski pristup u liječenju bakterijskih infekcija kod životinja. Njihova primjena ima za cilj očuvanje zdravlja, sprječavanje ekonomskih gubitaka i smanjenje rizika od širenja infekcija. Međutim, njihova neadekvatna upotreba direktno doprinosi razvoju i širenju antibakterijske rezistencije (Prescott, 2008; McEwen i Collignon, 2018).

Antibakterijski lijekovi primjenjuju se kod životinja prvenstveno u terapijske svrhe, pri čemu se liječenje može provoditi pojedinačno ili, u slučaju oboljenja većeg broja životinja, grupno (tzv. masovna terapija). Pored toga, koriste se u okviru metafilakse, odnosno za liječenje grupa životinja koje su izložene povećanom riziku od infekcije, što je ranije bilo naročito zastupljeno u intenzivnoj stočarskoj proizvodnji. Treći vid primjene je profilaktički, odnosno njihova primjena u cilju sprječavanja bolesti u odsustvu dokazane infekcije. Ovakav pristup danas je strogo ograničen zbog povećanog rizika od razvoja i širenja AMR (Guardabassi i Prescott, 2015; McEwen i Collignon, 2018; Šeol i sar., 2010).

Nakon Drugog svjetskog rata započeo je intenzivan razvoj industrijske poljoprivredne proizvodnje i uzgoja životinja kao odgovor na rastuće potrebe za dovoljnom količinom hrane životinjskog porijekla. Primjena antibiotika kao promotora rasta u intenzivnom peradarstvu datira iz 1940-ih godina, kada su tetraciklini dodavani u hranu, čime je poboljšan i ubrzan rast pilića (Hoeverstadt i sar., 1986; Dibner i Richards, 2005; Niewold, 2007). S obzirom na to da je praksa dodavanja tetraciklina u hranu za perad rezultirala pozitivnim efektima, poput bolje konverzije hrane i bržeg rasta životinja, ubrzo su se počeli primjenjivati i drugi antimikrobni lijekovi.

Sjedinjene Američke Države su još 1951. godine odobrile upotrebu antibiotika u hrani za životinje bez veterinarskog recepta (Jones i Ricke, 2003), dok su evropske zemlje tokom 1950-ih i 1960-ih godina, istu praksu ozvaničile i regulisale nacionalnim propisima. U početku su se antimikrobni lijekovi poput tetraciklina, tilozina i bacitracina, mogli primjenjivati u niskim koncentracijama kao dodaci hrani za životinje, dok su veće doze bile ograničene isključivo za terapijsku primjenu.

Antibiotici koji su se prvenstveno koristili kao promotori rasta u pojedinim slučajevima bili su isti oni koji su namijenjeni u terapijske svrhe. Antibiotici primijenjeni u svrhu promocije rasta ili profilakse određenih oboljenja aplicirani su u nižim ili tzv. subterapijskim dozama u odnosu na terapijske doze, zbog čega se u stručnoj literaturi za ove grupe antibiotika ponekad koristi zajednički naziv „subterapijski antibiotici". Ubrzo je uočeno da primjena subterapijskih doza pojedinih antibakterijskih lijekova dovodi do povećanja prirasta životinja, poboljšanja konverzije hrane te smanjenja učestalosti infektivnih oboljenja povezanih

s intenzivnim proizvodnim sistemima, ali istovremeno stvara i selekcijski pritisak koji pogoduje razvoju i širenju rezistentnih sojeva bakterija i doprinosi razvoju rezistencije (Landers i sar., 2012; Marshall i Levy, 2011).

Zabrinutost zbog upotrebe promotora rasta prvi put je jasno definisana u Swannovom izvještaju (SWANN, 1969) u kojem su predstavljeni dokazi o štetnim posljedicama njihove primjene i pojavi rezistencije. U navedenom izvještaju preporučeno je da se antimikrobni lijekovi koji se koriste u svrhu liječenja, ne koriste kao promotori rasta, kao i da se lijekovi značajni za humanu medicinu ne koriste kao aditivi u hrani za životinje. Ove preporuke prihvatio je veliki broj zemalja, što je rezultiralo uvođenjem nove legislative. Na taj način pojedini antimikrobni lijekovi bili su zabranjeni, a drugi definisani ili kao promotori rasta (bez veterinarskog recepta), ili isključivo za terapijsku primjenu (uz veterinarski recept). Ovakav pristup bio je, u većoj ili manjoj mjeri, primjenjivan u brojnim evropskim zemljama i dijelom u Sjevernoj Americi.

Sredinom 1990-ih godina pojedini proizvođači u peradarskoj proizvodnji učinili su značajne napore u poboljšanju higijene, dezinfekcije i biosigurnosti s ciljem smanjenja rizika od pojave bakterijskih infekcija, što je predstavljalo početak smanjenja upotrebe antimikrobnih lijekova kao promotora rasta (Wierup, 2001; Engster i sar., 2002; World Health Organization, 2002).

U veterinarskoj praksi danas se koriste različite grupe antibakterijskih lijekova. Beta-laktami (aminopenicilini, sami ili u kombinaciji s inhibitorima beta-laktamaza, cefalosporini 3. i 4. generacije) široko se primjenjuju u terapiji respiratornih, gastrointestinalnih i reproduktivnih infekcija (Caneschi i sar., 2023; McEwen i Collignon, 2018). Tetraciklini se, zbog širokog spektra djelovanja, često koriste u intenzivnoj stočarskoj proizvodnji (Guardabassi i Prescott, 2015). Aminoglikozidi se najčešće primjenjuju u kombinaciji s drugim antibioticima, prvenstveno u liječenju težih oblika infekcija, uz oprez zbog njihove potencijalne nefrotoksičnosti (Bengtsson i Greko, 2014). Makrolidi i linkozamidi imaju značajnu ulogu u liječenju respiratornih i gastrointestinalnih infekcija, posebno kod peradi i goveda (Landers i sar., 2012). Fluorokvinoloni su se ranije češće koristili, ali je njihova upotreba danas strogo ograničena, s obzirom na to da pripadaju grupi kritično važnih antibakterijskih lijekova za humanu medicinu, naročito kod životinja za proizvodnju hrane (Lhermie, 2020; EMA, 2023; WHO, 2019).

S obzirom na sve više dokaza o povezanosti dugotrajne primjene subterapijskih doza antibakterijskih lijekova i razvoja antibakterijske rezistencije, Evropska unija postepeno je uvodila regulatorne mjere s ciljem ograničavanja ove prakse. Prva evropska zemlja koja je zabranila upotrebu promotora rasta bila je Švedska, još 1986. godine. Danska je 1995. godine zabranila upotrebu avoparcina kao promotora rasta, nakon čega je slijedila Njemačka, da bi već 1997. godine i ostale zemlje Evropske unije usvojile istu odluku. Vijeće Ministara EU je 1998. godine zabranilo upotrebu svih antibiotika značajnih za humanu medicinu kao dodataka u hrani za životinje. Evropska unija je u julu 1999. godine zabranila upotrebu pojedinih antibiotika kao promotora rasta u hrani za perad, uključujući spiramicin, tilozin, virdžinijamicin i cink bacitracin, dok su u septembru iste godine zabranjena i dva derivata kvinoksalina - karbadoks i olakvindoks.

Zvanična zabrana upotrebe ovih lijekova kao promotora rasta u ishrani životinja na nivou cijele EU stupila je na snagu 1. januara 2006. godine. Ova zabrana provedena je u skladu s Uredbom (EZ) br. 1831/2003, čime je postavljen važan temelj za odgovorniju upotrebu antibakterijskih lijekova u veterinarskoj medicini (Castanon, 2007; Millet i Maertens, 2011). Ove mjere imaju i direktan utjecaj na javno zdravlje, jer smanjenje nepotrebne primjene antibakterijskih lijekova u stočarstvu smanjuje rizik širenja rezistentnih bakterija na ljude i okolinu, što je ključni princip One Health pristupa (McEwen i Collignon, 2018; WHO/FAO/WOAH/UNEP, 2022).

Antimikrobni lijekovi koji se koriste u terapijske i profilaktičke svrhe u većini zemalja regulisani su specifičnom veterinarskom i farmaceutskom legislativom, a njihova upotreba ograničena je obavezom izdavanja na veterinarski recept. Nekontrolisana i prekomjerna upotreba antimikrobnih lijekova češće se javlja u zemljama u kojima je farmerima omogućena nabavka lijekova bez veterinarskog recepta.

Pored regionalnih regulatornih mjera, na globalnom nivou razvijene su smjernice koje definišu standarde odgovorne i racionalne upotrebe antimikrobnih sredstava u veterinarskoj medicini. U tom kontekstu Terrestrial Animal Health Code (Kodeks o zdravlju kopnenih životinja), koji je 2022. godine objavila Svjetska organizacija za zdravlje životinja (WOAH), čini ključni međunarodni okvir za upravljanje

upotrebom antimikrobnih lijekova. Ovim dokumentom definišu se odgovornosti nadležnih tijela i svih učesnika u lancu veterinarske zdravstvene zaštite, od odobravanja do primjene lijekova na životinjama, s ciljem očuvanja njihove efikasnosti i smanjenja rizika po javno zdravlje (WOAH, 2022).

Veterinarska praksa i rizik od razvoja rezistencije

Nepravilna primjena antibakterijskih lijekova, uključujući empirijsku terapiju bez prethodno urađenog antibiograma, neodgovarajuće trajanje terapije te primjenu izvan odobrenih indikacija (off-label primjena), čini ključni faktor koji doprinosi selekciji i širenju rezistentnih bakterija (Landers i sar., 2012; Guardabassi i Prescott, 2015). Dodatno, učestala upotreba antibakterijskih lijekova, naročito u situacijama kada nije jasno potvrđena bakterijska etiologija, značajno povećava selekcijski pritisak na mikrobnu zajednicu životinja, čime se pogoduje razvoju i preživljavanju rezistentnih sojeva. U intenzivnim proizvodnim sistemima ovaj problem je posebno izražen zbog grupne terapije, što može dovesti do brzog širenja rezistentnih mikroorganizama unutar populacije (Guardabassi i Prescott, 2015; McEwen i Collignon, 2018; WHO, 2019).

Zbog toga je koncept antimikrobnog upravljanja od suštinskog značaja jer podrazumijeva racionalnu, odgovornu i dokazima zasnovanu primjenu antibakterijskih lijekova s ciljem očuvanja njihove efikasnosti i zaštite javnozdravstvenog sektora (Doron i Davidson, 2011; Gehring i sar., 2023; McEwen i Collignon, 2018). Ovaj koncept uključuje primjenu terapije zasnovane na rezultatima mikrobiološke dijagnostike, izbor antibakterijskih lijekova užeg spektra djelovanja, kada je to moguće, optimizaciju doze i trajanja terapije, kao i kontinuirano praćenje rezistencije. Također, značajan segment ovog koncepta odnosi se na prevenciju infekcija kroz unapređenje biosigurnosnih mjera, vakcinaciju i poboljšanje uslova držanja životinja, čime se smanjuje potreba za primjenom antibakterijskih lijekova (Doron i Davidson, 2011; Shrestha i sar., 2023).

Kritično važni antibakterijski lijekovi i ograničenja njihove upotrebe

Kako je spomenuto u uvodu, WHO i EMA definišu određene antibakterijske lijekove kao kritično važne za humanu medicinu. Njihova primjena u veterinarskoj medicini preporučuje se samo kada ne postoje alternativni terapijski izbori, uz antibiogram i pod strogom kontrolom. AMEG klasifikacija razvrstava antibakterijske lijekove u četiri kategorije (A–D) (EMA, 2023; WHO, 2019).

- Kategorija A (Avoid): obuhvata lijekove poput vankomicina i karbapenema koji se ne smiju koristiti u veterinarskoj praksi, jer su od kritičnog značaja za humanu medicinu i imaju neprihvatljiv rizik po javno zdravlje.
- Kategorija B (Restrict): lijekovi ove kategorije imaju strogo ograničenu primjenu u veterinarskoj medicini. Upotrebljavaju se samo kada ne postoje druge alternative, uz obaveznu mikrobiološku dijagnostiku i antibiogram. U ovu kategoriju spadaju fluorokvinoloni, cefalosporini treće i četvrte generacije te kolistin (polimiksin E). Svi navedeni antibakterijski lijekovi smatraju se kritično važnim za humanu medicinu, zbog čega njihova primjena zahtijeva strogu kontrolu i racionalno propisivanje kako bi se smanjio rizik razvoja i širenja antibakterijske rezistencije.
- Kategorija C (Caution): uključuje antibiotike poput makrolida i aminoglikozida, koji se mogu koristiti u veterinarskoj medicini uz oprez, posebno kada lijekovi iz kategorije D nisu efikasni ili prikladni za konkretnu indikaciju.
- Kategorija D (Prudence): obuhvata peniciline, tetracikline i sulfonamide koji se smatraju lijekovima prve linije u veterinarskoj praksi, uz obavezno pridržavanje principa racionalne upotrebe, adekvatnog doziranja i trajanja terapije (EMA, 2023; WHO, 2019).

AMEG klasifikacija je osnovni mehanizam za odgovorno propisivanje antibakterijskih lijekova u veterinarskoj praksi i sastavni je dio strategije prevencije i kontrole AMR (EMA, 2023; Gehring i sar., 2023; McEwen i Collignon, 2018).

Mehanizmi nastanka antibakterijske rezistencije i načini prenosa

Iako je fokus ovog rada na antibakterijskim lijekovima i bakterijskoj rezistenciji, termin antimikrobna rezistencija (AMR) koristi se u širem kontekstu i odnosi se na bakterije, gljivice i viruse, koji su sposobni preživjeti i razmnožavati se u prisustvu antimikrobnih lijekova. U ovom poglavlju ukratko su prikazane osnovne vrste i mehanizmi antibakterijske rezistencije, kao i ključni procesi koji doprinose njenom širenju (Belay i sar., 2024; Prestinaci i sar., 2015).

Razumijevanje vrsta i mehanizama antibakterijske rezistencije omogućava razvoj efikasnijih strategija liječenja infekcija uzrokovanih rezistentnim patogenima. Uvid u načine izbjegavanja djelovanja antibakterijskih lijekova od strane bakterija omogućava razvoj novih terapijskih pristupa usmjerenih na prevazilaženje mehanizama rezistencije, čime se poboljšavaju ishodi liječenja. Osim toga, doprinosi unapređenju nadzora i praćenja rezistentnih bakterija, što omogućava pravovremeno prepoznavanje novih prijetnji i primjenu odgovarajućih mjera kontrole infekcija. Nadalje, poznavanje mehanizama rezistencije čini osnovu za primjenu koncepta antimikrobnog upravljanja čime se podstiče racionalna i odgovorna upotreba antibakterijskih lijekova u cilju smanjenja razvoja rezistencije (Belay i sar., 2024).

Antimikrobna rezistencija posebno je izražena kod bakterija, gdje predstavlja jedan od najvećih savremenih javnozdravstvenih i ekonomskih izazova na globalnom nivou. Svjetska zdravstvena organizacija od 2012. godine intenzivira aktivnosti usmjerene na praćenje i suzbijanje AMR. Na skupštini održanoj u maju 2015. godine usvojen je Globalni akcioni plan kao i Globalni sistem nadzora (GLASS), s ciljem unapređenja racionalne upotrebe antibakterijskih lijekova (WHO, 2015; Prestinaci i sar., 2015).

Globalni akcioni plan o antibakterijskoj rezistenciji navodi pet osnovnih ciljeva:

1. Poboljšati svijest i razumijevanje AMR putem komunikacije, obrazovanja i osposobljavanja.
2. Pojačati bazu znanja i dokaza putem nadzora i istraživanja.
3. Smanjiti učestalost infekcija efikasnim sanitarnim, higijenskim i mjerama prevencije i kontrole infekcija.
4. Optimizirati upotrebu antibakterijskih lijekova u humanoj i veterinarskoj medicini.
5. Razviti ekonomske argumente za održiva ulaganja koja uzimaju u obzir potrebe svih zemalja i povećati ulaganja u nove lijekove, dijagnostičke metode, vakcine i druge intervencije (WHO, 2015).

Međutim, pouzdani nadzorni podaci i dalje nedostaju u mnogim dijelovima svijeta, posebno u zemljama s ograničenim resursima, što otežava sveobuhvatnu procjenu globalnog opterećenja AMR. Dostupni podaci ukazuju na kontinuirani globalni porast stope rezistencije, uz izražene regionalne razlike između pojedinih zemalja i kontinenata (van Boeckel i sar., 2015).

Vrste otpornosti na antibakterijske lijekove

Prisutnost bakteriostatskih/baktericidnih lijekova može omogućiti rast rezistentnih mikroorganizama u koncentracijama koje normalno inhibiraju njihovu proliferaciju. Ova otpornost često nastaje mutacijama ili prenosom genetskih elemenata koji su otporni na antibakterijske lijekove (stečena otpornost). Međutim, otpornost može biti i intrinzična, ovisno o inherentnim karakteristikama ćelije i genima divljeg tipa (Belay i sar., 2024; Cox i Wright, 2013).

Otpornost na lijekove može se klasificirati u tri kategorije: intrinzična/prirodna, stečena i adaptivna, koje su određene načinom razvoja otpornosti (Belay i sar., 2024; Bo i sar., 2024).

Prirodna ili intrinzična rezistencija je nasljedna osobina bakterija koja ih čini neosjetljivim na određene antibakterijske lijekove zbog odsustva ili nedostupnosti ciljnih mjesta djelovanja. Ova vrsta rezistencije može biti intrinzična (uvijek prisutna u bakteriji) ili inducirana, pri čemu se geni, koji se prirodno nalaze u bakterijama, eksprimiraju tek do nivoa otpornosti nakon izlaganja antibakterijskom lijeku. Intrinzična otpornost je karakteristika stalno prisutna unutar bakterijske vrste, neovisna o prethodnom izlaganju antibakterijskim lijekovima i nije povezana s horizontalnim prenosom gena (HGT) (Belay i sar., 2024; Cox i Wright, 2013; Uddin i sar., 2021). Intrinzična antimikrobna rezistencija predstavlja inherentnu osobinu mikroorganizma koja ga čini prirodno otpornim na određene antibakterijske lijekove, zbog čega je njihova primjena u terapiji neefikasna (Belay i sar., 2024). Na primjer, anaerobne bakterije prirodno su rezistentne na aminoglikozide, dok su mnoge Gram-negativne bakterije (npr. *Pseudomonas* spp.), rezistentne na makrolide i određene beta-laktame (Reygaert, 2018).

Stečena rezistencija se smatra većim problemom u veterinarskoj praksi. Odnosi se na rezistenciju koja nastaje kada bakterija, prethodno osjetljiva na antibakterijski lijek, postane rezistentna (Belay i sar., 2024; Uddin i sar., 2021). Nastaje kada antibakterijski lijekovi stvaraju selekcijski pritisak, što omogućava preživljavanje i širenje bakterija koje posjeduju odgovarajuće gene rezistencije. Takva rezistencija zabilježena je kod gotovo svih patogenih bakterija uključujući i komensalne mikroorganizme, što

naglašava potrebu za odgovornom upotrebom ovih lijekova (Prescott, 2008; Reygaert, 2018).

Adaptivna rezistencija definiše se kao sposobnost mikroorganizama da reverzibilno prilagode svoj fenotip i postanu otporni na jedan ili više antibakterijskih lijekova kao odgovor na specifične signale iz okoline. To je odgovor bakterija na različite uslove okoline, kao što su stres, stanje rasta, pH, koncentracije jona, uslovi hranjivih supstanci ili izloženost subinhibitornim koncentracijama antibakterijskih lijekova. Adaptivna rezistencija je privremene i reverzibilne prirode, što se razlikuje od drugih vrsta otpornosti na lijekove (Belay i sar., 2024; D'Aquila i sar., 2023). Omogućuje bakterijama da brzo reaguju na antibakterijsko djelovanje, ali nakon što inducirajući signal više nije prisutan, bakterije se obično vraćaju svojoj izvornoj osjetljivosti na lijek (Lazar i sar., 2023).

Osnovni mehanizmi rezistencije na antibakterijske lijekove

Bez obzira na način kojim mikroorganizam postaje rezistentan, postoje ključni mehanizmi koji dovode do njenog razvoja (Bedenić i sar., 2015; Belay i sar., 2024; Bengtsson i Greko, 2015; Blair i sar., 2014; Ćupić i sar., 2019; Guardabassi i Prescott, 2015; Kapoor i sar., 2017; McDermott i sar., 2003; McEwen i Collignon, 2018; Šeol i sar., 2010).

Enzimska inaktivacija podrazumijeva da bakterije proizvode enzime koji razgrađuju ili hemijski modifikuju lijek. Primjeri uključuju beta-laktamaze kod bakterija poput *E. coli* i *Staphylococcus* spp., koje hidroliziraju beta-laktamske antibiotike (penicilini i cefalosporini). Osim toga, hloramfenikol-acetiltransferaza acetilira hloramfenikol, dok različiti enzimi mogu acetilirati, fosforilirati ili adenilirati aminoglikozidne antibiotike.

Posebnu kliničku važnost imaju karbapenemaze, podgrupa beta-laktamaza, koje inaktiviraju karbapeneme - antibiotike tzv. rezervne terapije u humanoj medicini, koji se koriste za liječenje teških i multirezistentnih infekcija. Njihova pojava i širenje, naročito kod Gram-negativnih bakterija, predstavlja značajan javnozdravstveni problem.

Modifikacija ciljnog mjesta vezivanja lijeka podrazumijeva prirodne varijacije ili stečene promjene na ciljnom mjestu koje sprječavaju vezivanje lijeka. Ove promjene često proizlaze iz spontanih mutacija bakterijskog genoma ili sticanja gena rezistencije. Bakterije mogu promijeniti strukturu svog ćelijskog zida, membrane ili drugih ćelijskih komponenti na koje antibakterijski lijekovi djeluju, čineći ih manje osjetljivima na te lijekove. Usljed promjena u strukturi ćelijskog zida, smanjuje se broj mjesta vezivanja za lijekove koji ga specifično ciljaju, kao što je slučaj modifikacije penicilin-vezujućih proteina (PBP) kod *S. aureus*, što rezultira rezistencijom na meticilin. Određene bakterije mogu proći kroz mutacije DNK koje mijenjaju strukturu njihovih ribozoma, koji su ćelijske komponente odgovorne za sintezu proteina. Ove promjene mogu ometati sposobnost antibakterijskih lijekova, poput makrolida i tetraciklina, da se vežu za ribozome i efikasno inhibiraju rast i razmnožavanje bakterija.

Smanjena propustljivost vanjske membrane bakterija podrazumijeva smanjen unos lijeka u ćeliju, a posebno je izražena kod Gram-negativnih bakterija. Porinski kanali u vanjskoj membrani omogućavaju prolaz hidrofilnih molekula, a smanjenje broja porina ili mutacije koje mijenjaju selektivnost kanala dovode do smanjenog unosa beta-laktama i fluorokvinolona, čime se razvija rezistencija.

Efluksni sistemi podrazumijevaju da bakterije posjeduju membranske transportne pumpe koje izbacuju toksične supstance, uključujući antibakterijske lijekove, iz ćelije. Glavne porodice ovih pumpi su ABC, MATE, SMR, MFS i RND. RND pumpe, prisutne gotovo isključivo kod Gram-negativnih bakterija, imaju najveći klinički značaj jer izbacuju supstance iz čitave ćelijske ovojnice. Efluksni sistemi mogu biti specifični za pojedine antibakterijske lijekove (makrolidi, tetraciklini i fluorokvinolini) i često doprinose razvoju multirezistentnih sojeva bakterija.

Zaobilaženje metaboličkih puteva podrazumijeva da bakterije razvijaju alternativne biohemijske puteve ili preuzimaju metaboličke produkte iz okoline, čime se smanjuje efekat antibakterijskog lijeka. Na primjer, neki sojevi razvili su rezistenciju na sulfonamide i trimetoprim tako što postaju sposobni da preuzimaju folnu kiselinu iz okoline ili je sintetiziraju u suficitu, čime se prevazilazi kompetitivni antagonizam.

Ovi mehanizmi često djeluju istovremeno i mogu dovesti do razvoja multirezistentnosti (Bengtsson i Greco, 2015; McEwen i Collignon, 2018).

Prenos rezistencije na antibakterijske lijekove

Prenos rezistencije može biti vertikalan i horizontalan.

Vertikalni prenos podrazumijeva prenošenje rezistentnih gena s roditeljskih bakterija na potomke tokom diobe bakterijske ćelije. Ovaj mehanizam karakterističan je za nasljeđivanje već postojećih (intrinzičnih ili stečenih) osobina rezistencije, koja se stabilno prenosi u bakterijskoj populaciji. Primjer je *E. coli* koja nosi gen za beta-laktamazu te ga prenosi na sve kćerke ćelije nakon diobe. Vertikalni prenos ne omogućava razmjenu genetskog materijala između različitih bakterijskih vrsta (Ćupić i sar., 2019; McEwen i Collignon, 2018).

Horizontalni prenos omogućava širenje rezistentnih gena između različitih bakterijskih ćelija, pa čak i različitih vrsta. Ovaj mehanizam je ključni faktor širenja stečene rezistencije u bakterijskim populacijama (Ćupić i sar., 2019; Norman i sar., 2015).

Osnovni mehanizmi horizontalnog prenosa su konjugacija, transdukcija i transformacija.

Konjugacija je prenos bakterijskih gena s jedne bakterije na drugu pomoću seksualnog pilusa (direktnim kontaktom između ćelija). Ovo je najčešći oblik horizontalnog prenosa. Na ovaj način *S. aureus* može zamijeniti genetski materijal s *Enterococcus faecalis* ili *E. coli* (Ćupić i sar., 2019; Norman i sar., 2015).

Transdukcija je prenos bakterijskih gena putem bakteriofaga (virusa koji inficira bakterije) pri čemu fag može prenijeti rezistentni gen s jedne bakterije na drugu. Ovaj mehanizam značajan je kod prenosa gena između istih ili srodnih vrsta bakterija kao što je slučaj kod *S. aureus* (Ćupić i sar., 2019; Michaelis i Grohmann, 2023).

Transformacija je preuzimanje slobodnih DNK fragmenata iz okoline, koji potiču iz mrtvih bakterija, i njihovu integraciju u genom primatelja. Ovo se dešava kod *S. pneumoniae* koji može preuzeti gene za rezistenciju na peniciline (Ćupić i sar., 2019; Michaelis i Grohmann, 2023).

Horizontalni prenos omogućavaju i mobilni genetski elementi, poput transpozona i integrona, koji prenose i omogućavaju ekspresiju gena za rezistenciju između bakterija. Transpozoni se mogu premještati unutar genoma ili između plazmida i hromozoma, dok integroni djeluju kao genetske platforme za prikupljanje i ekspresiju gena rezistencije tzv. genske kasete (Ćupić i sar., 2019; Michaelis i Grohmann, 2023). Na primjer $kanMX_3$ i $kanMX_4$ kaseta omogućavaju otpornost bakterija na kanamicin (Goldstein i McCusker, 1999).

Zahvaljujući ovim mehanizmima horizontalni prenos omogućava brzo širenje rezistencije između bakterija različitih vrsta i populacija. Ovo je naročito važno u okruženjima s intenzivnom upotrebom antibakterijskih lijekova (Michaelis i Grohmann, 2023; Norman i sar., 2015).

Porijeklo rezistencije na antibakterijske lijekove

Rezistencija na lijekove može biti hromozomska ili posredovana mobilnim genetskim elementima (ekstrahromozomska).

Hromozomska rezistencija nastaje zbog spontanih mutacija u bakterijskom hromozomu ili promjena u ekspresiji gena, koje mogu dovesti do promjena u strukturi ciljnog mjesta djelovanja, smanjenoj propustljivosti membrane ili povećanje aktivnosti efluksnih pumpi, čime se onemogućava ili smanjuje djelovanje antibakterijskog lijeka (Bedenić, 2009; Bonomo, 2019).

Ekstrahromozomska rezistencija uključuje mobilne genetske elemente (plazmide i integrone), koji omogućavaju horizontalni prenos ili akumulaciju gena rezistencije doprinoseći širenju multirezistentnih bakterija (Bedenić, 2009; Guardabassi i Prescott, 2015; Landers i sar., 2012).

Osim genetskih mehanizama, bakterije mogu razviti i fenotipsku rezistenciju, koja je obično privremena i inducibilna, a predstavlja sposobnost bakterija da prežive izloženost antibioticima (*in vitro*) bez trajnih genetskih promjena. Nastanak ove rezistencije često je povezan s uslovima okoline ili stanjem mirovanja bakterijskih ćelija. Za razliku od genotipske rezistencije, fenotipska rezistencija se ne nasljeđuje. Primjeri uključuju formiranje biofilma, u kojem bakterije pokazuju smanjenu osjetljivost na antibakterijske lijekove. Formiranje biofilma doprinosi smanjenoj penetraciji lijeka i povećanoj toleranciji bakterijskih zajednica. Također uključuje sporulaciju (kod određenih bakterija), koja ih čini otpornim na nepovoljne uslove. Fenotipski mehanizmi otežavaju liječenje infekcija i mogu posredno doprinijeti selekciji trajnih genetskih oblika rezistencije (Liu i sar., 2024; McEwen i Collignon, 2018; Paterson, 2019).

Navedeni mehanizmi, posebno stečena rezistencija, mogu dovesti do razvoja unakrsne rezistencije, multirezistencije te ekstenzivne i potpune rezistencije

(Belay i sar., 2024).

Multirezistencija i unakrsna rezistencija

Poseban problem u savremenoj veterinarskoj i humanoj medicini je pojava multirezistentnih bakterija (MDR, engl. multidrug resistant organisms), koje se u svakodnevnom govoru nazivaju i "superbakterije" (Belay i sar., 2024; Magiorakos i sar., 2012).

Multirezistencija se kod bakterija može razviti putem dva glavna mehanizma. Prvi način je da bakterije stiču više gena, od kojih svaki pruža otpornost na određeni lijek, često lociran na mobilnim genetskim elementima, poput plazmida (R plazmidi). Drugi način javlja se usljed promjena u ekspresiji ili funkciji postojećih gena, uključujući povećanu aktivnost efluks pumpi, enzimsku inaktivaciju, kao i promjene u strukturi ciljnih mjesta vezivanja (Belay i sar., 2024).

Prema međunarodno prihvaćenoj definiciji, multirezistencija (engl. multi-drug resistance) podrazumijeva stečenu otpornost bakterije na najmanje jedan u tri ili više klasa antibakterijskih lijekova (Belay i sar., 2024; Magiorakos i sar., 2012).

Termin proširena rezistencija (XDR, engl. extensively drug-resistant) odnosi se na neosjetljivost na najmanje jedan lijek u svim, osim jedne ili dvije klase antibakterijskih lijekova, dok potpuna rezistencija (PDR, engl. pandrug-resistant) podrazumijeva rezistenciju na sve dostupne klase antibakterijskih lijekova (Belay i sar., 2024; Magiorakos i sar., 2012).

Osim toga značajan problem ima i tzv. unakrsna rezistencija (engl. cross resistance) koja označava otpornost bakterija na različite antibakterijske lijekove slične hemijske strukture ili mehanizma djelovanja, iako prethodno nisu bile izložene tim lijekovima (Belay i sar., 2024; Blair i sar., 2015; Ćupić i sar., 2019; Reygaert, 2018).

Unakrsna rezistencija može biti jednostrana i obostrana. Jednostrana (nepotpuna) javlja se kada rezistencija na jedan antibakterijski lijek uzrokuje smanjenu osjetljivost na drugi koji mu je sličan. Primjer je inducibilna rezistencija na klindamicin kod *S. aureus* rezistentnog na makrolide (MLDB inducibilni genotip). Nasuprot tome, obostrana (potpuna) rezistencija podrazumijeva istovremenu rezistenciju na više antibakterijskih lijekova iste ili srodne grupe. Primjer je produkcija beta-laktamaza kod *E. coli* ili konstitutivni MLSB fenotip kod *S. aureus*, koji uzrokuje rezistenciju na makrolide, linkozamide i streptogramine (Blair i sar., 2015; Guardabassi i Prescott, 2015).

Multirezistencija u veterinarskoj praksi predstavlja značajno ograničenje u izboru terapije, otežava empirijsko liječenje te povećava rizik terapijskog neuspjeha, posebno u intenzivnoj stočarskoj proizvodnji gdje se infekcije mogu brzo širiti (Guardabassi i Prescott, 2015; McEwen i Collignon, 2018).

AMR od kliničkog značaja u veterinarskoj medicini

AMR uključuje i humanu i veterinarsku medicinu. Određene bakterije posebno su relevantne zbog svoje sposobnosti da izbjegnu djelovanje antibakterijskih lijekova i šire multirezistentne sojeve. Američko društvo za zarazne bolesti identificiralo je grupu takvih mikroorganizama poznatih pod nazivom ESKAPE patogeni, a u koju spadaju: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* i *Enterobacter* spp. (Abram i sar., 2018; Kelly i sar., 2024; Pendleton i sar., 2013).

Prema Svjetskoj zdravstvenoj organizaciji (WHO) ESKAPE patogeni nalaze se na popisu kritičnih ili visokoprioritetnih patogena i navedeni su kao hitne ili ozbiljne prijetnje javnom zdravlju od strane Centara za kontrolu i prevenciju bolesti (CDC) (Kelly i sar., 2024).

Iako se ovi patogeni najčešće povezuju s humanom medicinom, njihov zoonotski potencijal i prisutnost u veterinarskoj medicini čine ih značajnim za nadzor i kontrolu (Guardabassi i Prescott, 2015; Pendleton i sar., 2013).

Prenos rezistentnih bakterija sa životinja na ljude odvija se različitim putevima, ali može biti i obrnuto, kao u slučaju meticilin-rezistentnog *Staphylococcus aureus* (MRSA). Kod životinja se mogu razlikovati tri vrste AMR: AMR kod specifičnih životinjskih patogena, AMR kod zoonotskih patogena i AMR kod komensalnih bakterija pri čemu je posljednja kategorija posebno značajna zbog velike biomase i ekološkog utjecaja (Caneschi i sar., 2023).

Putem stajnjaka i gnojiva, ostaci antibakterijskih lijekova, ARB (bakterije otporne na antibakterijske lijekove) i ARG (geni otporni na antibakterijske lijekove) mogu dospjeti u okolinu što omogućava njihovo širenje na divlje životinje i ljude (Caneschi i sar., 2023).

U kontekstu životinja koje se koriste za proizvodnju hrane, značajan utjecaj na pojavu i širenje AMR ima

način primjene antibakterijskih lijekova i njihova farmakokinetika (Caneschi i sar., 2023). Najčešće korištene klase uključuju tetracikline, beta-laktame, kinolone i sulfonamide, pri čemu je oralna primjena najzastupljeniji put aplikacije (Simoons-Smit, 2000). Tetraciklini imaju nisku oralnu bioraspoloživost kod svinja (5–15%) (Nielsen i Gyrd-Hansen, 1996) i peradi (≤5%) (Pollet i sar., 1983), kao i ampicilin (10%) kod svinja (Bibbal i sar., 2007). Neresorbirani lijekovi brzo mijenjaju crijevnu mikropopulaciju i ostaju mikrobiološki aktivni u fecesu, čime utječu i na mikroorganizme prisutne u okolini (Caneschi i sar., 2023; Hansen i sar., 2002).

Rezistencija na tetracikline često je povezana s ko-selekcijom gena rezistencije na druge, klinički značajne antibakterijske lijekove, uključujući i one važne za humanu medicinu (Herrick i sar., 2014). Primjeri uključuju prisustvo gena rezistencije na karbapeneme, iako se ovi antibiotici u veterinarskoj praksi ne koriste kod životinja za proizvodnju hrane. Ipak, geni rezistencije pronađeni su kod takvih životinja, posebno kod svinja i pilića, što ukazuje na značaj horizontalnog prenosa gena (Caneschi i sar., 2023).

Primjena životinjskog gnojiva u poljoprivredi, koje može sadržavati rezistentne bakterije i ostatke antibakterijskih lijekova, predstavlja potencijalni izvor širenja ARB u okolinu, što može dovesti do njihovog daljeg prenosa, uključujući i na populacije divljih životinja. Bliski kontakt između kućnih ljubimaca i ljudi (npr. maženje, lizanje ili fizičke ozljede), kao i kućno okruženje, olakšava prenos bakterija i gena otpornih na antibakterijske lijekove (Caneschi i sar., 2023).

Kod pasa i mačaka također su identificirani multirezistentni geni i geni rezistencije na više klasa antibakterijskih lijekova. Analizom genoma bakterija iz pseće sline utvrđeni su geni rezistencije na aminoglikozide, karbapeneme, cefalosporine, makrolide, linkozamide, tetracikline i druge klase antibakterijskih lijekova. Ovi geni otpornosti imaju potencijal opstanka i širenja unutar organizma ljudi i životinja (Caneschi i sar., 2023).

Kontinuirano praćenje rezistentnih sojeva, odgovorna primjena antimikrobnih lijekova i provođenje biosigurnosnih mjera ključni su za smanjenje rizika od širenja AMR (Šeol Martinec, 2019).

Patogeni od kliničkog značaja uključuju Gram-pozitivne i Gram-negativne bakterije koje uzrokuju infekcije kod životinja, a predstavljaju i izvor zoonotskih infekcija. Zoonotski prenos može se ostvariti putem hrane životinjskog porijekla, direktnog kontakta sa životinjama, kontaminirane okoline ili u zdravstvenim ustanovama (Liu i sar. 2024, McEwen i Collignon, 2018).

Gram-negativni patogeni

U ovu grupu ubrajaju se *Salmonella* spp., *Campylobacter* spp. i *Pseudomonas aeruginosa.*

Salmonella enterica je važan uzročnik alimentarnih infekcija kod ljudi i životinja. Patogeni sojevi pokazuju značajnu otpornost na tetracikline, sulfonamide, streptomicin, kanamicin, hloramfenikol i neke beta-laktame. Također se bilježi porast otpornosti na novije antibakterijske lijekove ili njihove kombinacije, uključujući amoksicilin i klavulansku kiselinu ili nalidiksinsku kiselinu i ceftriakson (van Boeckel i sar., 2015; Palma i sar., 2020).

Kod *Campylobacter* spp. najvažniji uzročnik je *Campylobacter jejuni,* ali izolati pokazuju izraženu otpornost na fluorokvinolone i makrolide, uz varijabilnu rezistenciju na neke druge klase lijekova, uključujući linkozamide, hloramfenikol, aminoglikozide, tetracikline, beta-laktame, kotrimoksazol i tilozin (Bojanić i sar., 2017; Palma i sar., 2020; Shen i sar, 2018).

Pseudomonas aeruginosa prirodno je rezistentna na veliki broj antimikrobnih lijekova. Čest je uzročnik oportunističkih i bolničkih infekcija kod pasa uključujući otitis i infekcije rana. Dugotrajna terapija i subterapijske doze dodatno doprinose razvoju rezistencije. Također je zabilježen i prenos multirezistentnih sojeva između životinja, ljudi i kontaminirane hrane (Šeol Martinec, 2019).

Gram-pozitivni patogeni

U ovu grupu ubrajaju se *Enterococcus* spp. i *Staphylococcus* spp.

Enterococcus spp., koji uključuje najznačajnije vrste *E. faecalis* i *E. faecium*, čini globalno važan oportunistički patogen. Prirodno nastanjuje crijevnu mikropopulaciju ljudi i životinja, ali može perzistirati u gastrointestinalnom traktu domaćina duže vrijeme, bez pojave kliničkih simptoma, uz sposobnost preživljavanja u bolničkom okruženju (Luo i sar., 2024).

Ovi sojevi pokazuju visok nivo prirodne i stečene rezistencije na brojne antibakterijske lijekove, posebno na aminoglikozide i beta-laktame, dok je rezistencija na

vankomicin naročito značajna (Palma i sar., 2020).

Staphylococcus aureus i *S. pseudintermedius* prirodno naseljavaju kožu i sluznicu ljudi i životinja (Palma i sar., 2020), ali pojedini sojevi mogu uzrokovati različite infektivne bolesti kod obje vrste domaćina (Ward i sar., 2015).

MRSA (meticilin-rezistentni *S. aureus*) pokazuje rezistenciju na sve beta-laktamske antibiotike zbog prisustva mecA gena, koji kodira modificirani penicilin-vezujući protein (PBP2a). Razlikuju se bolnički (HA-MRSA), zajednički (CA-MRSA) i stočarski (LA-MRSA, najčešće CC398) sojevi. LA-MRSA posebno je značajan u svinjogojstvu i može se prenositi između životinja i ljudi, naročito kod profesionalno izloženih osoba (Šeol Martinec, 2019).

MRSP (meticilin-rezistentni *S. pseudintermedius*) važan je patogen pasa i mačaka, čest uzročnik dermatoloških i postoperativnih infekcija. Multirezistentni sojevi (npr. ST71 u Evropi) pokazuju rezistenciju na više klasa antibakterijskih lijekova, uključujući beta-laktame, fluorokvinolone i makrolide. Iako je zoonotski potencijal manji u poređenju s MRSA, zabilježen je prenos na ljude (Loeffler i Lloyd, 2010; Matanović i sar., 2012).

Strategije prevencije i kontrole antimikrobne rezistencije u veterinarskoj medicini

Efikasna kontrola AMR zasniva se na kombinaciji regulatornih mjera, racionalne upotrebe antimikrobnih lijekova, kontinuirane edukacije te integriranog pristupa zdravlju ljudi, životinja i okoline primjenom principa "Jedno zdravlje" (*One Health*). Ovaj pristup naglašava povezanost humane i veterinarske medicine i okoline, s ciljem zajedničkog djelovanja na prevenciji AMR. Na taj način omogućava se praćenje i nadzor širenja rezistentnih bakterija, ograničavanje nastanka rezistencije, smanjenje prenosa između životinja, ljudi i okoline, očuvanje efikasnosti postojećih antimikrobnih lijekova te unapređenje saradnje između veterinarskog, medicinskog i javnozdravstvenog sektora, uz razvoj zajedničkih strategija prevencije (Krnjajić i sar., 2024; McEwen i Collignon, 2018; WHO, 2015; WOAH, 2016).

Racionalna i odgovorna primjena antimikrobnih lijekova čini osnovu kontrole AMR. Programi antimikrobnog upravljanja usmjereni su na očuvanje dugoročne efikasnosti lijekova i usporavanje razvoja rezistencije (Vlahović-Plačevski, 2019). Glavni ciljevi ovih programa su smanjenje morbiditeta izazvanog infekcijama multirezistentnim bakterijama, produženje terapijske efikasnosti antibakterijskih lijekova te smanjenje troškova liječenja (WHO, 2015).

Ključni elementi antimikrobnog upravljanja obuhvataju provođenje mikrobiološke dijagnostike i antibiograma prije započinjanja terapije, izbor odgovarajućeg antimikrobnog lijeka kao i optimizaciju doze i dužine terapije. Također uključuju kontrolu profilaktičke primjene kritično važnih antibakterijskih lijekova te praćenje terapijskog odgovora i evaluaciju ishoda liječenja (Guardabassi i Prescott, 2015; EMA, 2023).

U veterinarskoj praksi ove mjere imaju za cilj ograničiti upotrebu kritično važnih antibakterijskih lijekova, kontrolu potrošnje lijekova u stočarstvu i veterinarskim ambulantama te implementaciju dobre veterinarske prakse, kao i razvoj nacionalnih programa nadzora i kontrole AMR (WHO, 2015; EMA, 2023).

Kontinuirano usavršavanje ljekara, veterinara, farmaceuta, kao i edukacija vlasnika životinja, od ključnog je značaja za racionalnu upotrebu antimikrobnih lijekova. Ovi programi podrazumijevaju pravilan izbor i primjenu lijekova, razumijevanje mehanizma nastanka rezistencije, prepoznavanje rizika prenosa rezistentnih bakterija sa životinja na ljude te primjenu biosigurnosnih i higijenskih mjera na farmama i u veterinarskim ustanovama (Bengtsson i Greko, 2014; Guardabassi i Prescott, 2015).

Monitoring obuhvata praćenje rezistencije bakterija izolovanih iz životinja, hrane i okoline, povezivanje laboratorija, istraživačkih institucija i regulatornih tijela u jedinstven sistem nadzora te analizu prikupljenih podataka u cilju razvoja strategija prevencije i kontrole AMR (WHO, 2015; WOAH, 2016).

Važnu ulogu u kontroli AMR imaju i preventivne mjere, uključujući vakcinaciju, unapređenje biosigurnosti i higijene te optimizaciju uslova držanja životinja. Vakcine i monoklonska antitijela mogu doprinijeti prevenciji bolesti uzrokovanih rezistentnim patogenima, čime se smanjuje potreba za primjenom antibakterijskih lijekova i selekcijski pritisak na razvoj rezistencije. Pored toga, sve veći značaj imaju i alternativni pristupi, poput primjene prebiotika i probiotika za modulaciju crijevne mikropopulacije, fitogenih dodataka i imunomodulatora, koji doprinose očuvanju zdravlja životinja i smanjenju selekcijskog pritiska (Fischetti, 2018; Guidara i sar., 2024; McEwen i Collignon, 2018).

U tom kontekstu primjena bakteriofaga i specifičnih enzima usmjerenih protiv patogena, zajedno s razvojem brzih molekularnih dijagnostičkih metoda za detekciju rezistencije i primjenu ciljane terapije, predstavlja perspektivan pravac u savremenim strategijama kontrole AMR (van Belkum i sar., 2020; Czaplewski i sar., 2016).

Dodatni aspekti AMR u veterinarskoj medicini

AMR kod bakterija izolovanih iz životinja bilježi stalan porast na globalnom nivou (McEwen i Collignon, 2018). Intenzivna stočarska proizvodnja i masovna primjena antibakterijskih lijekova u uzgoju životinja doprinose selekciji multirezistentnih bakterija (Landers i sar., 2012).

Praćenje propisivanja i potrošnje antibakterijskih lijekova ključni je element strategije kontrole AMR. Sistematsko prikupljanje i analiza podataka omogućavaju poređenje između različitih ustanova, regija i država, kao i procjenu efikasnosti intervencija usmjerenih na racionalnu upotrebu antibakterijskih lijekova. Promjene u potrošnji često se koriste kao indikator uspješnosti implementiranih smjernica (WHO, 2015; EMA, 2023).

Jedna od najčešće korištenih metoda za praćenje potrošnje antimikrobnih lijekova je metoda definisanih dnevnih doza za životinje (DDDvet), koja omogućava ujednačeno poređenje potrošnje između različitih populacija i proizvodnih sistema (EMA, 2016; EMA, 2023).

Podaci o potrošnji antibakterijskih lijekova prikupljuju se kroz nacionalne i međunarodne programe nadzora, poput Evropskog sistema ESVAC (European Surveillance of Veterinary Antimicrobial Consumption). Ovaj sistem omogućava analizu promjena u potrošnji antimikrobnih lijekova u veterinarskoj medicini i stočarskoj proizvodnji, uključujući farme i veterinarske ustanove (EMA, 2023).

Prikupljeni podaci o potrošnji lijekova mogu se koristiti za poređenje između farmi i zemalja (engl. benchmarking) čime se identifikuju oblasti s povećanim rizikom i potreba za ciljanim intervencijama. Postoji jasna povezanost između ukupne potrošnje antibakterijskih lijekova i nivoa rezistencije među populacijama životinja, što dodatno naglašava značaj racionalizacije njihove primjene (van Boeckel i sar., 2015; EMA, 2023; McEwen i Collignon, 2018).

Trajni sistemi nadzora i registri propisivanja lijekova u veterinarskoj medicini omogućavaju precizno praćenje upotrebe antimikrobnih lijekova po vrstama životinja i mjestima primjene, što predstavlja ključni mehanizam u razvoju strategija usmjerenih na smanjenje AMR (EMA, 2023; Ruzante i sar., 2022; Udwahani i sar., 2025).

Sigurnost hrane životinjskog porijekla u kontekstu upotrebe antibakterijskih lijekova dodatno se osigurava kroz uspostavljanje i poštivanje maksimalno dozvoljenih količina ostataka (MDK; engl. Maximum Residue Limits - MRL), koje predstavljaju najvišu dozvoljenu koncentraciju ostataka farmakološki aktivnih supstanci u hrani bez rizika po zdravlje ljudi. Na međunarodnom nivou MDK vrijednosti definišu se u skladu sa smjernicama Codex Alimentarius komisije, dok ih u EU definiše Evropska agencija za lijekove (European Medicines Agency - EMA) na osnovu naučne procjene rizika (FAO/WHO, Codex Alimentarius Commission, 2024; EMA, 2023). U Bosni i Hercegovini primjenjuju se nacionalni propisi usklađeni s ovim standardima, čime se osigurava kontrola rezidua i harmonizacija s međunarodnim standardima (Sl. glasnik BiH, br. 61/11).

U tom kontekstu, važan aspekt racionalne upotrebe antibakterijskih lijekova u veterinarskoj medicini predstavlja i poštivanje karence. Karenca predstavlja vremenski period koji mora proteći od posljednje primjene lijeka do klanja životinje ili upotrebe proizvoda životinjskog porijekla (mlijeko, jaja, med) za ishranu ljudi. Njeno poštivanje osigurava da koncentracije ostataka antibakterijskih lijekova u hrani ne prelaze MDK, čime se smanjuje rizik po zdravlje ljudi, uključujući toksične i alergijske reakcije te potencijalni doprinos razvoju AMR kroz hroničnu izloženost subterapijskim koncentracijama ostataka. Istovremeno, poštivanje karence predstavlja važan dio sistema kontrole sigurnosti hrane i doprinosi odgovornoj i održivoj primjeni antibakterijskih lijekova u veterinarskoj praksi (Ćupić i sar., 2019; Getahun i sar., 2023; Rana i sar., 2019).

ZAKLJUČCI

Antimikrobna rezistencija (AMR) je ozbiljan globalni javnozdravstveni problem u veterinarskoj medicini, sa stalnim porastom rezistentnih bakterijskih sojeva kod životinja.

Nepravilna upotreba antibakterijskih lijekova, uključujući profilaktičku primjenu, subterapijske doze i empirijsku terapiju bez prethodnog antibiograma, čini

glavni faktor razvoja AMR.

Prirodna i stečena rezistencija, kao i pojava multirezistentnih i unakrsno rezistentnih sojeva dodatno otežavaju liječenje infekcija i ugrožavaju javno zdravlje.

Zoonotski potencijal rezistentnih bakterija naglašava potrebu za integriranim pristupom "Jedno zdravlje", povezujući zdravlje ljudi, životinja i okoline.

Strategije prevencije obuhvataju racionalnu upotrebu antimikrobnih lijekova, primjenu principa antimikrobnog upravljanja, mikrobiološku dijagnostiku, kontrolu profilaktičke primjene te kontinuiranu edukaciju stručnjaka i vlasnika životinja.

Alternativne metode kontrole infekcija, uključujući vakcinaciju, primjenu prebiotika i probiotika, bakteriofaga kao i savremenih dijagnostičkih metoda, doprinose smanjenju upotrebe antimikrobnih lijekova i ograničavanju selekcije rezistentnih sojeva.

Monitoring potrošnje antimikrobnih lijekova putem sistema poput ESVAC i primjena DDDvet metode ključni su za praćenje i smanjenje rizika od AMR.

Poštivanje maksimalno dozvoljenih rezidua i karence u hrani životinjskog porijekla predstavlja važan segment zaštite javnog zdravlja i kontrole izloženosti populacije ostacima antibakterijskih lijekova.

SUKOB INTERESA

Autori potvrđuju da nema sukoba interesa.

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Antimicrobial resistance in veterinary medicine: Practice and control strategies

ABSTRACT

Antimicrobial resistance (AMR) is the ability of microorganisms (bacteria, viruses, fungi and parasites) to survive or reproduce in the presence of an antimicrobial drug that would otherwise inhibit or destroy them. Today, AMR represents a serious global public health and economic challenge in both human and veterinary medicine. It occurs as a result of improper, long-term and intensive use of antimicrobial drugs, including prophylactic administration, as well as the use of subtherapeutic doses, which enable the selection of bacteria resistant to these drugs.

Pathogens of clinical importance in veterinary medicine include Gram-negative (*Salmonella spp*., *Campylobacter spp*. and *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Staphylococcus spp*. and *Enterococcus spp*.), which cause infections in animals and pose a zoonotic risk.

Resistance can be natural or acquired. Acquired resistance develops under the selective pressure of antibacterial drugs and spreads through horizontal or vertical gene transfer. Key mechanisms include enzyme inactivation, target site modification, changes in membrane permeability, efflux pumps, and bypass of metabolic pathways. Horizontal transmission is the main mechanism driving the spread of multidrug resistance (MDR, XDR, PDR), often accompanied by cross-resistance.

The prevention and control of AMR is based on the rational use of antibacterial drugs, microbiological diagnostics and antibiogram, limitation of critically important drugs, education and application of the "One Health" approach, as well as control of intake through the DDDvet and ESVAC systems. In addition, compliance with the MRL and withdrawal periods in food of animal origin represents an important segment of public health protection and control of exposure to drug residues.

Alternative methods, including vaccination, probiotics, bacteriophages and molecular diagnostic methods, contribute to reducing the use of antibacterial drugs and the spread of AMR.

The effective implementation of these strategies enables preservation of therapeutic efficacy and reduction of the transfer of resistant bacteria from animals to humans.

Keywords: Antimicrobial resistance, veterinary medicine, multidrug-resistant bacteria, rational use of antimicrobial drugs, control strategies.

STRUČNI RAD • PROFESSIONAL PAPER

Uzgoj lovačkih pasa

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SAŽETAK

Motive lova s psima na prostoru Bosne i Hercegovine (BiH) nalazimo na stećcima sredinom srednjeg vijeka. Kao dokaz ove tvrdnje je naša autohtona rasa lovnih pasa - bosanski oštrodlaki gonič - barak. Lovna kinologija, iako zanemarena na ovim prostorima, je dio oficijelne kinologije koja je organizirana u svijetu putem međunarodnih kinoloških federacija, a BiH je u sastavu FCI (*Fédération Cynologique Internationale*). Autori su u ovom radu poseban značaj posvetili bosanskom oštrodlakom goniču - baraku, zatim drugim lovnim psima s akcentom na selekciju, obuku i upotrebu u skladu sa zakonskim odredbama Bosne i Hercegovine. Selekcija, obuka i upotreba gonića i drugih lovnih pasmina pasa je vrlo kompleksna i zahtijeva kontinuiran angažman lovaca.

Ključne riječi: Bosanski stećak, barak, lovna kinologija, lovstvo

UVOD

Već hiljadama godina od doba lovaca-sakupljača pa do danas, pas je bio i ostao čovjekov najbolji prijatelj i pomagač u lovu, o čemu svjedoče brojni arheološki ostaci i historijski nalazi na kojima nerijetko susrećemo prikaze pasa. O povezanosti čovjeka i psa svjedoče i oslikane pećine iz prethistorijskog razdoblja na kojima su prikazane scene iz lova, gdje nerijetko susrećemo i psa kao lovčevog pomagača (Jašić i sar., 2024). U prilog navedenom, postoji naslikan motiv lova s lovačkim psima na čuvenom bosanskom stećku iz Zgošće na teritoriji Općine Kakanj u BiH. U prošlosti, dok sredstva za lov nisu još bila toliko razvijena, lovački psi bili su neophodni. Služili su za traženje, gonjenje, donošenje, ali i hvatanje divljači. Napretkom tehnologije i nauke, čovjek je tražio načine da što bolje upotpuni svoje potrebe. Tako je počeo sa selektivnim uzgojem i usmjeravanjem pasa za specifične načine lova (Fogle, 2005; Katica i dr., 2025).

Kada je riječ o kinologiji, neizbježno je spomenuti *Fédération Cynologique Internationale* (FCI), tj. Međunarodnu kinološku federaciju. To je jedna od krovnih organizacija koja okuplja kinološka društva diljem svijeta i vrši klasifikaciju i standardizaciju rasnih pasa. Svi rasni lovni psi dijele se u deset FCI grupa i 35 sekcija. Važno je znati da su lovne pasmine uglavnom raspoređene od grupe II, u kojoj se nalazi jedan pas za namjenu u lovu (argentinski pas ili *dogo argentino);* u FCI grupu III spadaju terijeri, od kojih se izdvaja njemački lovni terijer, u IV FCI grupi su jazavičari, u V FCI grupi su nordijski, japanski i još neki drugi lovački psi osnovnog tipa. U VI FCI grupi su goniči i srodne rase i krvosljednici. U VII FCI grupi su ptičari, kontinentalni i ostrvski (tj. engleski i irski) i poenteri, u grupi VIII su psi za vodu, cunjavci, retriveri i u X FCI grupi su hrtovi s oko dvadesetak pasmina (Ćutuk i sar., 2024).

Hrtovi se u našoj zemlji i u većini Evropske unije više ne koriste za lov, ali su historijski na ovim prostorima korišteni u tu svrhu. Osim podjele po navedenim grupama, lovačke pse razvrstavamo po zemlji porijekla, boji, dužini i gustini dlake, visini i nekim karakteristikama pojedinih dijelova tijela (Ćutuk i sar., 2024; Karahasanović i sar., 1981).

Cilj rada je da kroz paradigmu bosanskog oštrodlakog gonića - baraka i drugih lovnih pasa naglasimo važnost selekcije, obuke i upotrebe istih u skladu sa zakonskim odredbama BiH.

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Goniči

Većinu goniča svrstavamo u VI FCI grupu. Smatra se da su oni najstariji lovački psi, od kojih su nastale ostale grupe. Po izgledu ih dijelimo na kratkodlake, oštrodlake, kratkonoge i dugonoge. Prilagođeni su za lov gonjenjem, tj. divljač dotjeruju do vlasnika-lovca (na što im i ime ukazuje). Pri podizanju divljači, javljaju se vlasniku, koji dolazi da pronađenu divljač odstrijeli. Pogodni su za pojedinačni, ali i grupni lov s nekoliko pasa, a koriste se i u hajkama na štetočine s mnogo lovaca i pasa (Richter, 1976; Karahasanović i sar., 1981). Shodno potrebama lovca, kod goniča se mogu razviti i druge osobine u radu, koje ih čine svestrano upotrebljivim. Tako se lahko mogu naučiti da rade na krvnom tragu, a niže rase i u jami. Koriste se za traženje i lov divlje svinje, lisice ili samo zeca za što goniči najčešće i služe u BiH. Radni ispit za goniče se po FCI propisima izvodi u otvorenom lovištu isključivo na lisicu i zeca, jer se na toj divljači najbolje primjećuju vrline ovih pasa. Također, mogu se, poput cunjavaca, upotrebljavati i za istjerivanje fazana, donošenje sitne divljači, oblajavanje, čuvanje odloženih stvari, itd. U BiH i regiji je praksa da se radni ispit obavlja i na divlju svinju (u namjenskim ograđenim površinama), za što je izdat poseban pravilnik (KSuBiH, 2023).

Bosanski oštrodlaki gonič - barak

Bosanski oštrodlaki gonič - barak je naša jedina autohtona lovačka pasmina. Spada u goniče i vrlo je stara pasmina. Barak je na savremeniji način prvo izučavan u doba austrougarske uprave pa ga možemo naći u zapisima austrijskog oficira Franza Laske. Prema njemu, barak predstavlja osnovnu vrstu mnogih pasmina oštrodlakih lovačkih pasa u srednjoj Evropi. Ovo mišljenje potkrepljuje dokumentima francuskih pisaca koji govore da su njihove oštrodlake pasmine nastale od pasa iz orijentalnih provincija Sredozemlja, tj. Balkana (Laska, 1905).

U FCI standardu, pod brojem 155, prvi put je zvanično evidentiran 1965. godine kao ilirski gonič, po nekadašnjoj rimskoj provinciji i narodu koji je živio na širem prostoru BiH. Trenutnim imenom je ozvaničen u dopunjenom standardu 1973. godine. Prema standardu iz 1973. godine to je snažan pas s dugom i čekinjastom dlakom, duge i srednje široke glave, izraženih i gustih obrva. Izraz mu je ozbiljan, strog, ali veseo. Osnovna boja je žutocrvena ili zemljanosiva, s manjim bijelim površinama na donjim dijelovima. Temperamentan, hrabar i uporan. Visina grebena je 46-56 cm, poželjno 52 cm. Kuje su nešto niže. Težina je 16 - 24 kg, poželjno 20 kg. Trup treba da je 10% duži od visine. Upotreba: dobar, istrajan i uporan gonič sa srednje visokim do dubokim glasom (Tadić, 1990; FCI, 1996).

Bosanski oštrodlaki gonič - barak je, pored drugih autohtonih pasmina regije (posebno trobojnog i posavskog goniča), poznat i zastupljen među našim lovcima. Brojno stanje se ogledalo u malom broju primjeraka, ali se naporima bosanskohercegovačkih kinologa i lovaca znatno popravilo, tako da sada u BiH imamo nekoliko uzgajivača i barake redovno viđamo na raznim lokalnim i međunarodnim smotrama i izložbama (Ćutuk i dr., 2024).

Lovački psi drugih namjena

Goniči su grupa koja se kod nas pretežno koristi u lovu, ali susrećemo i krvosljednike, jamare, ptičare i cunjavce. Što se tiče krvosljednika, svako lovačko društvo obavezno ih je posjedovati. To su psi s izvanredno razvijenim čulom njuha, sposobni za traženje ranjene divljači po krvnom tragu, isključivo na povocu (Fogle, 2005). U lovu se nerijetko promaši hitac, tj. ne dođe do smrtonosne rane, tako da divljač pobjegne. U tom slučaju se upotrebljavaju ovi specijalizirani psi, mada se i naše pasmine goniča mogu obučiti za slijeđenje krvnog traga (Richter, 1976).

Jamari su psi čija je glavna osobina rad u jami, odnosno pod zemljom. Zbog svog niskog rasta i malih dimenzija, lahko se uvlače u jazbine lisice, jazavca i drugih vrsta divljači koje obitavaju u jamama, uspješno ih savladavaju (imaju naročito jake zube i njušku, što im pomaže u borbi s divljači) i istjeruju, kako bi ih lovac odstrijelio. Veoma su korisni u lovu na štetočine. Iznad zemlje ih mnogi lovci koriste i kao goniče. Od pasmina se kod nas upotrebljavaju jazavičari i lovni terijeri (Karahasanović i dr., 1981; Ćutuk i dr., 2024).

Ptičari su psi koji se koriste, kako im ime kaže, za lov na ptice, ali i na drugu sitnu divljač. Odlikuju se traženjem u trku, s više-manje dignutom glavom upijajući miris divljači donesen vjetrom, markiranjem na način da na udaljenosti i od nekoliko desetina metara stanu kao ukopani, obično s dignutom prednjom nogom (tako lovcu označavaju lokaciju divljači) te donošenjem (aportiranje) odstrijeljene divljači. Koriste se za rad na suhom, ali i u vodi. Za pokriveni teren nisu korisni, jer se dosta udalje od lovca, koji ih onda gubi iz vida. Iz tog su razloga rijetko u upotrebi u BiH, zbog našeg većinski planinskog, nepreglednog terena (Richter, 1976; Durantel, 2007).

Cunjavci kod nas nisu popularni za lov, a zbog njihove ljepote ih češće susrećemo na izložbama pasa i kao ljubimce. Njihova karakteristika je dizanje sitne divljači. Oni moraju neprestano biti u pokretu i trčati, što je njihova specifičnost u odnosu na druge grupe lovačkih pasa. Također moraju ostati neprimjetni pa je vrlo bitno da znaju i da se šunjaju/cunjaju kroz lovišta prekrivena maglom i gustim rastinjem. Zbog toga se upotrebljavaju za lov na zeca, fazana, šljuke i močvarice (Richter, 1976; Durantel, 2007).

Uzgoj i obuka svih navedenih grupa lovačkih pasa, pod čime se podrazumijevaju svi postupci koje uzgajivač poduzima od rođenja psa i tokom njegovog čitavog radnog vijeka, ne razlikuju se naročito u najranijoj dobi, ali se u kasnijem uzrastu prilagođavaju odabranoj pasmini. To se radi u skladu s njenim karakteristikama u izgledu, sposobnostima i vrsti lova za koji se koriste, kako bi se najbolje istakle njihove prednosti i sklonosti u lovu (Durantel, 2007).

Uzgoj pasa

Nabavljanje psa i briga o njemu, velika su obaveza i trošak za lovca, a još veća za uzgajivača, koja sa sobom nosi posebne odgovornosti. U kontekstu lovne kinologije, u ovo spadaju: izbor ishrane, navikavanje psa na određene zvukove i mirise, učenje pravilnom ponašanju u lovištu te kontroliranje nagona. Prikladna obuka i polaganje propisanih ispita zakonska su obaveza ukoliko psa želimo koristiti za lov. Uzgajivač vodi brigu o psu u svim njegovim životnim stadijima: od spolne zrelosti, parenja, bremenitosti, koćenja, do podizanja štenadi i njihovog odrastanja (Durantel, 2007; Litričin, 1990).

Cilj uzgoja mora biti očuvanje i, po mogućnosti, proširenje genetičke različitosti pasmine. Zadatak svakog uzgajivača je ispitati je li predviđeni pas dobar za uzgoj, s obzirom na njegove mentalne i fizičke osobine. Osnovni preduvjeti za uzgoj psa su zdravlje te razvoj i karakter primjereni odabranoj pasmini. Goniče svrstavamo u sljedeće dobne kategorije, koje su definisali nacionalni savezi koji vode brigu o određenoj pasmini: 3 - 6 mjeseci baby/štenad, 6 - 9 mjeseci najmlađi, 9 - 15 (ili 18 mjeseci) mladi, 15 - 24 mjeseca intermedia i zreli psi 18 ili 24+ mjeseca (KSuBiH, 2012).

Briga o štenadima

Štenci progledaju 11-13 (nekad 15) dana nakon rođenja. Mliječni zubi im izbijaju u pravilu kada navrše 21 dan, a posljednji stalni zub javlja se u 7. mjesecu života. Sišu svako 2 - 3 sata, u početku 5 puta dnevno, a kasnije sve rjeđe. U početku se primarno hrane majčinim mlijekom, a od druge sedmice im se u prehranu dodaje zašećereno kravlje mlijeko, kaša od riže ili zobenog brašna (Fogle, 2005).

Od 4. do 5. sedmice, štenad polahko odvikavamo od majčinog mlijeka i u ishranu im se dodaje ugrijana mesna supa, svježe isjeckano meso ili jetra. Do šeste sedmice u potpunosti prelaze na raznoliku tečnu i čvrstu hranu. Također je poželjno u ishranu dodati hrskavice i pola kašičice ribljeg ulja dnevno. Do šeste sedmice štenad je potrebno i vakcinisati. U upotrebi su različite vakcine za zdravstvenu zaštitu pasa od različitih proizvođača. Štenad u toj dobi treba izvoditi napolje kako bi se adaptirala na vanjsku sredinu. Nosna pečurka im treba biti hladna i vlažna, bitno je da su vesela i aktivna. Svako drugo zapažanje nam govori da nešto nije u redu u tom periodu razvoja (Potočić i dr., 1963).

S navršena dva mjeseca života, treba se uraditi i druga vakcinacija i poslije toga se štenad može predati drugim vlasnicima, mada je bolje da s majkom ostanu tri mjeseca. Što se tiče ishrane, svako ima različite navike, ali bi se trebalo povesti računa o preporukama veterinara. Štenad možemo kupati nakon navršena 3 mjeseca, a temperatura okruženja bi im trebala u početku biti oko 30°C, a kasnije 18-25°C. U tom periodu u njihovom boksu treba odrediti mjesto gdje će vršiti nuždu. Životni prostor uvijek treba biti uredan, a psi redovno i zdravo nahranjeni, očetkani, čisti, zaštićeni od vanjskih i unutrašnjih parazita i vakcinisani. Nakon tri mjeseca, treba krenuti sa socijalizacijom. Po FCI-u, štene od starosti 3-6 mjeseci se može voditi na izložbe pasa (Litričin, 1990).

Obuka lovačkih pasa

Kod štenadi od mjesec dana već možemo primijetiti kako će u budućnosti reagovati na pucanj udaranjem šipkom o boks - koje će štene hodati radoznalo, koje će pobjeći u kućicu. To testiramo do trećeg mjeseca. U fazi opipa u razvoju šteneta (2 - 4 mjeseca), poželjno je da se pređe na startni pištolj, iz kojeg se prvo puca iz daljine dok pas nešto radi pa mu se polako sve više i više približavamo. Na taj način psa navikavamo na zvuk pucnja, tako da ga on kasnije povezuje s lovom. Plašljive pse treba isključiti iz daljnjeg uzgoja, jer takvi psi nisu pogodni za lov. U dobi od tri mjeseca, štene se mora naučiti da prati svog vlasnika i od njega uvijek traži kontakt; da odgovara na komandu *dođi, sjedi, lezi*

i vlasniku ide uz lijevu nogu. Koliko je štene poslušno najviše je odraz rada lovca. Štene polako počinje jačati čulo njuha, na koje uvijek reaguje (Alihodžić i Starogorčić, 2014).

Poslije šest mjeseci, u zavisnosti od toga na koju divljač učimo štene, treba ga polako navoditi na svježe jutarnje tragove i ohrabrivati ga da pretražuje. Bolje ga je pustiti i da traži duže vremena sam, nego da se oslanja isključivo na druge, odrasle pse, jer će se naviknuti da drugi psi dižu divljač, a da im se on samo priključuje. Kad je sam, sve zavisi od njegovog rada. Uspostavljanje autoriteta vrši se preko povodca, tako najlakše kontroliramo njegovo kretanje i reakcije. Psu dajemo komandu za koju ga, nakon uspješnog izvršavanja, nagrađujemo hranom. Sve ostalo - povišen ton, burna reakcija, fizičko kažnjavanje psa je kontraefektivno (Durantel, 2007; Potočić i dr., 1963).

Goniči mogu loviti sve vrste divljači, ali se po FCI standardu priznaje samo ispit urođenih osobina na lisicu i zeca. U BiH se goniči također koriste i za lov divlje svinje. Tokom obučavanja psa na divljač, neophodno je izvršiti odstrel. Psa treba naučiti da nakon svog rada postigne neki vid nagrade, da osjeti miris i krv te divljači. Psa u mladosti učimo da ne trga i ne dere divljač iz razloga što njegov lovački nagon potrebno držati pod strogom kontrolom. Odličan gonič ne pušta ni drugog čovjeka (mimo svog vlasnika), a neće dozvoliti ni drugim psima dolazak do divljači (Ćutuk i sar., 2024).

Što se tiče radnih osobina lovačkih pasa, dosta lovaca ima bolje rezultate sa ženkama nego s mužjacima. Od početka su privrženije vlasniku, brže se adaptiraju na uslove praktičnog lova i bolje opserviraju teren. Ženka lovnih pasmina pasa vrhunskog kvaliteta može dati potomstvo traženih radnih osobina, ukoliko se provedu sve neophodne mjere i radnje da bi se imao zdrav pas koji će se obučiti u radu na odgovarajući način. Parnjaci kod lovnih pasmina pasa biraju se i na osnovu eksterijernih i na osnovu radnih osobina (Ćutuk i dr., 2024, Durantel, 2007).

Zakonske obaveze za lovce u vezi s uzgojem i držanjem pasa

Pored osnovnih egzistencijalnih potreba, uzgajivač je obavezan voditi računa i o zakonskim propisima vezanim za svoje pse. U FBiH, legislativa po pitanju lovačkih pasa u vezi je sa Zakonom o lovstvu i Pravilnikom o vrsti i broju pasa za lov na pojedine vrste divljači u određenim područjima (Sl. novine FBiH 4/06 i 5/08).

To su ključni zakonski i podzakonski materijalni propisi koji se bave ovom tematikom i služe kao osnov lovačkim udruženjima po pitanju lovne kinologije.

Druge stručne pravilnike, zakonski neobavezujuće ili obavezujuće po kinološkim pravilima, objavili su Kinološki savezi u BiH. Kinološki savez izdaje rodovnik kojim se dokazuje čistokrvnost i pasminska pripadnost psa, propisuje uvjete za ispit urođenih osobina i svaki pojedini radni ispit te izdaje certifikat za položene radne ispite.

Prema Zakonu o lovstvu FBiH (Sl. novine FBiH 4/06), u lovu se isključivo smiju koristiti čistokrvni lovački psi koji posjeduju rodovnicu jedne od članica Međunarodne kinološke federacije (FCI), imaju položen ispit urođenih osobina i ispit u radu i koji imaju pozitivnu ocjenu u obliku (eksterijeru). Svako lovačko društvo (korisnik lovišta) obavezno je da u svom vlasništvu ima pse koji ispunjavaju prethodno navedene kriterije. Zakonska obaveza korisnika lovišta u FBiH vezano za odredbe Zakona o lovstvu je i pas obučen za praćenje krvnog traga ili krvosljednik s položenim ispitom, naročito u lovištima gdje je predviđen odstrel krupne divljači, koja kod nas obuhvata glavne lovno-uzgojne vrste (srna, divlja svinja, medvjed, jelen i dr.). Također, Zakonom je omogućeno i uslovljeno da se sredstva koja se stiču odstrelom divljači koriste za nabavku, uzgoj, obuku i držanje lovačkih pasmina pasa. Zakonom o lovstvu izričito je zabranjeno: loviti nerasnim psima i hrtovima, loviti papkastu lovostajem zaštićenu divljač pomoću pasa, psima proganjati divljač izvan terena ograđenog za trening u vremenu od 5. januara do 31. jula. Nerasnim psima smatraju se psi koji nisu registrovani kod nadležne kinološke organizacije i koji nemaju odgovarajući rodovnik.

Lovci, tj. vlasnici su dužni svoje pse označiti, vakcinisati i upisati u registar pasa u skladu s odredbama Zakona o veterinarstvu (Sl. novine FBiH, 46/00) i prijaviti pse i nova legla jednoj od članica Međunarodne kinološke federacije u BiH (Sl. novine FBiH, br. 4/06, 8/10 i 5/08).

Identifikacija je trajno označavanje pasa jedinstvenom elektronskom oznakom – mikročipom, a nekada (sve do 2013. godine) je bilo obavezno tetoviranje. Svi psi koji se nalaze na teritoriji BiH moraju biti identificirani i evidentirani u skladu s odredbama Pravilnika o identifikaciji i vođenju evidencije pasa, mačaka i pitomih vretica u BiH (Sl. glasnik BiH, broj 96/16). Značaj identifikacije ogleda se u odgovarajućoj kontroli posebno opasnih zaraznih i parazitarnih bolesti od kojih

obolijevaju i ljudi i životinje (zoonoze), prije svega bjesnila, zatim ehinokokoze, lajšmanioze, ali i drugih bolesti (Katica i sar., 2025).

Kinološka pravila i organizacija kinologije

Prema pravilniku o kinološkim manifestacijama iz 2012, ocjenu eksterijera vrši ovlašteni kinološki sudija, u organizaciji lovačkog društva ili kinološkog saveza u okviru radnog ispita. Ona potvrđuje da pas fizički odgovara standardu svoje pasmine zbog strukture i proporcija tijela, koje omogućavaju funkcionalnost u radu. Bez prethodno nabrojanih osobina, pas se ne može okarakterisati kao rasni i iz tog razloga ne može biti upisan u rodovnu knjigu. Prilikom procjene uzgojnih vrijednosti pasa vezano za eksterijer (vanjski izgled), procjenjuju se tjelesne karakteristike koje su propisane standardom svake rase, a između ostalog procjenjitelji uzgojnih vrijednosti ili kinološke sudije su i glavni selekcioneri uzgoja lovnih pasa (KSuBiH, 2012a).

Od kvaliteta rada kinoloških sudija zavisi i kvalitet jedne rase. Danas u lovačkim društvima i organizacijama (nerijetko i u čitavom društvu ili organizaciji) postoji samo nekoliko vrhunskih lovnih pasa, što ukazuje da trenutno ovlašteni selekcioneri uzgoja u lovnoj kinologiji rade nedovoljno dobar posao. Kinološke sudije moraju penalizirati sve vidne deformitete tako da mnogi lovni psi trebaju postati ljubimci, a ne radni psi.

Pozitivna ocjena upućuje na to da pas nije deformisan, da se slaže sa standardom svoje pasmine i nije negativan za uzgoj (neće prenijeti fizičke nedostatke na potomstvo). Ocjena eksterijera u lovnoj kinologiji se obično vrši na smotrama. To su lokalne kinološke manifestacije na kojima se ocjenjuje oblik/eksterijer psa, koje organiziraju kinološka društva i pasminski klubovi, članice saveza kao i lovačke organizacije i društva. Mogu se organizirati i uzgojne smotre kao najprestižnija uzgojna manifestacija putem koje vrhunski primjerci neke pasmine pasa budu preporučeni za dalji uzgoj, kao i u svrhu popularizacije kinologije (KSuBiH, 2012a).

Rodovnik je dokaz da neki pas pripada FCI priznatoj pasmini, a izdaje ga KSuBiH. U svijetu imamo i druge međunarodne kinološke federacije kao što je AKC, BKC, UCI ili australijski kinološki savez kao i još neke druge manje poznate kinološke organizacije. Pomoću rodovnika se prati rodoslovlje pasa, njihovih osobina i sposobnosti u lovu, tako da možemo reći da je rodovnik dokaz uzgojnog rada (KSuBiH, 2012b).

Uzgojni pregled je obvezan za sve mužjake i ženke svih pasmina s kojima se želi obavljati uzgoj u okviru KSuBiH. Na uzgojni pregled mogu se dovesti ženke i mužjaci s ocjenom oblika najmanje vrlodobar. Minimalna starost za pristupanje je 12 mjeseci. Uzgojni pregled za mužjake vrijedi doživotno, uz uvjet da nakon devete godine starosti mužjak jednom godišnje mora biti priveden na uzgojni pregled ukoliko se poslije te dobi koristi za priplod. Uzgojni pregled za ženke vrijedi do navršene devete godine života. Procjena uzgojne vrijednosti obavlja se prema vanjskom izgledu psa, ocjeni eksterijera, precima, potomcima, nagradama, karakteru, radnim ispitima, HD snimci kukova i laktova (za pasmine za koje je to neophodno), kondiciji psa, a uz zadovoljenje minimalnih kriterija za stjecanje uzgojne vrijednosti (KSuBiH, 2012b).

Radni ispiti služe za ispitivanje stvarne vrijednosti i lovne upotrebljivosti čistokrvnih lovačkih pasa. U BiH se najčešće održavaju na divlju svinju (na njega izlaze psi iz III, IV, VI i VIII FCI grupe), te zeca i lisicu. Na ispitima u radu na divlju svinju ispituje se: rad na divlju svinju u prihvatilištu, i proširen rad (ispit) na divlju svinju u prihvatilištu s krvnim tragom. Na proširenim ispitima rada za lovne pse, potreban je teren za ispitivanje na krvnom tragu, ponašanje na pucanj te odloživost. Radni ispiti mogu biti lokalni, državni i međunarodni. Lokalni se dijele na ispit urođenih osobina (IUO) i radni ispit (KSuBiH, 2023).

Ispitom urođenih osobina (IUO) ocjenjuju se nasljedne osobine vezane za lov, koje lovački pas mora posjedovati. Ispit urođenih osobina predstavlja osnovu svakog daljeg ispitivanja takmičarske i upotrebne vrijednosti psa. Kao i radni ispit, prilagođen je FCI grupi pasa koji se izvode na ispit. U pravilu ga polažu mladi psi starosti 9-18 mjeseci koji nisu još prošli dovoljno radne obuke i nisu iskusni u lovu. Zakazuje ga lovačko društvo na prilagođenom poligonu ili otvorenom terenu, u zavisnosti od predmetne divljači, vodeći računa o vremenskim prilikama (Karahasanović i sar., 1981; Ćutuk i sar., 2024).

Ispitivanje rada pasa u prihvatilištu na divlju svinju traje do 16 minuta, osim ako sudije ne odluče drukčije. Ako pas ne pronađe divlju svinju u roku od 6 minuta, automatski se diskvalificira. Vrijeme oblajavanja (iz discipline ustrajnost u radu) je 5 minuta. Discipline koje se ispituju su: ponašanje na pucanj (vezan, nevezan), način traženja i pretraživanja, kvalitet njuha – nosa, glas kod divlje svinje na mjestu, oštrina na divlju svinju, ustrajnost napadanja na divlju svinju, glas u gonjenju

(sljedoglasan, vidoglasan), poslušnost i vodljivost. Na proširenom ispitu se još vrednuju i rad na krvnom tragu, oblajavanje i pokazivanje. Ove osobine su kod pasa urođene (po čemu je ispit i nazvan), ali se uz napor uzgajivača i vlasnika usavršavaju i dovode na viši nivo (KSuBiH, 2023).

Kod radnih ispita za zeca i lisicu, pretraživanje terena traje 20-35 minuta (ovisno o terenu, o brojnosti divljači i vremenskim uvjetima), ako pas ne napravi pogrešku prije isteka tog vremena, koja ga isključuje iz daljnjeg natjecanja. Kod ispita za zeca i lisicu je specifično što se može polagati i u paru ili grupi. To moraju biti psi istog vlasnika, bez obzira na spol. Svaki pas se ocjenjuje posebno, i zbir bodova daje konačan rezultat grupe. Rad u grupi naglašava povezanost i usklađenost u radu pasa. Na početku rada, psima se daje pet minuta za zagrijavanje. Ako pas u tom vremenu uspješno obavi neku radnju, taj uspjeh se uračunava u ocjenu, ako napravi pogrešku ona se ne uzima u obzir (KSuBiH, n.d.). Na ispitu urođenih osobina ispituju se sljedeće discipline: ponašanje na pucanj, ustrajno traženje i pronalaženje, gonjenje divljači, glas, nos - njuh, poslušnost i vodljivost. Pozitivnu ocjenu postiže pas koji osvoji minimalan broj bodova u skladu s odredbama pravilnika, tj. ako dobije pozitivne ocjene u svih šest disciplina. Na proširenim radnim ispitima se još ocjenjuju i krvni trag ili vlečka i ponašanje kod mrtve divljači (Ćutuk i dr., 2024; KSuBiH, 2023; KSuBiH, n.d.).

Nakon uspješno ispunjenih svih navedenih uvjeta, pas se legalno može voditi u lov te na različite kinološke manifestacije.

ZAKLJUČAK

Lovna kinologija kao dio lovstva ima poseban značaj u BiH, a bosanski oštrodlaki gonič – barak je autohtona pasmina pasa iz BiH. Apostrofirana je važnost selekcije, obuke, stručnog kinološkog rada te vođenja rodoslovlja kao dokaza uzgojno-selekcijskog rada u oblasti lovne kinologije u BiH. Biološke osnove lovnih pasa su temeljna pretpostavka za uspješno bavljenje lovnom kinologijom i usko vezane za ekološke aspekte BiH i regiona. Savremeno društvo u BiH mora uvažavati stvarno stanje na terenu te u skladu s tim donositi nove i mijenjati postojeće zakone koji će biti u skladu s najnovijim stručnim i naučnim saznanjima, kako bi bili usklađeni sa stvarnim stanjem.

SUKOB INTERESA

Autori potvrđuju da nema sukoba interesa.

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Hunting Dog Breeding

ABSTRACT

Motifs depicting hunting with dogs in the territory of Bosnia and Herzegovina can be found on medieval tombstones dating back to the Middle Ages. Evidence supporting this historical tradition is represented by the country's indigenous hunting dog breed, the Bosnian Coarse-haired Hound – Barak**.** Although hunting cynology has been somewhat neglected in this region, it constitutes an integral part of official cynology, which is organized worldwide through international canine federations. Bosnia and Herzegovina is a member of the Fédération Cynologique Internationale (FCI). In this paper, special attention is devoted to the Bosnian Coarse-haired Hound – Barak, as well as to other hunting dog breeds, with particular emphasis on their selection, training, and use in accordance with the legal regulations of Bosnia and Herzegovina. The selection, training, and utilization of hounds and other hunting dog breeds are highly complex processes that require the continuous commitment and involvement of hunters.

Keywords: Bosnian *stećak*, Bosnian Coarse-haired Hound Barak, hunting cynology, hunting

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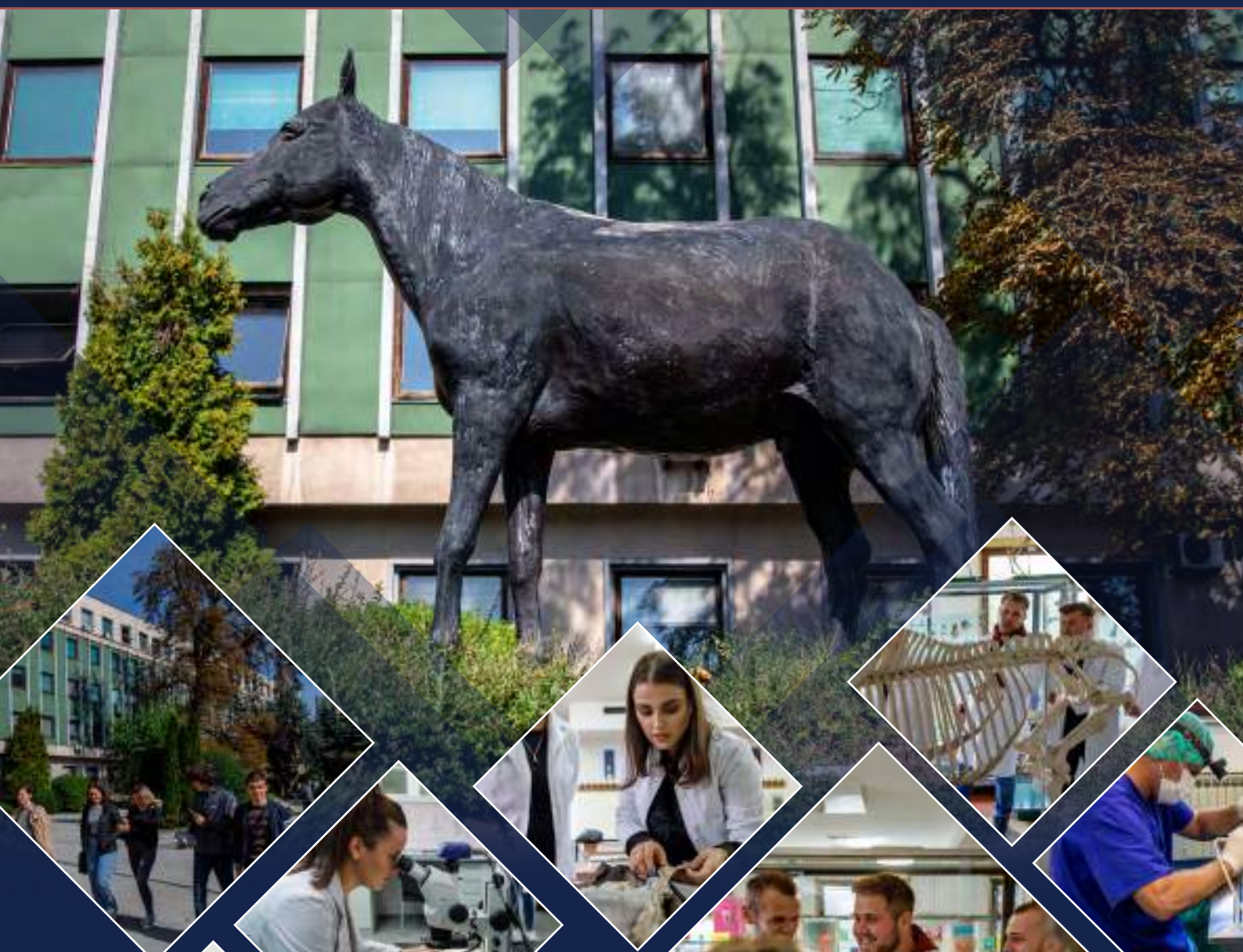

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