UNIVERSIDADE CATÓLICA DOM BOSCO
PROGRAMA DE PÓS-GRADUAÇÃO STRICTO SENSU EM
CIÊNCIAS AMBIENTAIS E SUSTENTABILIDADE AGROPECUÁRIA

Determinação dos intervalos de referência de parâmetros hematológicos e bioquímicos, e suas relações no parasitismo por *Leishmania* spp. e Ancilostomatideos na saúde de quatis (*Nasua nasua*) de Campo Grande, Mato Grosso do Sul

Gabriel Carvalho de Macedo

Campo Grande
Mato Grosso do Sul
Julho 2021

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UNIVERSIDADE CATÓLICA DOM BOSCO
Inspira o futuro

A Influência do parasitismo por *Leishmania* spp. e Ancilostomatideos na Saúde de quatis (Carnivora, Procyonidae, *Nasua nasua*) de Campo Grande, Mato Grosso do Sul.

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TITULAÇÃO: Doutor em Ciências Ambientais e Sustentabilidade Agropecúaria
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A presente defesa foi realizada por webconferência. Eu, Heitor Miraglia Herrera, como presidente da banca assinei a folha de aprovação com o consentimento de todos os membros, ainda na presença virtual destes.

Prof. Dr. Heitor Miraglia Herrera –UCDB

Prof. Dr. Filipe Martins Santos – UCDB

Profa. Dra. Gisele Braziliano de Andrade – UCDB

Profa. Dra. Grasiela Edith de Oliveira Porfírio Petry – UCDB

Profa. Dra. Daniele Bier Borges – UCDB

Profa. Dra. Thyara de Deco Souza e Araujo - UFMS

"Educação não transforma o mundo. Educação muda

as pessoas, Pessoas transformam o mundo"

Paulo Freire

Dedico este trabalho aos meus pais, Dinair Carvalho de Lima Conceição e José Carlos de Macedo, por terem sido os grandes responsáveis pela minha formação educacional, e à minha esposa Juliana Akemi Matsubara Miyajima, minha companheira de vida.

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Parque Estadual do Prosa	PEP
Vila da Base Aerea	VBA
Prosa State Park	PSP
Air Force Base Village	AFBV
International Union for Conservation of Nature	IUCN
Emerging infectious diseases	EID
Red Blood Cell Count	RBC
White Blood Cell Count	WBC
Hemoglobin	Hb
Packed Cell Volume	PCV
Mean Corpuscular Volume	MCV
Mean Corpuscular Hemoglobin Concentration	MCHM
Creatine quinase	CK
Creatine quinase specific for heart tissue	CK-MB
Lactate dehydrogenase	LDH
Alkaline phosphatase	AP
Alanine aminotransferase	ALT
Aspartate transaminase	AST
Total serum protein	TSP
High density lipid	HDL
Reference Intervals	RI
Secretaria do Meio Ambiente	SEMA
United States of America	USA
Ácido etilenodiamino tetra-acético	EDTA
Clinical and Laboratory Standard Institute	CLSI

Confidence intervals	CI
Standard deviation	SD
Corticotropin-releasing hormone	CRH
Adrenocorticotropin hormone	ACTH
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior	CAPES
Red Blood Cell Indicator	RBCI
Coagulation Indicator	COI
Immune Investment Indicator	IMII
Infection Response Indicator	IRI
Kidney Damage Indicator	KDI
Liver Damage Indicator	LDI
Cardiac Damage Indicator	CDI
Skeletal Muscle Damage Indicator	SMDI
Nutritional Profile Indicator	NPI
Protein Profile Indicator	PPI
Wildlife Rehabilitation Center	WRC
Deoxyribonucleic acid	DNA
Polymerase Chain Reaction	PCR
Kinetoplast DNA	kDNA
Uninfected	UN
Leishmania-infected	LI
Ancylostomatid-infected	AI
Coinfected	CI
Variance analysis	ANOVA
AFBV males	AM
AFBV females	AF
PSP males	PM
PSP females	PF
Body condition	BC
Tumor Necrosis Factor- Alpha	TNF-α
Gamma-interferon	IFN-γ

RESUMO

A presença da fauna silvestre em centros urbanos traz novas interfaces de conflitos que conferem riscos à saúde dos animais silvestres através da emergência de antropozoonoeses, do risco de contaminação por produtos tóxicos, e desbalanços nutricionais decorrentes do acesso a alimentos provenientes de seres humanos. O presente estudo objetivou avaliar aspectos relacionados à saúde e ao parasitismo por *Leishmania* spp. e ancilostomatídeos em quatis (*Nasua nasua*) amostrados no Parque Estadual do Prosa (PEP) e na Vila da Base Aérea (VBA) em Campo Grande, Mato Grosso do Sul, entre março de 2018 a abril de 2019. Intervalos de referência de parâmetros hematológicos e bioquímicos foram estabelecidos a partir da centralidade de 95% da população amostrada. Foram observadas variações de acordo com o sexo (hemoglobina, volume corpuscular médio [VCM], fosfatase alcalina [FA] e creatinina), idade (creatinina, albumina, glicose, VCM, FA e globulinas), e fragmento florestal (linfócitos, creatinina, VCM, neutrófilos, alanina aminotransferase [ALT] e aspartato aminotransferase [AST]). O diagnóstico de *Leishmania* spp. e ancilostomatídeos foi realizado por meio de técnicas moleculares e parasitológicas respectivamente. A análise de coordenadas principais revelou que (i) os perfis nutricional (colesterol HDL e glicose) e protéico (albumina e proteínas totais) foram influenciados pela infecção única por *Leishmania* spp. e pela coinfecção com ancilostomatideos, (ii) os perfis muscular (creatina quinase [CK]) e hepático (ALT) foram influenciados pela infecção por *Leishmania* spp., (iii) o perfil de células vermelhas foi influenciado pela infecção por ancilostomatídeos, (iv) o perfil renal foi influenciado pela coinfecção. A partir dos resultados obtidos, conclui-se que a saúde de quatis em ambientes urbanos pode ser influenciada por diversos fatores intrínsecos e extrínsecos, que devem ser considerados na interpretação de parâmetros hematológicos e bioquímicos.

Palavras-chave**:** Ancilostomatideos, Fragmentos florestais urbanos, Intervalos de referência, *Leishmania* spp., Medicina da Conservação, Procyonidae.

ABSTRACT

The presence of fauna in urban centers brings new conflict interfaces that pose risks to the health of wild animals through the emergence of anthropozoonoes, the risk of contamination by toxic products, and nutritional imbalances resulting from the access to food discarded by humans. This study aimed to evaluate aspects related to health and parasitism by *Leishmania* spp. and hookworms in coatis (*Nasua nasua*) sampled at Prosa State Park (PSP) and at Air Force Base Vilage (AFBV) in Campo Grande, Mato Grosso do Sul, between March 2018 and April 2019. Reference intervals for hematological and biochemical parameters were established from the centrality of 95% of the sampled population. Variations were observed according to sex (hemoglobin, mean corpuscular volume [MCV], alkaline phosphatase [AP] and creatinine), age (creatinine, albumin, glucose, MCV, AP and globulins), and forest fragment (lymphocytes, creatinine, MCV, neutrophils, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). The diagnosis of *Leishmania* spp. and hookworms were performed using molecular and parasitological techniques respectively. The principal coordinate analysis revealed that (i) the nutritional (HDL cholesterol and glucose) and protein (albumin and total proteins) profiles were influenced by the single infection by *Leishmania* spp. and by co-infection with hookworms, (ii) muscle (creatine kinase [CK]) and liver (ALT) profiles were influenced by *Leishmania* spp. infection, (iii) red cell profile was influenced by hookworm infection, (iv) the renal profile was influenced by the coinfection. From the results obtained, it is concluded that the health of coatis in urban environments can be influenced by several intrinsic and extrinsic factors, which must be considered in the interpretation of hematological and biochemical parameters.

Key-words**:** Ancylostomatids, *Leishmania* spp., Procyonidae**,** Reference intervals, Urban forest fragments, Conservation medicine.

INTRODUÇÃO

A saúde das populações de animais silvestres vem sendo ameaçada devido as modificações dos ambientes naturais e consequente perda dos habitats originais. Tais modificações têm promovido alterações nas dinâmicas das infecções parasitárias, principalmente diminuindo a especificidade, ou seja, parasitas comuns a animais de vida livre passam a infectar o homem e seus animais de companhia, e vice-versa (DASAK et al., 2000). Também neste contexto, a exposição direta dos animais silvestres às ações antrópicas pode promover quadros de imunossupressão, resultando, de forma direta e indireta, na emergência de doenças na fauna silvestre (ACEVEDO-WHITEHOUSE; DUFFUS, 2009).

A urbanização altera drasticamente a composição das comunidades de vida selvagem, levando à perda de biodiversidade e ao aumento na abundância de espécies que se adaptam às áreas urbanas, como o guaxinim (*Procyon lotor*), o texugo (*Meles meles*), a raposa vermelha (*Vulpes vulpes*) e a fuinha (*Martes foina*) (ROSATTE et al., 1991; PRANGE et al., 2003). Esse fenômenono é principalmente relacionado à ausência de predadores naturais, bem como à disponibilidade de alimentos provenientes do descarte de lixo por seres humanos (ESTEVAM et al., 2020).

A exemplo destas espécies, o quati da América do Sul (*Nasua nasua*) é descrito como uma espécie altamente abundante em fragmentos florestais urbanos no Brasil (SOUZA; BEISIEGEL, 2002; BOVENDORP; GALETTI, 2007; COSTA et al., 2009; HEMETRIO, 2011; BARRETO et al., 2021), podendo gerar uma série de conflitos como atropelamentos (BARRETO et al., 2021), consumo de alimentos descartados por seres humanos, encontros agonísticos com animais domésticos, ataques a seres humanos (BITTNER et al., 2010) e exposição à doenças infecciosas associadas aos seres humanos e animais domésticos (MILANELO et al., 2009; MAIA et al., 2016; PANTOJA et al., 2017; MORAES et al., 2019; ESTEVAM et al., 2020).

Embora a avaliação da saúde de animais silvestres tenha sido largamente voltada para as espécies ameaçadas de extinção (REFERENCIA), animais cujas populações têm prosperado nos ambientes urbanos devem ser monitorados, a fim de se identificar possívei causas de doenças crônicas que possam promover efeitos negativos em uma determinada escala temporal, resultando no declínio populacional. Neste sentido, intervalos de referência de parâmetros hematológicos e bioquímicos são extremamente úteis para avaliar o estado de saúde em diferentes indivíduos de cada espécie, além de auxiliar no diagnóstico e prevenção de doenças (MACEDA-VEIGA et al., 2015).

Contudo, o uso de intervalos de referência para a avaliação da saúde da fauna é enviesado, principalmente porque a grande maioria de espécies silvestres ainda carecem de informações robustas sobre a hematologia e bioquímica sérica. Adicionalmente, a interpretação dos intervalos de referência deve ser feita levando-se em consideração fatores intrínsecos e extrínsecos ao indivíduo, que podem influenciar consideravelmente os valores (TRYLAND, 2006). Consequentemente, o tamanho amostral pode ser reduzido, comprometendo assim a representatividade da amostra.

OBJETIVO GERAL

Avaliar aspectos parasitários e de saúde de quatis (*Nasua nasua*) que habitam fragmentos florestados em Campo Grande, Mato Grosso do Sul.

OBJETIVOS ESPECÍFICOS

1. Estabelecer intervalos de referência de parâmetros hematológicos e bioquímicos de quatis (*Nasua nasua*) que habitam fragmentos florestados em Campo Grande, Mato Grosso do Sul.
2. Avaliar a influencia de fatores intrínsecos (idade e sexo) e extrínsecos (área) nos parâmetros hematológicos e bioquímicos de quatis (*Nasua nasua*) que habitam fragmentos florestados em Campo Grande, Mato Grosso do Sul.
3. Avaliar a influencia da infecção por *Leishmaina* spp. e ancilostomatideos nos parâmetros hematológicos e bioquímicos de quatis (*Nasua nasua*) que habitam fragmentos florestados em Campo Grande, Mato Grosso do Sul.

REVISÃO BIBLIOGRÁFICA

A AVALIAÇÃO DA SAÚDE DOS ANIMAIS SILVESTRES

O monitoramento da saúde de animais silvestres tem sido historicamente direcionado à geração de informações a respeito de doenças infecciosas que representam risco à sociedade, sendo principalmente vinculado à vigilância epidemiológica (STEPHEN; DUNCAN, 2017). De fato, as doenças infecciosas emergentes em seres humanos e animais domésticos são predominantemente originárias da fauna silvestre (JONES et al., 2008; WOODS et al., 2019), e são resultantes das mais diversas interações entre o homem e os animais que habitam a natureza, como a expansão de fronteiras agrícolas, o tráfico de animais silvestres e o avanço de áreas urbanas sobre o ambiente natural (BRADLEY; ALTIZER, 2007; WOLFE et al., 2007; KARESH et al., 2012; JONES et al., 2013; MALIK et al., 2020).

O processo de urbanização tem resultado em sérias consequências relacionadas à saúde e ecologia das parasitoses devido ao estreitamento do contato entre animais domésticos, silvestres e seres humanos. Neste processo, a simplificação de habitat e a alteração das redes tróficas produzem um efeito negativo na riqueza e positivo na abundância de espécies (BRADLEY; ALTIZER, 2007). Consequentemente, os sistemas parasito-hospedeiro são influenciados, ou seja, há diminuição da diversidade faunística local e seleção positiva de espécies com alta competência como reservatório. Tal fenômeno é conhecido na ecologia parasitária como efeito amplificador (KEESING et al., 2006; 2010), e está diretamente ligado às causas de surtos epizoóticos.

Pelo exposto, deve-se considerar que animais silvestres que se adaptam e respondem positivamente à antropização, principalmente por apresentarem altas densidades, podem ter grande importância epidemiológica por atuarem como reservatórios de parasitas zoonóticos. São exemplos clássicos os morcegos e as capivaras nos ciclos de transmissão de *Leishmania* spp., e *Rickettsia* spp., respectivamente (VERDADE; FERRAZ, 2006; ESBÉRARD et al., 2014; POLO et al.,

2017; MONTENEGRO et al., 2017; DE REZENDE et al., 2017; SHAPIRO et al., 2013).

Embora o contato próximo entre humanos e animais silvestres seja, do ponto de vista epidemiológico, uma relação negativa, por contribuir para a perpetuação de parasitas na natureza, a vida selvagem pode fornecer uma série de pontos positivos para a sociedade humana, como valores científicos, ecológicos, históricos e recreativos (CONOVER, 1997). Contudo, os benefícios da presença da fauna silvestre em centros urbanos são difíceis de serem quantificados por serem intangíveis, mas seus impactos na sociedade e na saúde ecossistêmica devem ser considerados (DALLIMER et al., 2014).

Com a crescente urbanização, o contato entre a sociedade e os ambientes naturais tem se tornado cada vez menor, e a vida nas cidades tem proporcionado uma exposição continua a fatores estressantes, incluindo problemas de mobilidade, poluição sonora, visual e do ar (VILELA et al., 2016). Tal situação tem contribuído para o crescimento exponencial de patologias psicossomáticas em seres humanos (PRINCE et al., 2007). Entretanto, inúmeras evidências têm demonstrado que a fauna silvestre, como um importante componente da “infra-estrutura verde urbana”, pode promover o bem-estar e contribuir positivamente para saúde mental humana (MALLER et al., 2006; TZOULAS et al., 2007; KENIGER et al., 2013; LOVELL et al., 2014). De acordo com Kaplan e Kaplan (1989), a presença da natureza nas cidades pode promover a melhora do comportamento e o funcionamento cognitivo, facilitar as redes sociais, estimular a prática de atividades físicas, reduzir os níveis de crime, agressão e violência, promover uma educação não formal e aumentar o valor estético do meio ambiente.

Neste contexto, o monitoramento da saúde é fundamental para as estratégias de conservação e perpetuação da vida selvagem. Entretanto, a avaliação da saúde é complexa porque não deve ser medida apenas pela presença ou ausência de infecção. De fato, é esperado que animais silvestres enfrentem infecções por parasitas múltiplos durante a sua vida (COX, 2001). Diferentemente, uma condição clínica que possa ser considerada como “doença” irá ocorrer quando há um desequilíbrio entre as relações parasita-hospedeiro-ambiente em um determinado período (ARAÚJO et al., 2003), por exemplo, quando há imunossupressão ou uma alta carga parasitária (RYSER-DEGIORGIS, 2013).

De acordo com Stephen (2014), a saúde dos animais silvestres deve ser medida quanto à resiliência e a sua capacidade de se adaptar às mudanças, ou seja, a forma como respondem às pressões do ambiente externo. As respostas fisiológicas às pressões antrópicas e naturais, incluindo o parasitismo, podem ser acessada tanto a nível populacional, através do monitoramento dos índices reprodutivos ao longo do tempo, dos níveis de degradação do habitat, parâmetros demográficos e variáveis genéticas (LEROY et al., 2017; MAYOR et al., 2017), quanto a nível individual, aplicando-se conceitos médicos através de exames clínicos, incluindo medidas corporais (SÁNCHEZ et al., 2018), e laboratoriais, incluindo a hematologia, a bioquímica sérica e exames parasitológicos e toxicológicos (TRYLAND, 2006; RUYKYS et al., 2012; CLARKE et al., 2013; PACIONI et al., 2013; MACEDA-VEIGA et al., 2015).

A hematologia e bioquímica sérica são ferramentas amplamente utilizadas no monitoramento da saúde de animais silvestres, permitindo veterinários identificarem disfunções orgânicas e suas mais variadas causas. A hematologia contempla as contagens celulares de monócitos e neutrófilos como indicadores de resposta a infecções e inflamações, linfócitos como indicadores da resposta imunológica, hemácias, hemoglobina, hematócrito e índices hematimétricos para a avaliação do estado de anemia, além da contagem de plaquetas que indica desordens na coagulação (MACEDA-VEIGA et al., 2015). A bioquímica sérica também pode ser utilizada como valiosa ferramenta para auxiliar o diagnóstico de doenças metabólicas, definir o estado funcional dos órgãos e o perfil nutricional (BOYD, 1984). Rotineiramente, os exames bioquímicos avaliam a função renal (ureia, creatinina), hepática (aspartato aminotransferase, alanina aminotransferase), cardíaca (creatina fosfoquinase), condições orgânicas e metabólicas (glicose, proteínas totais, albumina, amilase, cálcio, fósforo, magnésio e cloretos).

A interpretação dos resultados dos exames hematológicos e bioquímicos é normalmente realizada levando-se em consideração os intervalos de referência estabelecidos para a espécie, os quais compreendem os valores de 95% de indivíduos saudáveis de uma determinada população (FRIEDRICHS et al., 2012). Tal princípio foi introduzido pela primeira vez na medicina humana em 1969, e subsequentemente aplicado em animais domésticos (GRÄSBECK; SARIS, 1969; LUMSDEN; MULLEN, 1978; LUMSDEN et al., 1979; LUMSDEN et al., 1980a;

LUMSDEN et al., 1980b; FRIENDSHIP et al., 1984). Desde então, é considerado um componente integral no diagnóstico laboratorial e nas tomadas de decisões clínicas.

Comparativamente aos animais domésticos, a avaliação da saúde de animais silvestres por meio de análises hematológicas e bioquímicas é muitas vezes comprometida devido à falta de valores de referência para diversas espécies. De fato, dificuldades logísticas de campo impedem a obtenção de um número amostral representativo o suficiente para a obtenção dos valores de referência. No caso do quati da América do Sul, informações a respeito da hematologia e bioquímica sérica foram descritas em estudos pontuais com baixos tamanhos amostrais. Rodrigues et al. (1996) descreveram os parâmetros sanguíneos de onze quatis em cativeiro no Horto Botânico de Niterói e Zoológico Municipal de Volta Redonda. Aproximadamente vinte anos depois, Yupanqui et al. (2008) estabeleceram intervalos de referência das enzimas alanina aminotransferase (ALT), aspartato aminotransferase (AST), bilirrunina, fosfatase alcalina (FA), proteínas totais séricas e albumina de 19 quatis cativos em zoológicos da cidade de Lima, no Peru. Recentemente, Riekehl Junior et al. (2017) compararam valores bioquímicos de duas populações de quatis habitando áreas com diferentes níveis de interferência humana na cidade de Foz do Iguaçu.

Considerando as dificuldades logísticas na obtenção de amostras de animais de vida-livre, a grande maioria dos registros hematológicos e bioquímicos são obtidos a partir de indivíduos de cativeiro (WEISS et al., 1994; LEWIS et al., 1998; IHRIG et al., 2001; MATTOSO et al., 2012; SHRIVATAV et al., 2012; KOHYAMA; INOSHIMA, 2017; LESCANO et al., 2018; LIU et al., 2021). Entretanto, embora tais informações sejam extremamente importantes para a conservação de espécies, principalmente daquelas em risco de extinção, essas devem ser interpretadas com cautela antes de ser atribuídas à indivíduos de vida livre da mesma espécie, especialmente devido as diferentes condições fisiológicas resultantes de diferentes formas de alimentação, de habitat e de condições estressantes (HICKEY, 1982; HAIGH et al., 1994; FANCOURT; NICOL, 2019).

Um outro ponto a ser considerado para o estabelecimento de valores de referência em populações de animais silvestres diz respeito às variações nos parâmetros sanguíneos decorrentes da influência de fatores intrínsecos e extrínsecos (TRYLAND, 2006). Tais variações podem levar à diminuição do número amostral, mas devem ser sempre consideradas para que não haja interpretações

errôneas da condição clínicas dos animais. Em mamíferos de vida livre, por exemplo, variações hematológicas e bioquímicas relacionadas tanto a fatores individuais, como sexo, idade e estado reprodutivo (REISS et al., 2008; MILLER et al., 2009; GARCÍA et al., 2010; CLARKE et al., 2013; CASAS-DÍAZ et al., 2015; KHATRI-CHHETRI et al., 2015; PECK et al., 2015; SEGUEL et al., 2016; BURREL et al., 2018; FANCOURT; NICOL, 2019), como a fatores externos, como a sazonalidade e o habitat (MAY-JÚNIOR et al., 2009; MILLER et al., 2009; GARCÍA et al., 2010; SERIEYS et al., 2013; KHATRI-CHHETRI et al., 2015; FANCOURT; NICOL, 2019), são documentadas.

ASPECTOS BIOLÓGICOS E ECOLÓGICOS DE *Nasua nasua*

Nasua nasua (Carnivora, Procyonidae) é um mamífero amplamente distribuído na América do Sul, habitando desde a Colômbia e Venezuela ao norte, até Uruguai e Argentina ao sul (Figura 1) (GOMPER e DECKER, 1998). No Brasil o quati não consta na lista de espécies ameaçadas de extinção (MMA, 2018) e pode ser encontrado em todos os biomas, geralmente sendo o carnívoro mais abundante (ROBINSON; REDFORD, 1986; SILVEIRA, 1999). Ocupa habitats essencialmente florestados, incluindo florestas deciduais, galerias, chaco e savana (GOMPER e DECKER, 1998).

Figura 1. Distribuição de *Nasua nasua*. Fonte: International Union for Conservation of Nature. *Nasua nasua*. The IUCN Red List of Threatened Species, 2021.

São animais diurnos, escansoriais e considerados carnívoros oportunistas. Sua dieta inclui invertebrados, grande variedade de frutos, bromélias e eventualmente pequenos vertebrados (EMMONS, 1990; REDFORD e STEARMAN, 1993; GOMPPER e DECKER, 1998; BEISIEGEL, 2001). Por apresentarem altas taxas de frugivoria, constante movimentação diária, e ingerir e dispersar sementes intactas, exercem importante papel como dispersores de sementes (COSTA; MAURO, 2008; ALVES-COSTA et al., 2004). O forrageamento ocorre principalmente no solo, exceto em ambientes com grande oferta de bromélias no dossel, onde o forrageamento pode ocorrer em árvores também (BEISIEGEL, 2001). Ainda, devido à sua plasticidade quanto ao hábito alimentar, esses animais podem se alimentar de lixo proveniente de seres humanos em áreas antropizadas (ALVES-COSTA et al., 2004).

Os quatis são mamíferos de médio porte que apresentam comprimento total de aproximadamente um metro e peso variando entre 3 e 7 kg (machos geralmente maiores do que fêmeas) (EMMONS; FEER, 1990). Apresentam grande variação em relação à coloração da pelagem, do alaranjado e avermelhado a marrom escuro e cinza (TEIXEIRA; AMBRÓSIO, 2007). As principais características morfológicas são a cauda longa e “anelada”, geralmente mantida perpendicular ao corpo durante o forrageamento, e o focinho alongado e de grande mobilidade (Figura 2) (GOMPER e DECKER, 1998).

Figura 2. Características físicas do quati (*Nasua nasua*). Fonte: Gabriel Carvalho de Macedo.

Apresentam organização social extremamente peculiar, com alta variedade de comportamentos cooperativos não encontrados em outras espécies de carnívoros (HIRSCH, 2011). A estrutura social normalmente consiste de grupos formados por fêmeas e filhotes (geralmente com mais de 30 indivíduos por grupo) (GOMPPER e DECKER 1998). Machos ao atingirem maturidade sexual (em torno de 3 anos de idade) tornam-se solitários, e se aproximam dos grupos durante o período de acasalamento (final da primavera), embora já tenham sido relatados convivendo com os grupos em outros períodos (RUSSELL, 1981). Esta formação social dicotômica é uma maneira de se evitar competição intra-específica por recursos (RUSSEL, 1982; 1983); em contrapartida, a ocorrência de machos adultos nos grupos pode estar relacionada com redução de carga parasitária, proteção contra predadores e monopolização de fêmeas para acasalamento (GOMPPER; KRINSLEY, 1992; COSTA et al., 2009).

Estudos têm demonstrado que as populações de quatis dentro ou próximas às áreas urbanas têm respondido positivamente a ambientes antropizados. No Parque Ecológico do Tietê e no Parque Estadual da Ilha Anchieta, em São Paulo, foram reportadas densidades populacionais de 125 indivíduos/km^2 e 25,06 indivíduos/km^2 respectivamente (SOUZA; BEISIEGEL, 2002; BOVENDORP; GALETTI, 2007). No Parque das Mangabeiras em Belo Horizonte, Minas Gerais, a população de quatis foi estimada em 52,8 indivíduos/km^2 (HEMETRIO, 2011). Em Campo Grande, Mato Grosso do Sul, Costa et al. (2009) estimaram uma população de 33,7 indivíduos/km^2 no Parque Estadual do Prosa (PEP). Comparativamente, no Pantanal, hábitat relativamente livre de interferência humana, Desbiez e Borges (2010) estimaram densidades de 16,5 e 9 indivíduos/km^2 em áreas florestadas e campos inundáveis, respectivamente.

De acordo com Estevam et al. (2020), as altas densidades populacionais de quatis em fragmentos florestais urbanos podem ser consequencia da ausência de predadores naturais e do acesso a fontes alimentares oriundas de seres humanos (Figura 3). Tal fenômeno é, de fato, observado em outras espécies de carvnívoros em ambientes urbanos, como o guaxinin (*Procyon lotor*), o texugo (*Meles meles*), a raposa-vermelha (*Vulpes vulpes*) e a fuinha (*Martes foina*) (ROSATTE et al., 1991; PRANGE et al., 2003).

Figura 3. Uso de resíduos sólidos por quatis como fontes de alimento no ambiente urbano. Fonte: Gabriel Carvalho de Macedo.

O PARASITISMO EM *Nasua nasua:* INTER-RELAÇÕES COM *Leishmania* spp.

A Leishmaniose é uma doença causada por parasitas intracelulares do gênero *Leishmania* spp., transmitidos por aproximadamente 70 espécies diferentes de insetos dos gêneros *Phlebotomus* spp. (Ásia, África e Europa) e *Lutzomyia* spp. (América) (BOELAERT; SUNDAR, 2014). Os parasitas deste gênero são reportados em 98 países, causando de 700.000 a um milhão de novos casos anualmente, com aproximadamente 350 milhões de pessoas sob risco de adquirir a doença (DE VRIES et al., 2015; BURZA et al., 2018; INCEBOZ, 2019; WHO, 2020).

Devido à ampla ocorrência em países subdesenvolvidos, considera-se que a Leishmaniose é uma doença tropical e subtropical negligenciada. De fato, os principais fatores de risco incluem a pobreza, a migração populacional, falta de higiene, imunossupressão e má nutrição (MANN et al., 2021). Dessa forma, a Leishmaniose é endêmica nos continentes asiático, africano, americano e também na região do Mediterrâneo (TORRES-GUERRERO et., 2017). Adicionalmente, as diferentes espécies de *Leishmania* spp. apresentam ocorrências geográficas distintas. Por exemplo, *L. donovani* está presente em países da região sul do

continente asiático; *L. chagasi* está presente na América Latina; *L. infantum* é normalmente detectada em países da região do Mediterrâneo, Oriente Médio e Brasil; *L. mexicana* é endêmica no Texas (BERN et al., 2006; MCLLWEE et al., 2018).

As espécies de *Leishmania* spp. já reportadas são subdividas em dois subgêneros distintos, baseados no desenvolvimento do parasita no trato digestivo do insetor vetor: *Leishmania* (intestino médio e anterior) e *Viannia* (intestino médio, anterior e grosso) (MANN et al., 2021). O subgênero *Leishmania* inclui as espécies *L. amazonensis*, *L. chagasi*, *L. mexicana*, *L. pifanoi*, *L. venezuelensis*, *L. donovani*, *L. infantum*, *L. tropica*, e *L. aethiopica*, enquanto que o subgênero *Viannia* inclui as espécies *L. braziliensis*, *L. guyanensis*, *L. lainsoni*, *L. shawi*, *L. naiffi*, *L. peruviana*, *L. panamensis* e *L. colombiensis* (TORRES-GUERRERO et al., 2017).

Em seres humanos, as manifestações clínicas da doença variam entre cutânea, mucocutânea e visceral. A forma cutânea, local ou difusa, é principalmente caracterizada por uma edemaciação no local da picada do inseto vetor, que rapidamente progride para uma pápula acompanhada de prurido, formação de pústula em torno de dois dias e consequente formação úlcera. A forma mucocutânea é caracterizada por destruição da mucosa nasofaríngea; as lesões aparecem inicialmente na mucosa nasal e se espalham para as musocas oral e faríngea, laringe, pele e lábios. Já a forma visceral, caracterizada por lesões no sistema reticuloendotelial, pode levar a quadros subclínicos, sintomáticos e/ou oligosintomáticos, que incluem hepatoesplenomegalia, linfadenopatia, anemia, leucopenia, trombocitopenia, anorexia, perda de peso, entre outros sinais clínicos (TORRES-GUERRERO et al., 2017).

Em animais domésticos, principalmente os cães, considerados hospedeiros reservatórios que exercem importante papel na epidemiologia da Leishmaniose (HIDE et al., 2007), as manifestações clínicas mais comuns são as lesões de pele, perda de peso, anorexia, linfadenopatia, lesões oculares, sangramento nasal, distúrbios no sistema locomotor, digestivo e renal (AYELE; SEYOUM, 2016). O perfil hematológico e bioquímico é bastante variável de acordo com as espécies de *Leishmania* envolvida0073 e o estágio da infecção, podendo apresentar alterações da série vermelha e branca, bem como das concentrações de enzimas que indicam o estado funcional de órgãos, principalmente rim e fígado (ULCHAR et al., 2015; MONTARGIL et al., 2018).

A ocorrência de *Leishmania* spp. em quatis é pouco descrita, e as consequências deste parasitismo na saúde são desconhecidas. O parasitismo por *Leishmania* spp. em quatis foi relatado pela primeira vez no final da década de 80 por Lainson et al. (1989), o qual isolou *Leishmania* (*Viannia*) *shawi* a partir de um quati na região amazônica. Vinte anos depois, Voltarelli et al. (2009) detectaram imunoglobulinas anti-*L. (V.) braziliensis* em dois indivíduos no Parque do Ingá, uma unidade de conservação florestal situada na região central de Maringá, Paraná. Mais tarde, Paiz et al. (2015) detectaram anticorpos anti-*L. Infantum* em amostras de dois quatis capturados no município de Botucatu, São Paulo, entre 2007 e 2013. Recentemente, anticorpos anti-*Leishmania* spp. foram detectados em quatis capturados na região do Maciço do Urucum, fronteira entre Brasil e Bolívia (PORFÍRIO et al., 2018).

Assim como em inúmeras espécies de carnívoros silvestres, o papel dos quatis como hospedeiros reservatórios de *Leishmania* spp., bem como as resultantes da infecção na saúde destes animais permanecem desconhecidos. Embora existam dificuldades logísticas na obtenção de amostras biológicas de carnívoros de vida livre, o estudo do parasitismo por *Leishmania* spp. acerca deste grupo taxonômico é fundamental para o entendimento da ecologia deste parasita (ROQUE; JANSEN, 2014), especialmente aquelas espécies de hábitos sinantrópicos e fácil adaptação aos ambientes urbanos.

O PARASITISMO EM *Nasua nasua:* INTER-RELAÇÕES COM ANCILOSTOMATIDEOS

Ancilostomatidae é uma família de helmintos intestinais pertencentes ao filo Nematoda, cuja principal característica é a presença de um aparato bucal composto por dentes e/ou placas cortantes, que permitem que o parasita se fixe na mucosa intestinal e se alimente de sangue do seu hospedeiro (HOTEZ et al., 2004). Ao todo, 18 gêneros compõem a família Ancilostomatidae, dentre os quais, *Ancylostoma* spp. e *Necator* spp. se destacam pela sua importância na medicina humana (LOUKAS et al. 2005). De fato, estimativas apontam que estes parasitas infectam aproximadamente 500 milhões de pessoas em regiões tropicais (PULLAN et al., 2014), causando principalmente quadros de anemia associada à deficiência de ferro (LOUKAS et al., 2016). Além disso, ancilostomatideos podem infectar animais domésticos (TRAVERSA, 2012; SHEPHERD et al., 2018), também causando

quadros de anemia, perda de peso, diarréia e morte, principalmente em animais jovens.

Embora os impactos econômicos, epidemiológicos e sanitários, resultantes da infecção por ancilostomatídeos em seres humanos e animais domésticos, sejam amplamente reportados (TRAVERSA, 2012; BARTSCH et al., 2016), pouco se sabe sobre as inter-relações entre estes parasitas e as espécies de animais silvestres, especialmente aquelas que ocorrem em centros urbanos. Nestas regiões, mamíferos selvagens têm sido reportados infectados por espécies de ancilostomatideos comuns em animais domésticos e seres humanos, como *A. caninum*, *A. ceylanicum*, *A. braziliense*, *N. americanus* e *Uncinaria stenocephala* (SMOUT et al., 2013; HASEGAWA et al., 2014; MORAES et al., 2019).

Algumas espécies de animais silvestres, devido ao seu estilo de vida, podem estar mais predispostas à infecção por ancilostomatídeos. Os procionideos, por exemplo, apresentam o comportamento de forrageamento no solo, o que de fato, pode contribuir para infecções por ancilotomatídeos, visto que estes parasitas são transmitidos de forma oral ou percutânea (LOUKAS et al., 2005). Deveras, procionideos já foram reportados parasitados por cinco gêneros distintos de ancilostomatídeos (*Ancylostoma* spp., *Arthrocephalus* spp., *Arthrostoma* spp., *Necator* spp. and *Uncinaria* spp.) (SEGUEL; GOTTDENKER, 2017). Especificamente acerca de *N. nasua*, apenas *A. braziliense* e *U. bidens* foram reportados, em indivíduos no Parque Nacional do Iguaçu (MORAES et al., 2019).

Os capítulos a seguir foram elaborados segundo as normas das seguintes revistas:

Capítulo 1: Preventive Veterinary Medicine

Capítulo 2: PloS One

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Hematological and serum biochemistry reference intervals of southern coatis (*Nasua nasua*) that inhabit urban forest fragments at Brazilian Midwest

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ABSTRACT

Wildlife hematology and biochemistry are still an unclear science. Monitoring the health of wildlife that live in urban forest fragments constitutes a powerful tool for prevention of emerging infectious diseases (EID), as well for conservation. In this sense, the present study aimed to establish hematological and biochemical RI of southern coatis captured in two

urban forest fragments in Brazilian Midwest (Prosa State Park – PSP; Air Force Base Village - AFBV"). Hematological parameters as Red blood cell (RBC), white blood cell (WBC) (including differential WBC count), hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelets, and biochemical parameters as creatine kinase (CK and CK-MB fraction), lactate dehydrogenase (LDH), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate transaminase (AST), urea, creatinine, albumin, total serum proteins (TSP), total cholesterol, HDL cholesterol, glucose and triglycerides were obtained from 89 individuals captured between March 2018 to April 2019. Upper and lower reference limits were calculated from the central 95% interval. Independent groups according to age, sex and forest fragment were compared through Mann–Whitney U test and Student's t-test according to data distribution. We observed that males presented higher mean of Hb, MCV and AP, and lower mean of creatinine than females; adults presented higher mean of creatinine, albumin and glucose, and lower levels of MCV, AP and globulin than juveniles; PSP animals presented higher mean of lymphocytes and creatinine, and lower levels of MCV, neutrophils, AST, and ALT than AFVB animals. The RI established in the present study provide a baseline information of the physiological status of *N. nasua* living in urban forest fragments and will certainly contribute to future research on the health of this species.

KEY-WORDS: Procyonidae, wildlife health, urban fragments, age, gender, blood parameters.

INTRODUCTION

Monitoring the health of wildlife that live in urban forest fragments constitutes a powerful tool for conservation and prevention of emerging infectious diseases (EID) in both

humans, wild and domestic animals (Buttke et al., 2015; Cunningham et al., 2017). In this context, the One health perspective breaks paradigms in relation to the way that society face wildlife, not only as the major source of infectious pathogens for humans and domestic animals (Jones et al., 2008), but also as a vital component of the urban greening agenda, improving human mental health and wellbeing (Maller et al., 2006; Soulsbury and White, 2015). Furthermore, wildlife is recognized as a promoter of key-ecosystem services, such as pollination (Kremen et al., 2007), seed dispersal (Alves-Costa and Eterovick, 2007), trophic regulation (Ray et al., 2005; Terborgh et al., 2010), pests' control (Karp and Daily, 2014) and dilution effect of EID (LoGiudice et al., 2003).

According to Stephen (2014), wildlife health must be measured by the individual and environmental characteristics that interact and affect the animal resilience and its ability to cope with the changes. In this sense, the evaluation of physiological responses to natural and anthropogenic stressors is of utmost importance. Nowadays, biologists and veterinarians have access to methodologies that allow to approach the wildlife resilience at both populational (reproductive indexes over time, habitat degradation, demographic parameters and genetic variables) and individual (body measurements, clinical and laboratorial tests as hematology and serum biochemistry) levels (Maceda-Veiga et al., 2015; Mayor et al., 2017; Leroy et al., 2017; Sanchez et al., 2018).

Hematology and serum biochemistry have been widely employed in the wildlife health evaluation for allowing access many organic dysfunctions. Additionally, such analysis also permits to observe the homeostasis of analyzed individuals when incorporates reference intervals (RI), which principle is to take the central 95% of a healthy reference population (Solberg, 1993). Unquestionably, the RIs are considered an indispensable tool for clinical decisions, fundamental for decision in reintroduction programs (Woodford, 2001; Friedrichs et al., 2012). Yet, these analyses are impaired by the lack of information of RI in many free-

living mammal species, especially due to logistical difficulties in the assessment of a representative number of sampled animals.

We must also consider that hematological and biochemical RIs for wild mammals may present variations due to intrinsic and extrinsic factors (Tryland, 2006). In some wild species, it is relatively documented the hematological and biochemical variations related to age, sex and reproductive status (Reiss et al., 2008; Miller et al., 2009; García et al., 2010; Clarke et al., 2013; Casas-Díaz et al., 2015; Khatri-Chhetri et al., 2015; Peck et al., 2015; Seguel et al., 2016; Burrel et al., 2018; Fancourt and Nicol, 2019), as well seasonality and habitat (May-Júnior et al., 2009; Miller et al., 2009; García et al., 2010; Serieys et al., 2013; Khatri-Chhetri et al., 2015; Fancourt and Nicol, 2019). Certainly, these variations lead to sample reduction, nonetheless it must be always considered in order to avoid misinterpretation of health condition.

The perception of society that human-induced environmental changes has negatively affect the resilience and survival of many wild species (Acevedo-Whitehouse and Duffus, 2009) does not constitute a rule. In fact, it is reported that some mammal species, as racoons, foxes, martens and badgers are capable of respond positively to urbanization (Rosatte et al., 1991; Prange et al., 2003). For instance, the populations of the South American coati (Carnivora, Procyonidae, *Nasua nasua*) have adapted to urban centers in Brazil and displayed high population densities (Souza and Beisiegel, 2002; Bovendorp and Galetti, 2007; Costa et al., 2009; Hemetrio, 2011; Barreto et al., 2021), which is associated to the absence of natural predators and the easy access to human food remnants (Estevam et al., 2020). Moreover, high coati population densities in urban areas may generate conflicts with humans and domestic animals such as attacks on humans (Bittner et al., 2010), agonistic encounters with dogs (de Macedo, personal communication), foraging in trash cans (Figure 1), running over (Costa et al., 2009; Barreto et al., 2021), and exposure to infectious diseases associated to humans and

100 their domestic animals (Milanelo et al., 2009; Maia et al., 2016; Pantoja et al., 2017; Moraes
101 et al., 2019; Estevam et al., 2020).
102

103

104 **Figure 1**. Southern coatis visiting an outdoor trash can in a residential area at Campo Grande,
105 Mato Grosso do Sul, Brazil.
106

107 Assessment of hematological and biochemical RI of wild mammals is a key factor for
108 wildlife conservation because it provides baseline information about the health status of
109 endangered species (García et al., 2010; Khatri-Chhetri et al., 2015; Burrell et al., 2018;
110 Fancourt and Nicol, 2019; Nabi et al., 2019), of species in decreasing populations due to
111 parasitism, hunting and other environmental pressures (Aleuy et al., 2013; Clarke et al., 2013;
112 Pacioni et al., 2013; Girling et al., 2015), and of captive animals (Shrivatav et al., 2012;
113 Mattoso et al., 2012; Kohyama and Inoshima, 2017). Still, species presenting high-density
114 populations must be monitored in order to identify chronic and/or underlying diseases that
115 may promote sublethal effects in populations at a large-scale time. In this sense, the present
116 study aimed to establish hematological and biochemical RI of southern coatis of two urban
117 forest fragments in Brazilian Midwest.
118

MATERIAL AND METHODS

Study areas

The present study was carried out in two forest fragments located in Campo Grande, Mato Grosso do Sul, Brazil. The first is a 135 hectares environmental protection area named "Prosa State Park" (PSP) (Figure 2), an area composed by savanna, tall savanna woodland and riparian forest, surrounded by wire fences, and adjacent to other two areas (Parque das Nações Indígenas and Parque dos Poderes) that are visited daily by thousands of people. The PSP is inhabited by a diverse mammal fauna (SEMA, 2000), and shelter a wild animal rehabilitation center that receive dozens of wild species daily (https://www.imasul.ms.gov.br/centro-de-reabilitacao-de-animais-silvestres-cras/). The population density of southern coatis in PSP is estimated to be 12.1 individuals/hectare (Barreto et al., 2021).

The second is a 197 hectares residential and military training area named "Air Force Base Village" (AFBV) (Figure 2). In AFBV, the residential area is surrounded by three forest fragments characterized by cerrado, riparian forest and veredas, and inhabited by approximately 730 people (Barreto et al., 2021). Human population raise pet animals as dogs and cats, and several species of wild mammals, as *Cavia aperea*, *Hydrochoerus hydrochaeri*, *Cerdocyon thous* and *Alouatta caraya* have been sighted in the area. The population of southern coatis in AFBV is estimated in 21.9 individuals/hectare (Barreto et al., 2021).

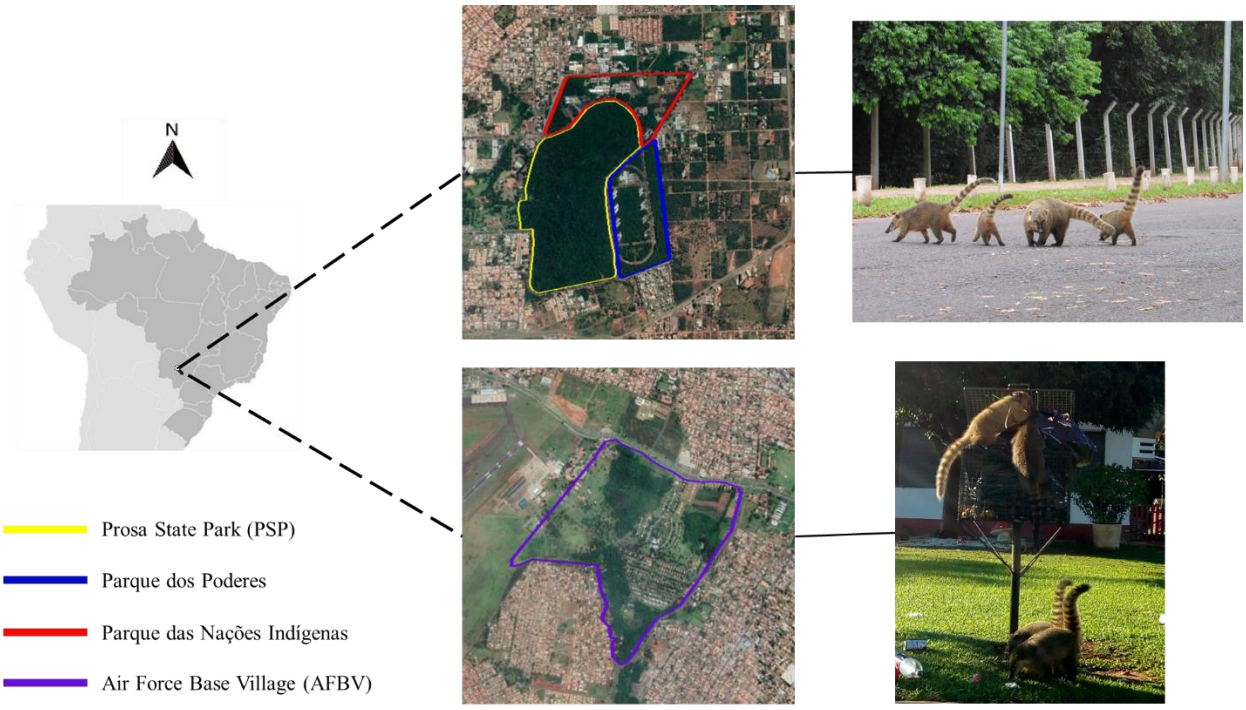

Figure 2. Study areas. PSP is surrounded by a wire fence and paved roads which the southern coatis use to cross to other areas (Parque das Nações Indígenas e Parque dos Poderes). In AFBV, the coatis are usually sighted exploring outdoor trash cans looking for food.

Field procedures

From March 2018 to April 2019, southern coatis were captured and recaptured in the studied areas through Box traps (90 cm × 45 cm × 50 cm; EquiposFauna®, Brazil) baited with bacon (15 to 25 grams). We accessed the two areas alternately at monthly intervals, with the recaptures being performed at least one month apart. In this sense, each capture and recapture were considered as a single event.

The animals were sedated through intramuscular injection of tiletamine hydrochloride and zolazepan hydrochloride association (Telazol 100g; Zoetis ®, USA) and tagged with subcutaneous transponders (Animal Tag ®, Brazil). Sex, body weight, head-body length and physiological parameters (heart and respiratory rate, and rectal temperature 10 minutes after the complete sedation) were registered. Other body measurements including tail length, shoulder height, neck and thorax circumference, teeth condition, and upper and lower canines

height were recorded in order to access the age of the animals, as described by Olifers et al. (2010) (adults = > 2 years old; subadults = 6 months to 2 years old; cubs = < 6 months).

The animals were inspected in relation to the presence of clinical abnormalities. After appropriate asepsis, blood samples were collected from the femoral vein using vacuum collection system, and deposited in Ethylenediamine tetraacetic acid (EDTA) and clot activator tubes (2 ml each). After total sedation recovery, the animals were released at the capture site. All field procedures were conducted in accordance with a license granted by the Chico Mendes Institute for Biodiversity Conservation (49662-7/2018) and by the Environmental Institute from Mato Grosso do Sul (71/404517/2017), an AFBV cooperation agreement (N°01/GAP-CG/2018), and was approved by the Ethics Committee for Animal Use of Universidade Católica Dom Bosco, Campo Grande, MS (001/2017).

Hematological and serum biochemistry variables

Hematological parameters as Red blood cell (RBC), white blood cell (WBC), hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelets were measured by an automated hematology analyzer device (POCH-iV 100, Syxmex®, Brazil). Differential counts of WBC were performed in blood smears fixed with methanol and stained with Panótico kit (Laborclin®, Brazil).

Serum concentrations of creatine kinase (CK and CK-MB fraction), lactate dehydrogenase (LDH), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate transaminase (AST), urea, creatinine, albumin, total serum proteins (TSP), total cholesterol, HDL cholesterol, glucose and triglycerides were determined by spectrophotometer analysis (Brasmed®, Brazil) using the Biotech ® and Gold ® commercial kits. Globulin values were determined based on the difference between TSP and albumin values.

Data analysis

For data analysis, exclusion criteria was based on clinical examination of coatis. Individuals showing clinical abnormalities were excluded from the analysis. Descriptive statistic for RI (mean, median, standard deviation and distribution) of weight, head-body length, and physiological, hematological and serum biochemistry variables were calculated. Outliers were detected and removed through the Tukey's test for normal data distribution and Reed test for non-normal data distribution. Upper and lower reference limits were calculated from the central 95% interval (between the 2.5 and 97.5 percentiles) according to the International Federation of Clinical Chemistry protocol and the Clinical and Laboratory Standard Institute guidelines (CLSI, 2008; Friederichs et al., 2012). The parametric method also determined the 90% confidence intervals (CI) around the limits. We then compared independent groups according to age, sex and home area through Mann–Whitney U test and Student's t-test according to data distribution. All statistical analysis were performed in R Statistical software (R Development Core Team, 2015).

RESULTS

During the sampling period, we obtained a total of 191 blood samples of southern coatis from the two studied locations. A total of 102 samples were excluded from the data analysis due to clinical abnormalities found in the animals, as wounds (50), lymphadenopathy (18), edema (14), obesity (7), diarrhea (3), fractures (3) and lactation (2), and also due to serum sample quality (nine hemolysed and six lipemic serum). In this sense, 89 samples were included in the analysis, corresponding to 39 males, 50 females, 39 animals from PSP and 50 from AFBV. Fifty-one samples were obtained from adults, 23 from subadults and 15 from cubs. Due to low sampling number of subadults and cubs, we classified the animals into two

204 age groups: adults (> 2 years old) and juveniles (< 2 years old). The RI for hematological and
205 serum biochemistry parameters are shown in Tables 1 and 2 respectively.
206
207 **Table 1**. Reference intervals of hematological parameters of 89 southern coati (*Nasua nasua*)
208 captures in two forest fragments of Campo Grande, Mato Grosso do Sul, Brazil, from March
209 2018 to April 2019.

Parameters	N	Outliers	Mean ± SD	Median	Lower limit (90% CI)	RI	Upper limit (90% CI)
RBC (10^{12}/L)	89	0	5.46 ± 0.48	5.41	4.41 - 4.54	4.47 - 6.34	6.28 - 6.41
Hb (g/L)	87	2	10.5 ± 0.9	10.7	8.9 - 9.1	9.0 - 12.0	11.9 - 12.1
PCV (%)	89	0	34.0 ± 3.0	34.0	27.8 - 28.6	28.2 - 40.0	39.6 - 40.4
MCV (fL)	89	0	59.4 ± 2.8	59.3	54.0 - 54.8	54.4 - 64.8	64.4 - 65.1
MCHC (g/L)	88	1	32.5 ± 0.9	32.4	30.9 - 31.1	31.0 - 34.6	34.5 - 34.7
Platelet (10^9/L)	86	3	582.7 ± 160.8	576.5	225.5 - 270.0	247.7 - 907.1	884.9 - 929.3
WBC (10^9/L)	86	3	14.6 ± 3.7	14.3	7.8 - 8.8	8.3 - 22.0	21.5 - 22.5
Neutrophil (10^9/L)	87	2	9.5 ± 4.3	8.6	3.4 - 4.6	4.0 - 19.6	19.0 - 20.2
Lymphocyte (10^9/L)	87	2	3.0 ± 1.9	2.7	0.05 - 0.6	0.3 - 7.4	7.2 - 7.7
Monocyte (10^9/L)	78	11	0.5 ± 0.3	0.4	0.07 - 0.20	0.12 - 1.21	1.16 - 1.26
Eosinophil (10^9/L)	84	5	1.4 ± 0.9	1.3	0 - 0.14	0.02 - 3.5	3.4 - 3.7

210 RBC: Red Blood Cell; Hb: Hemoglobin; PCV: Packed Cell Volume; MCV: Mean Corpuscular
211 Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; WBC: White Blood Cell; SD:
212 Standard Deviation; CI: Confidence Intervals; RI: Reference Intervals.
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Table 2. Reference intervals of serum biochemistry parameters of 89 southern coati (*Nasua nasua*) captures in two forest fragments of Campo Grande, Mato Grosso do Sul, Brazil, from March 2018 to April 2019.

Parameters	N	Outliers	Mean ± SD	Median	Lower limit (90% CI)	RI	Upper limit (90% CI)
CK (IU/L)	75	14	1439 ± 708	1395	329 - 539	434 - 2898	2793 - 3003
CKMB (IU/L)	87	2	2286 ± 924	2311	703 - 957	830 - 4431	4304 - 4558
LDH (IU/L)	86	3	1579 ± 672	1476	388 - 574	481 - 3134	3041 - 3227
AST (IU/L)	78	11	184.0 ± 73.6	178.3	32.9 - 54.3	43.6 - 362.3	351.6 - 373.0
ALT (IU/L)	87	2	106.4 ± 48.1	101.6	27.4 - 40.6	34.0 - 206.6	199.9 - 213.2
AP (IU/L)	77	12	21.9 ± 6.3	21.4	10.4 - 12.3	11.4 - 35.6	34.7 - 36.5
Urea (mg/dL)	84	5	22.6 ± 10.8	21.0	5.5 - 8.6	7.0 - 47.7	46.2 - 49.2
Creatinine (mg/dL)	84	5	1.05 ± 0.25	1.03	0.57 - 0.64	0.61 - 1.57	1.53 - 1.60
Albumin (g/dL)	81	8	1.95 - 0.85	1.99	0.21 - 0.45	0.33 - 3.90	3.78 - 4.02
Globulin (g/dL)	84	5	5.62 ± 1.07	5.61	3.19 - 3.49	3.34 - 7.57	7.42 - 7.72
TSP (g/dL)	89	0	7.72 ± 0.69	7.60	6.18 - 6.37	6.28 - 9.00	8.90 - 9.09
Total cholesterol (mg/dL)	78	11	129 ± 68	111	38 - 57	48 - 330	320 - 340
HDL cholesterol (mg/dL)	88	1	58 ± 26	52	10 - 17	13 - 109	106 - 113
Glucose (mg/dL)	85	4	77 ± 24	76	36 - 43	39 - 135	131 - 138
Triglycerides (mg/dL)	81	8	37 ± 17	37	8 - 13	11 - 77	75 - 80

CK: Creatine Kinase; CKMB: Creatine Kinase (MB fraction); LDH: Lactate Dehydrogenase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; TSP: Total Serum Protein; HDL: High Dense Lipoproteins; SD: Standard Deviation; CI: Confidence Intervals; RI: Reference Intervals.

By comparing the independent groups, we observed significant differences between gender, age and home area. Males presented higher mean of Hb ($p = 0.02$), MCV ($p = 0.004$), and AP ($p = 0.007$), and lower mean of creatinine ($p = 0.01$) than females (Table 3).

Adult southern coatis presented higher means of creatinine ($p = 0.01$), albumin ($p = 0.02$), and glucose ($p = 0.003$), and lower levels of MCV ($p = 0.01$), AP ($p = 0.008$) and globulin ($p = 0.0002$) than juveniles (Table 4).

Table 3. Reference intervals of hematological and serum biochemistry parameters of southern coatis (*Nasua nasua*) that differed ($p < 0.05$) between males and females.

Parameters	N	Outliers	Mean ± SD	Lower limit (90% CI)	RI	Upper limit (90% CI)
Male						
Hb (g/L)	39	0	10.8 ± 0.9	8.9 - 9.3	9.1 - 12.6	12.4 - 12.8
MCV (fL)	38	1	60.3 ± 2.4	56.1 - 57.1	56.6 - 64.6	64.1 - 65.1
AP (IU/L)	34	5	25.3 ± 7.7	13.4 - 16.8	15.1 - 42.5	40.8 - 44.2
Creatinine (mg/dL)	35	4	0.97 ± 0.25	0.53 - 0.64	0.58 - 1.49	1.43 - 1.54
Female						
Hb (g/L)	50	0	10.4 ± 0.8	8.9 - 9.2	9.0 - 11.8	11.6 - 11.9
MCV (fL)	49	1	58.7 ± 2.7	53.9 - 54.9	54.4 - 63.8	63.3 - 64.3
AP (IU/L)	46	4	20.8 ± 6.5	9.8 - 12.3	11.0 - 34.9	33.7 - 36.2
Creatinine (mg/dL)	48	2	1.10 ± 0.22	0.66 - 0.75	0.71 - 1.56	1.52 - 1.60

Hb: Hemoglobin; MCV: Mean Corpuscular Volume; AP: Alkaline Phosphatase; SD: Standard Deviation; CI: Confidence Intervals; RI: Reference Intervals.

Table 4. Reference intervals of hematological and serum biochemistry parameters of southern coatis (*Nasua nasua*) that differed ($p < 0.05$) between adults (> 2 years old) and juveniles (< 2 years old).

Parameters	N	Outliers	Mean ± SD	Lower limit (90% CI)	RI	Upper limit (90% CI)
Adult						
MCV (fL)	51	0	58.8 ± 2.7	53.6 - 54.6	54.1 - 64.0	63.6 - 64.5
AP (IU/L)	45	6	20.5 ± 5.0	10.6 - 12.5	11.6 - 30.0	29.0 - 30.9
Creatinine (mg/dL)	48	3	1.16 ± 0.25	0.68 - 0.78	0.73 - 1.67	1.62 - 1.71
Albumin (g/dL)	46	5	2.17 ± 0.89	0.45 - 0.78	0.62 - 3.90	3.73 - 4.07
Globulin (g/dL)	49	2	5.25 ± 1.03	2.95 - 3.33	3.14 - 6.86	6.67 - 7.04
Glucose (mg/dL)	51	0	87 ± 31	37 - 49	43 - 150	144 - 155
Juvenile						
MCV (fL)	38	0	60.2 ± 2.7	54.3 - 55.4	54.8 - 64.8	64.2 - 65.4
AP (IU/L)	37	1	25.9 ± 11.0	7.9 - 12.5	10.2 - 45.3	43.0 - 47.7
Creatinine (mg/dL)	36	2	0.92 ± 0.19	0.54 - 0.63	0.58 - 1.25	1.21 - 1.29
Albumin (g/dL)	36	2	1.74 ± 0.84	0.12 - 0.48	0.30 - 2.93	2.75 - 3.11
Globulin (g/dL)	35	3	6.14 ± 0.90	4.09 - 4.49	4.29 - 7.63	7.43 - 7.82
Glucose (mg/dL)	38	0	71 ± 19	34 - 42	38 - 108	104 - 112

MCV: Mean Corpuscular Volume; AP: Alkaline Phosphatase; SD = Standard Deviation; CI = Confidence Intervals; RI = Reference Intervals.

Regarding location, we observed that PSP animals presented higher means of lymphocytes ($p = 0.00001$) and creatinine ($p = 0.002$), and lower levels of MCV ($p = 0.005$), neutrophils ($p = 0.0001$), AST ($p = 0.02$), ALT ($p = 0.000000000003$) and TSP ($p = 0.00004$) than AFBV animals (Table 5).

Table 5. Reference intervals of hematological and serum biochemistry parameters of southern coatis (*Nasua nasua*) that differed ($p < 0.05$) between forest fragments.

Parameters	N	Outliers	Mean ± SD	Lower limit (90% CI)	RI	Upper limit (90% CI)
			PSP			
MCV (fL)	39	0	58.4 ± 2.3	53.3 - 54.2	53.8 - 62.0	61.5 - 62.4
Neutrophil (10^9/L)	37	2	7.6 ± 2.4	3.7 - 4.7	4.2 - 13.0	12.5 - 13.5
Lymphocyte (10^9/L)	39	0	4.1 ± 1.8	1.0 - 1.7	1.3 - 7.6	7.2 - 8.0
AST (IU/L)	35	4	158.4 ± 40.4	70.5 - 88.0	79.3 - 210.1	201.3 - 218.9
ALT (IU/L)	38	1	67.8 ± 24.0	22.7 - 32.7	27.7 - 111.0	106.0 - 116.0
Creatinine (mg/dL)	38	1	1.19 ± 0.30	0.62 - 0.74	0.68 - 1.79	1.72 - 1.85
			AFBV			
MCV (fL)	50	0	60.2 ± 2.9	54.6 - 55.7	55.2 - 64.9	64.4 - 65.5
Neutrophil (10^9/L)	49	1	10.9 ± 5.1	1.9 - 3.8	2.9 - 21.4	20.5 - 22.4
Lymphocyte (10^9/L)	46	4	1.9 ± 1.1	0.08 - 0.5	0.3 - 3.8	3.6 - 4.0
AST (IU/L)	47	3	259.0 ± 120.1	103.5 - 148.4	128.9 - 563.38	540.9 - 585.8
ALT (IU/L)	49	1	137.0 ± 41.5	58.8 - 74.0	66.4 - 210.7	203.1 - 218.3
Creatinine (mg/dL)	48	2	0.98 ± 0.21	0.57 - 0.65	0.61 - 1.37	1.33 - 1.40

MCV = Mean Corpuscular Volume; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; TSP = Total Serum Protein; SD = Standard Deviation; CI = Confidence Intervals; RI = Reference Intervals; PSP = Prosa State Park; AFPA = Air Force Private Area.

DISCUSSION

The present study provides comprehensive and unprecedent RI of hematological and serum biochemistry parameters of southern coatis, highlighting the variations within the sampled population. Previous studies regarding blood parameters of *N. nasua* did not approach RIs, and lacked a robust sample size. In this sense, by considering each capture and

recapture as a single event, we improved the sample size and consequently the representativeness in data distribution. As significant variations related to age, gender and home area were recorded in the present study, RIs for independent groups were successfully established. On the other hand, five hematological (RBC, PCV, platelets, WBC, eosinophils) and four biochemical variables (CK, urea, HDL cholesterol, triglycerides) did not present significant differences between groups.

Differences in hematological and biochemical values should be expected when studying the health of wild animal populations because intrinsic and extrinsic factors strongly influence these parameters (Tryland, 2006). In fact, variations related to age, gender, habitat, seasonality and parasitism have been reported worldwide in carnivores (Weiss et al., 1994; Miller et al., 2009; García et al., 2010; Olifiers et al., 2015; Burrell et al., 2018; Lescano et al., 2018; Santos et al., 2018, 2019), marsupials (Clarke et al., 2013; Peck et al., 2015; Casagrande et al., 2019; Nantes, et al., 2019; Zepeda-Espinosa et al., 2019), rodents (Fancourt and Nicol, 2019), primates (Ihrig et al., 2001), ungulates (Miller et al., 2013; Casas-Díaz et al., 2015), Pholidota (Khatri-Chhetri et al., 2015).

A higher adult male hemoglobin level is a conserved feature throughout mammal species (Murphy, 2014). The higher Hb means values observed in males may be explained by the direct effect of sexual hormones on erythropoiesis in bone marrow and erythropoietin production in kidney. Androgen hormones increase the sensitivity of erythroid precursors to erythropoietin and promote the renal microvasculature contraction, while estrogen hormones promote dilation (Shahani et al., 2009; Murphy, 2014). Consequently, there are modifications in hematocrit at microcirculation, leading to changes in oxygen supply and cell mass of RBCs. Interestingly, this mechanism does not lead to compensatory changes in erythropoiesis (Murphy, 2014), which may explain the non-difference in RBC mean between males and females. Additionally, testosterone promotes the increase of iron uptake from the diet and

290 regulates iron stores, correlating positively with Hb levels (Gabrielsen, 2017). In fact,
291 experimental studies in mice showed that androgens stimulate iron incorporation into RBCs
292 (Naets and Wittek, 1968; Molinari and Rosenkrantz, 1971).

293 In the same reasoning, the lower values of MCV recorded in female coatis, comparing
294 to males, may be attributed to the absence of testosterone and its positive effects in iron
295 uptake. On the other hand, the lower MCV values observed in adult coatis, comparing to
296 juveniles, was unexpected. There are evidences that changes in MCV might be associated
297 with differences in RBCs survival, such as the shorter RBC lifespan in adults. As a result, the
298 percentage of RBCs recently released from the bone marrow increases progressively with age,
299 as well as the MCV levels, since younger RBCs tend to have larger volumes (Yip et al., 1984;
300 Shperling and Danon, 1990; Gamaldo et al., 2011). In this sense, the observed significant
301 differences in MCV means regarding gender and forest fragments may be related to variations
302 in the dietary intake of iron, vitamin B12 and folic acid (Massey, 1992; Koury and Ponka,
303 2004). In addition, other causes of changes in MCV values in wild mammals includes the
304 parasitism by *Trypanosoma cruzi* and *T. evansi* (Santos et al., 2018; Nantes et al., 2019).

305 Our results revealed a higher AP mean in male and juvenile southern coatis (Tables 3
306 and 4). Age related differences in serum AP of mammals are quite described in literature. Due
307 to the increase in bone AP activity during growth, which reflects in the increase in serum AP,
308 young animals normally present higher levels than adults. (Kaneko et al., 1997; Zaidi et al.,
309 2010). Indeed, AP is highly expressed in mineralized tissue and plays an important role in
310 hard tissue formation, as it increases the rates of inorganic phosphate, facilitating the
311 mineralization (Vimalraj, 2020). On the other hand, gender related differences in serum AP
312 are reported in prompt studies with humans (Fenuku and Koli, 1975; Fukuda and Tanishima,
313 1979), but these differences also rely on the age effect. In this sense, we predict that the high
314 AP in males may be a consequence of production and secretion of corticosteroids induced by

315 stress. Under stress condition, the hypothalamus produces and releases corticotropin-releasing
316 hormone (CRH), which induces the secretion of adrenocorticotropin hormone (ACTH) from
317 pituitary gland (Guyton and Hall, 1997). Subsequently, ACTH stimulates the release of AP to
318 the extracellular environment (Martini et al., 2004). As reported, male southern coatis may
319 undergo to stress situations, especially due to the intra-specific mate competition (Russell,
320 1981; Hirsch, 2011). Moreover, since males and juveniles did not present high levels of other
321 liver enzymes (ALT and AST), hepatic damage may not be the cause of increase in AP.

322 Since we observed higher glucose levels in adults (Table 4), we hypothesize that stress
323 may have different consequences in the sampled animals according to the age category.
324 Although the same methods of capture, physical and chemical restrain were employed for
325 both age categories, the extent of the physiological responses to stress situations certainly
326 vary between old and young animals. Such variation relies on the effects of the ageing process
327 in glucose tolerance and sensitivity to insulin at its target tissues (DeFronzo, 1979; Fink et al.,
328 1983; Chen et al., 1985; Kahn et al., 1992). For instance, Liu et al. (1999) observed higher
329 fasting blood glucose in aged mice submitted to long-term stress, highlighting the negative
330 effect of the ageing process in pancreatic function. Unfortunately, we cannot confirm such
331 hypothesis in the sampled population because it was impossible to evaluate the time between
332 the last feeding of the coatis and the blood sampling. In this sense, the rise of blood glucose in
333 adults could be merely reflecting non fasting glucose.

334 Serum creatinine was influenced by both age, gender and forest fragment. Because
335 serum creatinine concentration is a product of muscle catabolism, thus have a direct
336 relationship to muscle mass (Spencer, 1986), higher levels are expected in adult animals. Such
337 difference could be also attributed to dietary factors, since adult coatis' diet may include more
338 protein sources, as vertebrate preys (Whiteside, 2009). In relation to the gender difference,
339 since male coatis tend to be one-third heavier than females (Whiteside, 2009), our results may

lead to misinterpretation of the serum creatinine condition due to the differences in sampling males (17 adults and 22 juveniles) and females (34 adults and 16 juveniles). Finally, as creatinine is primarily synthesized in liver (Ostermann et al., 2016), the lower serum creatinine levels recorded in AFBV coatis may be indicator of an underlying liver injury, since we observed higher levels of ALT and AST in the same animals (Table 5). Indeed, in AFBV, coatis are continuously exposed to chemical substances as detergents, paints, herbicides and pesticides that are discarded in the outdoor trash cans (Figure 1).

Differences in serum proteins were found between adults and juveniles (Table 4). The higher levels of globulins observed in juveniles, in comparison to adult coatis (Table 4), is quite interestingly because in many other wild mammal species, it is reported an opposite tendency, with adults presenting higher levels (Ihrig et al., 2001; Miller et al., 2009; Peck et al., 2015; Burrell et al., 2018), mainly associated to pathogens continuous exposure. In our case, the highest globulin levels recorded in juveniles, in relation to adults' coatis, may a consequence of ingestion of maternal colostrum since because coatis are weaned late (Nowak, 1991). On the other hand, the higher levels of albumin observed in adult animals could be explained by the association of the increasing age with the dietary behavior, as the feeding behavior of adult coatis includes many protein sources (Witheside, 2009).

It was demonstrated that coatis from AFBV presented higher levels of neutrophils and lower levels of lymphocytes than coatis from PSP (Table 5). This leukogram profile may indicate a stress-induced condition, since glucocorticoids are related to alterations in cell trafficking and redistribution, specifically the transmigration of lymphocytes from bloodstream to various tissues, and neutrophils from bone marrow to bloodstream (Bishop et al., 1968; Dhabhar, 2002). Indeed, southern coatis may be more exposed to stress in AFBV than in PSP, especially due to agonistic encounters with domestic dogs and continuous exposure to human presence in this area (de Macedo personal communication).

As enzymatic activities and blood condition hematology are well correlated with specific physiological states throughout life, any inference on the hematological and biochemical values should be made considering the aspects related to the animals and the environment in which they inhabit. Although some parameters evaluated in the present study were similar to those reported in previous studies with *N. nasua* (Rodrigues et al., 1996; Riehker Junior et al., 2017), comparisons were not performed here because of the differences in habitat, restraint techniques, diet, management and sample size. Indeed, our study also presented quite different results from the previous ones, certainly a consequence of the above-mentioned factors.

CONCLUSION

We report the first hematological and biochemical RI establishment for *N. nasua* and discuss the differences related to age, sex and home area. The RI established in the present study provide a baseline information of the physiological status of *N. nasua* living in urban forest fragments, and will certainly contribute to future research on the health of this species, as well for veterinarians and facilities that provide health care to free ranging coatis in urban areas.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Accessing health outcomes of *Leishmania* spp. and ancylostomatids infections in southern coatis (*Nasua nasua*) from urban forest fragments in Brazilian Midwest

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ABSTRACT

Wild animals are incriminated as the major source of emerging infectious diseases (EIDs) of humans and domestic animals, but the outcomes of parasitism in naturally parasitized fauna is

largely unknow. As the coevolution among parasites and their hosts has been drastically changed with human encroachment of natural environments, accessing wildlife health in urbanized areas is extremely important for biodiversity conservation and to improve knowledge on parasites enzooty. The present study evaluated the outcomes of *Leishmania* spp. and ancylostomatids infections in health of southern coatis from two forested fragments at Brazilian Midwest. A total of 77 southern coatis were sampled from March 2018 to April 2019. Infections by *Leishmania* spp. and ancylostomatids were determined by molecular and parasitological tests respectively. Health was inferred by hematological and serum biochemistry parameters, categorized into the following indicators: Red blood cell (RBCI), Coagulation (COI), Immune investment (IMII), Infection response (IRI), Kidney damage (KDI), Liver damage (LDI), Cardiac damage (CDI), Skeletal muscle damage (SMDI), Nutritional profile (NPI) and Protein profile (PPI). A path analysis was performed to observe the influences of parasites in the health indicators, and ANOVA and Kruskall Wallis were performed to compare groups according to parasite infections. We observed ancylostomatid infection influencing RBCI and CDI; *Leishmania* spp. infection influencing CDI, LDI, SMDI, NPI and PPI; coinfection influencing KDI, NPI and PPI. Health indicators were not influenced indirectly via BC, but BC influenced directly SMDI, NPI and PPI. Differences were observed in ALT, albumin, total serum proteins, total and HDL cholesterol and triglycerides among groups regarding parasite infection. In addition, we found significative differences according to gender and area irrespective of parasitism. Our results demonstrate for the first time the health outcomes of *Leishmania* spp. and ancylostomatid infections in southern coatis, contributing for the knowledge on the outcomes of natural infections in wild mammals.

INTRODUCTION

Wildlife has been pointed out as the major source of emerging infectious diseases (EIDs) to human and domestic animals [1, 2]. In this context, wild animals have been studied mainly as “parasitic reservoirs”, with a focus on the presence or absence of parasitic infections. However, the parasitism outcomes on the wellbeing of wild host species are largely unknown. Undoubtedly, the health evaluation of naturally parasitized fauna is complex and cannot be measured only by the absence or presence of a given parasite infection, because multiple parasitic infections is a normal state throughout the life of free-living animals [3-8], while disease is the result of an imbalance among parasite-host-environment relationships in a given period of time [9].

The influence of parasitism in the health of wild mammals has been classically recorded by experimental studies [10-14]. However, society's perception against animal experimentation and the severe guidelines of the ethics committees on the use of animals have hampered experimental infections [15]. On the other hand, in spite of many biotic and abiotic variables that can influence the parasite-host associations in nature, field logistics difficulties and sample size, studies on the outcome of natural infections on the health of free-living animals have been developed [6, 7, 16, 17].

Nowadays, monitoring wildlife health in urban forest fragments is of major concern because the exponential growth of human populations has resulted in habitat fragmentation, biodiversity loss and changes in parasites transmission routes [18, 19]. Moreover, despite the coevolutionary history of wild animals and their parasites, the anthropogenic changes can cause immunosuppression, resulting in harm to the health of wild animals [20].

Southern coatis (Procyonidae, *Nasua nasua*) are carnivores broadly distributed in South America, from Colombia and Venezuela (North) to Uruguay and Argentina (South) [21]. These animals have been reported as a reservoir hosts for zoonotic parasites including

Leishmania spp, and ancylostomatids, etiological agents of important neglected diseases in Brazil [22-25]. Due to the absence of natural predators and the large food supply of anthropic origin, southern coatis have presented high population densities in Brazilian urban forest fragments [26-29], resulting in cross-transmission among parasites that classically infect humans and domestic animals [25, 30-32].

Given the importance of monitoring wildlife health for both conservation and public health perspectives [33], the present study aimed to evaluate the influences of *Leishmania* spp. and ancylostomatid infections on hematological and serum biochemistry parameters of southern coatis that inhabit two forest fragments of Campo Grande, Mato Grosso do Sul, Brazil. Canine and human visceral leishmaniasis are endemic diseases at this municipality [34-36], and wild mammal hosts have been recently described parasitized by *Leishmania* spp. [37, 38], while the occurrence of ancylostomatids is underreported.

MATERIAL AND METHODS

Study areas

This study was carried out in two forest fragments of Campo Grande, with different levels of land use: (i) Prosa State Park (PSP) and (ii) Air Force Base Village (AFBV) (Figure 1). The PSP (-20.44987, -54.56529) is a 134 hectares environmental protection area, adjacent to a recreational park named Parque das Nações Indígenas and to a public administration area named Parque dos Poderes, with intense people flow. The vegetation cover is formed by *cerrado sensu stricto* (savanna), *cerradão* (tall savanna woodland) and riparian forest [27], and local fauna includes several mammalian species [39]. In addition, within the PSP there is a Wildlife Rehabilitation Center (WRC) that daily receives dozens of wild animal species from all over the state of Mato Grosso do Sul.

The AFBV (-20.47163, -54.65405) is a residential and military training area of approximately 197 hectares. Vegetation cover is formed by *cerrado*, riparian forest and *veredas* (a type of Cerrado vegetation that occurs mainly in gallery forests). The area shelters several wild animal species and is inhabited by approximately 730 people that raises pet animals, as dogs and cats [29].

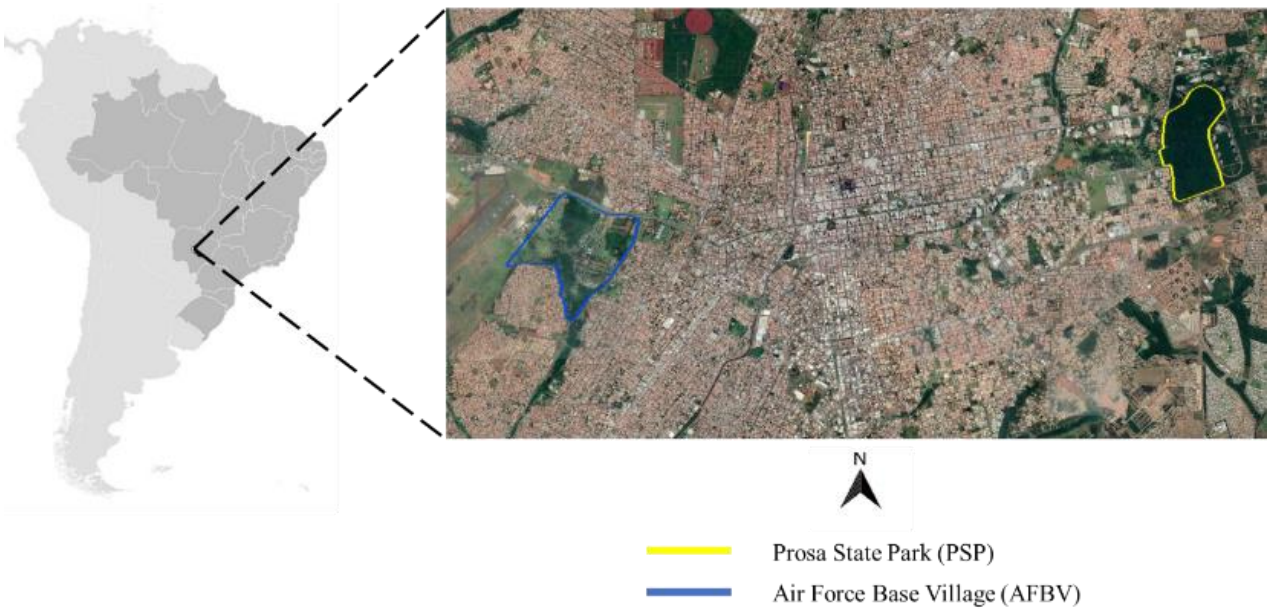

Figure 1. Study areas. The Prosa State Park is a permanent environmental protection area and the Air Force Base Village is a residential and military training area in Campo Grande, Mato Grosso do Sul, Brazil.

Field procedures

The captures were performed in Box Traps (90 × 45 × 50; Equipos Fauna®, Brazil) baited with bacon (15 to 25 grams daily). All captured coatis were sedated with an intramuscular injection of tiletamine hydrochloride and zolazepan hydrochloride (Telazol 100g; Zoetis®, USA) and tagged with subcutaneous transponders (Animal Tag®, Brazil). Sex, body mass (g), head-body length (mm) and clinical findings were registered. Additional body measurements as shoulder height (mm), tail length (mm), neck and thorax

circumference (mm), and teeth condition (including height of upper and lower canines) were registered in order to estimate age of the captured coatis, according to Olifiers and co-workers [40].

Blood and bone marrow were collected from each captured animal, with previous appropriate antisepsis. Blood was collected through vacuum needles from the femoral vein and placed in Ethylenediamine Tetraacetic Acid (EDTA) and clot activator tubes. Bone marrow was collected from sternal manubrium by hypodermic needles (0.40 x 1.2 mm) and 10 mL syringes and placed in EDTA tubes. Bone marrow collection was performed with previous local anesthesia (Lidovet 2g; Bravet®, Brazil). After total recovery from anesthesia, the animals were released at the capture site. In addition, fecal samples were collected from the traps without contact with the ground. For that, all the traps were elevated 10 cm from the ground and a sterile plastic was put under each trap. This plastic was replaced every time a different coati was trapped.

All field procedures were conducted in accordance with a license granted by the Instituto Chico Mendes de Conservação da Biodiversidade (license number 56912-2), Imasul (license number 05/2017, process Nº61/405959/2016), and Air Force cooperation agreement (Nº01/GAP-CG/2018). The present study was approved by the Ethics Committee for Animal Use of Universidade Católica Dom Bosco, Campo Grande, MS (license number 001/2017).

Hematological and serum biochemistry parameters

Red blood cell (RBC), white blood cell (WBC), hemoglobin (Hgb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelets were measured by an automated hematology analyzer device (POCH-iV 100, Syxmex®, Brazil), according to manufacturer's recommendations. Different leukocyte

counts were performed in blood smears fixed with methanol, stained with Panótico kit (Laborclin®, Brazil) and visualized in binocular microscope (Eclipse E200, Nikon®, Japan).

Serum concentrations of creatine kinase (CK and CKMB fraction), lactate dehydrogenase (LDH), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate transaminase (AST), urea, creatinine, albumin, total serum protein (TSP), total cholesterol, high-density lipoprotein (HDL) cholesterol, glucose and triglycerides were determined by spectrophotometer analysis (Brasmed®, Brazil) using the Biotech ® and Gold ® commercial kits. Globulin values were determined based on the difference between TSP and albumin values. In order to improve the specificity of CKMB, we calculated the CKMB/total CK ratio using the cut-offs described by Al-Hadi and Fox [41] and Godoy and co-workers [42]: < 6% indicating skeletal muscle damage; > 6% indicating myocardial injury; > 20% indicating the presence of macroenzimes.

Diagnosis of Leishmania spp. *and ancylostomatids*

Genomic DNA was extracted from 200 µL of bone marrow samples by the phenol-chloroform method, according to Sambrook and Russell [43]. The DNA was eluted in 50 µL elution buffer and stored at -20°C. The concentration and quality were assessed by spectrophotometry (Biodrop, Analítica ®, Brazil). In order to detect *Leishmania* spp. DNA from bone marrow samples, conventional Polymerase Chain Reactions (PCR) were performed using primers targeting the kDNA gene, designed by Schubach and co-workers [44]. The reactions were performed in a final volume of 25 µL containing 10 pmol of each oligonucleotide, 0.2 mM dNTP, 1.5 mM MgCl2, 10 mM Tris-HCL, 2.5 U of taq DNA polymerase (Invitrogen ®, USA) and 5 µL of extracted DNA. The following amplification cycle was used: 94ºC for 5 min followed by 30 cycles of 94ºC for 1 min, 61ºC for 1 min and 72ºC for 1 min, and a final extension at 72ºC for 5 min. The PCR products were visualized

after electrophoresis on a 1.5% agarose gel (Kasvi ®, Brazil) using Gel Red Nucleic Acid Stain (Biotium ®, USA) staining.

In order to detect ancylostomatid eggs from the collected feces, we performed a centrifuge-flotation technique using a saturated solution (1.2 g/mL density- 500 g of sucrose + 6.5 g of phenol + 320 mL of distilled water), according to Sheather [45]. The eggs were visualized under a light microscope (Axio Scope, Zeiss ®, Germany).

Data analysis

Descriptive statistic (mean ± standard deviation) was applied in order to obtain the mean hematological and serum biochemistry values of different groups: (i) uninfected (UN), (ii) *Leishmania*-infected (LI), (iii) ancylostomatid-infected (AI) and (iv) coinfection (CI). Shapiro-Wilk test was applied to check the normality of the hematological and biochemical parameters, and according to the data distribution, variance analysis (ANOVA) and Kruskal-Wallis test were applied to determine the significant differences among the groups. *Post hoc* Tukey and Mann-Whitney tests were used to assess pair-wise results of the ANOVA and Kruskal-Wallis. Then the same analyses were performed for different groups regarding gender and study area: (i) AFBV Males (AM), (ii) AFBV Females (AF), (iii) PSP Males (PM) and (iv) PSP Females (PF).

To determine the indirect influences of parasite infection in health indicators through body condition (BC), we carried out a path analysis according to Santos and co-workers [6]. We estimated BC based on the residuals from an ordinary linear regression between body mass and head-body length of coatis. Health indicators were categorized into: (i) Red blood cell indicator (RBCI) (RBC, Hb, PCV, MCV and MCHC), (ii) Coagulation indicator (COI) (platelets), (iii) Immune investment indicator (IMII) (globulin and lymphocytes), (iv) Infection response indicator (IRI) (monocytes, neutrophils and eosinophils), (v) Kidney

damage indicator (KDI) (urea and creatinine), (vi) Liver damage indicator (LDI) (AST, ALT and AP), (vii) Cardiac damage indicator (CDI) (CKMB), Skeletal muscle damage indicator (SMDI) (CK and LDH), Nutritional profile indicator (NPI) (triglycerides, total cholesterol, HDL cholesterol and glucose) and Protein profile indicator (PPI) (albumin and TSP). The variables were considered statistically significant for p values < 0.05. All data were analyzed using R software [46].

RESULTS

From March 2018 to March 2019, a total of 77 adult coatis were captured, corresponding to 39 and 38 animals from PSP and AFBV respectively (Table 1). At clinical evaluation, the most frequent findings were paw pad hyperkeratosis (33.7%), scars (31.1%) and wounds (32.4%). About 20.7% of the animals did not present any clinical finding (Supplementary Material S1).

In relation to the parasite infections, ancylostomatids were detected in 28.6% of the animals, *Leishmania* spp. was detected in 19.5%, coinfection was observed in 22.1%, and 29.9% of the animals were uninfected by these parasites (Table 1). Other nematode eggs were detected at centrifuge-flotation test: Oxyuridae (2), *Strongyloides* spp. (2) and *Dioctophyma renale* (1).

Table 1. Occurrence rate of *Leishmania* and ancylostomatid single infections, and coinfections in 77 adult southern coatis from two forested fragments in Campo Grande, Mato Grosso do Sul, Brazil. Data are show by gender and site of collection.

Parasites	Prosa State Park		Air Force Base Village		Total (77)
	Male (21)	Female (18)	Male (19)	Female (19)	
Leishmania spp.	2 (9.5%)	2 (11.1%)	5 (26.3%)	6 (31.6%)	15 (19.5%)
Acylostomatids	4 (19%)	5 (27.8%)	8 (42.1%)	5 (26.3%)	22 (28.6%)
Coinfection	7 (33.3%)	3 (16.6%)	3 (15.8%)	4 (21%)	17 (22.1%)
Uninfected	8 (38.1%)	8 (44.4%)	3 (15.8%)	4 (21%)	23 (29.9%)

Results of ANOVA and Kruskal-Wallis tests did not show significant differences among in hematological means of different groups regarding parasitism. On the other hand, with respect to serum biochemistry, we observed that LI presented higher ALT values than UN and CI ($p = 0.009$) and higher values of both total and HDL cholesterol ($p = 0.04$; $p = 0.03$) than AI and UN groups. The CI group presented higher TSP values than AI ($p = 0.007$) and higher triglycerides values than UN ($p = 0.02$). Albumin values were significantly lower in AI when compared to LI and CI, and significantly higher in LI when compared to UN ($p = 0.01$). In addition, CKMB/total CK ratio was above 20 % in all groups (Table 2).

When applying ANOVA and Kruskal-Wallis in parameters regarding gender and forest fragment, we observed that AM group presented higher neutrophil ($p = 0.0002$) and lower lymphocyte count ($p = 0.004$), while PM group presented higher monocyte count ($p = 0.003$) and lower serum HDL cholesterol ($p = 0.03$). We also found that AFBV animals presented higher serum ALT ($p = 3.65e-05$) and lower serum AP ($p = 0.001$) than PSP animals (Table 3).

Table 2. Hematological and serum biochemistry parameters of southern coatis (*Nasua nasua*) infected by *Leishmania* spp., ancylostomatids, and coinfected, at Campo Grande, Mato Grosso do Sul, Brazil. Values are expressed by mean ± standard deviation.

	Uninfected (n=23)	**Ancylostomatid (n= 22)**	***Leishmania* spp. (n= 15)**	**Coinfection (n= 17)**
Hematology				
RBC ($10x^6/mm^3$)	5.40 ± 0.39	5.47 ± 0.53	5.48 ± 0.59	5.43 ± 0.56
Hgb (g/dL)	10.47 ± 0.67	10.79 ± 1.08	10.46 ± 1.07	10.65 ± 1.22
PCV (%)	33.43 ± 2.23	35.18 ± 3.82	34 ± 3.04	34.41 ± 3.60
MCV (fL)	59.56 ± 2.50	60.51 ± 2.41	58.94 ± 2.83	59.27 ± 2.34
MCHC (g/dL)	32.59 ± 0.98	32.62 ± 0.83	32.42 ± 1.09	33.08 ± 1.08
Platelet ($10x^3/mm^3$)	567782 ± 134261	557409 ± 148593	512200 ± 161949	530176 ± 174168
WBC ($10x^3/mm^3$)	15671 ± 5335	17409 ± 6043	15646 ± 4185	15558 ± 3253
Neutrophil ($10x^3/mm^3$)	10701 ± 5894	11645 ± 6834	11139 ± 4058	10001 ± 4145
Lymphocyte ($10x^3/mm^3$)	2239 ± 2012	2332 ± 2030	1658 ± 1384	2534 ± 1563
Monocyte ($10x^3/mm^3$)	1442 ± 1020	1767 ± 1239	1415 ± 1382	1683 ± 1185
Eosinophil ($10x^3/mm^3$)	1102 ± 794	1507 ± 883	1240 ± 872	1304 ± 930
Basophil ($10x^3/mm^3$)	131 ± 187	156 ± 181	191 ± 317	34 ± 41
Serum biochemistry				
CK (U/L)	1522 ± 1493	1295 ± 630	3486 ± 2828	2286 ± 2100
CKMB (IU/L)	1815 ± 1028	2409 ± 1012	2416 ± 1219	2142 ± 669
CKMB/total CK ratio (%) *	438 (20.1 - 5851.9)	262.8 (61.8 - 1043.2)	143 (25.4 - 536.2)	164.3 (30 - 531.7)
LDH (IU/L)	1474 ± 753	1597 ± 734	1964 ± 1090	1913 ± 756
AST (IU/L)	218.13 ± 140.32	218.53 ± 151.74	243.53 ± 131.67	164.43 ± 70.58
ALT (IU/L)	91.24 ± 45.95**a**	100.01 ± 46.01	155.39 ± 66.62**b**	92.79 ± 56.51**a**
AP (IU/L)	33.47 ± 26.22	22.22 ± 11.25	24.16 ± 8.40	22.47 ± 7.57
Urea (mmol/L)	24.21 ± 16.90	24.18 ± 11.53	30.10 ± 13.72	47.82 ± 88.89
Creatinine (µmol/L)	1.36 ± 0.82	1.17 ± 0.38	1.23 ± 0.30	1.14 ± 0.29
Albumin (g/dL)	2.07 ± 1.23**a**,**b**	1.89 ± 1.29**a**	2.81 ± 1.11**b**,**a**	2.76 ± 0.98**b**
Globulin (g/dL)	5.42 ± 1.72	5.19 ± 1.33	5.76 ± 1.77	5.89 ± 1.83
TSP (g/dL)	7.50 ± 1.65	7.09 ± 1.17**b**	8.58 ± 1.80	8.66 ± 1.94**a**
Total cholesterol (mmol/L)	143.78 ± 106.5**7a**	139.18 ± 107.54**a**	228.80 ± 152.06**b**	165.11 ± 98.14
HDL cholesterol (mmol/L)	50.55 ± 24.15**a**	55.25 ± 26.03**a**	77.13 ± 32.93**b**	76.84 ± 44.80
Glucose (mmol/L)	85.43 ± 27.34	81.90 ± 27.12	102.46 ± 34.34	95.41 ± 34.70
Triglycerides (mmol/L)	43.65 ± 60.26**a**	43.47 ± 33.85	66.26 ± 89.53	77.66 ± 90.30**b**

Different bold letters indicate statistical difference ($p < 0.05$). * = Values expressed by mean (min-max); AI = Ancylostomatid infected; ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase; CI = Coinfected; CK = Creatine kinase; Hgb = Hemoglobin; LDH = Lactate dehydrogenase; LI = Leishmania infected; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; PCV = Packed cell volume; RBC = Red blood cells; TSP = Total serum proteins; UN = Uninfected; WBC = White blood cells;

Table 3. Hematological and serum biochemistry parameters of adult southern coatis (*Nasua nasua*) according to gender and forest fragment at Campo Grande, Mato Grosso do Sul, Brazil. Values are expressed by mean ± standard deviation.

	Prosa State Park (PSP)		Air Force Base Village (AFBV)	
	Males (21)	Females (18)	Males (19)	Females (19)
	Hematology			
RBC ($10x^6$/mm3)	5.42 ± 0.43	5.38 ± 0.40	5.56 ± 0.60	5.43 ± 0.59
Hgb (g/dL)	10.58 ± 0.82	10.39 ± 0.78	11.06 ± 1.32	10.37 ± 0.92
PCV (%)	33.76 ± 2.86	33.50 ± 2.96	36.00 ± 3.79	33.79 ± 2.82
MCV (fL)	59.57 ± 2.24	58.82 ± 1.84	60.46 ± 2.02	59.73 ± 3.58
MCHC (g/dL)	32.81 ± 0.78	32.88 ± 1.10	32.87 ± 1.13	32.15 ± 0.84
Platelet ($10x^3$/mm^3)	556428.57 ± 138664.55	567888.89 ± 77714.33	535473.68 ± 171237.77	523000.00 ± 198588.63
WBC ($10x^3$/mm^3)	15314.29 ± 3772.97	14700.00 ± 5475.51	18826.32 ± 5862.48	15657.90 ± 3747.05
Neutrophil ($10x^3$/mm^3)	8626.81 ± 3462.39**a**	9043.22 ± 5597.72**a**	15270.63 ± 6389.56**b**	10809.26 ± 3633.34**a**
Lymphocyte ($10x^3$/mm^3)	2907.33 ± 1851.52**a**	2826.94 ± 1575.64**a**	1115.95 ± 902.16**b**	1982.00 ± 2135.78**a**
Monocyte ($10x^3$/mm^3)	2327.62 ± 1522.65**b**	1580.06 ± 1063.28**a**	1192.21 ± 556.55**a**	1154.89 ± 973.51**a**
Eosinophil ($10x^3$/mm^3)	1350.67 ± 700.47	1132.61 ± 783.17	1112.32 ± 877.23	1547.74 ± 1059.74
Basophil ($10x^3$/mm^3)	101.86 ± 147.33	117.17 ± 135.44	135.21 ± 174.41	164.00 ± 321.95
	Serum biochemistrty			
CK (IU/L)	1343.71 ± 920.16	1468.00 ± 878.68	2564.79 ± 2275.31	2700.32 ± 2768.63
CKMB (IU/L)	2150.16 ± 1229.20	2189.65 ± 977.92	2154.51 ± 1106.37	2206.57 ± 720.34
LDH (IU/L)	1397.52 ± 610.21	1522.56 ± 518.58	1914.37 ± 1016.54	1995.95 ± 977.91
AST (IU/L)	161.50 ± 92.96	196.53 ± 105.57	218.22 ± 123.86	273.59 ± 170.85
ALT (IU/L)	66.89 ± 23.69**a**	67.49 ± 24.45**a**	122.89 ± 47.13**b**	171.20 ± 48.96**b**
AP (IU/L)	30.67 ± 11.70**a**	30.76 ± 24.28**a**	19.97 ± 6.21**b**	22.44 ± 18.72**b**
Urea (mmol/L)	20.52 ± 8.05	31.56 ± 17.48	27.76 ± 11.85	43.53 ± 85.16
Creatinine (µmol/L)	1.13 ± 0.30	1.40 ± 0.91	1.27 ± 0.44	1.17 ± 0.24
Albumin (g/dL)	1.92 ± 1.06	2.32 ± 1.02	2.50 ± 1.37	2.59 ± 1.38
Globulin (g/dL)	5.33 ± 1.12	5.10 ± 0.99	5.38 ± 1.48	5.48 ± 1.56
TSP (g/dL)	7.42 ± 1.97	8.02 ± 1.90	8.03 ± 1.59	8.00 ± 1.49
Total cholesterol (mmol/L)	125.71 ± 87.21	165.67 ± 112.89	152.32 ± 90.35	215.37 ± 159.40
HDL cholesterol (mmol/L)	48.61 ± 33.05**b**	68.86 ± 36.39**a**	67.53 ± 30.88**a**	68.33 ± 31.71**a**
Glucose (mmol/L)	75.67 ± 28.07	92.83 ± 32.92	88.11 ± 27.89	104.84 ± 29.38
Triglycerides (mmol/L)	52.10 ± 79.08	90.91 ± 104.91	42.24 ± 19.08	39.05 ± 27.03

Different bold letters indicate statistical difference ($p < 0.05$). ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase; CK = Creatine kinase; Hgb = Hemoglobin; LDH = Lactate dehydrogenase; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin; PCV = Packed cell volume; RBC = Red blood cells; TSP = Total serum proteins; WBC = White blood cells;

The path analysis showed that the single parasitism by *Leishmania* spp. and ancylostomatids, as well as their association, did not indirectly influence the health indicators via BC. Also, the path analysis revealed that *Leishmania* spp. single infection influenced the LDI (path coefficient = 0.31, $p < 0.05$) through a positive correlation to ALT ($r = 0.91$), and ancylostomatid single infection influenced the RBCI (path coefficient = 0.28, $p < 0.05$) by positive correlation with MCV ($r = 0.94$). Coinfection influenced the KDI (path coefficient = 0.27) through a positive correlation with urea ($r = 0.65$) (Figure 2).

Furthermore, path analysis showed direct influences from *Leishmania* spp. single infection, coinfection and BC on PPI and NPI through a positive correlation with albumin ($r = 0.93$) and TSP ($r = 0.68$), and HDL cholesterol ($r = 0.62$) glucose ($r = 0.74$) respectively. Moreover, Cardiac damage was influenced by ancylostomatid (path coefficient = -0.31, $p < 0.05$) and *Leishmania* spp. single infections (path coefficient = -0.25, $p < 0.05$) through a positive correlation with CKMB ($r = -0.90$). SMDI was influenced by BC (path coefficient = 0.21, $p < 0.05$) and *Leishmania* spp. single infection (path coefficient = 0.34, $p < 0.05$) through a positive correlation with LDH ($r = 0.95$) and CK ($r = 0.79$) (Figure 2).

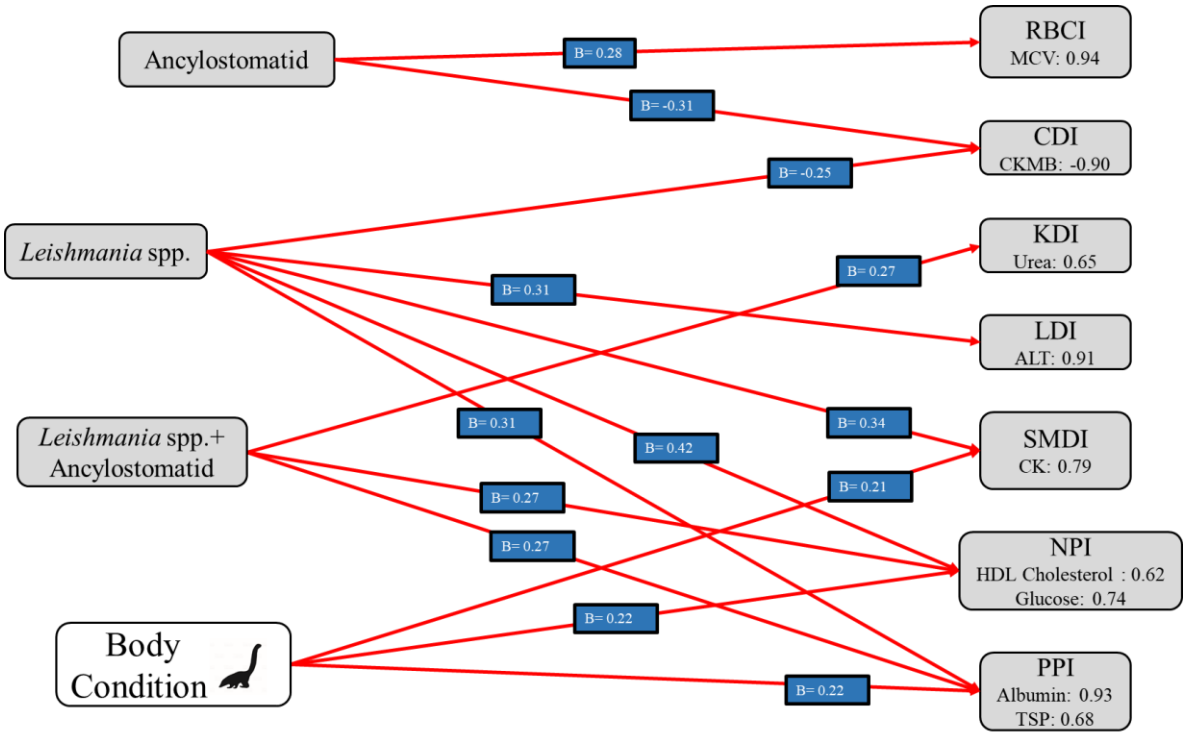

Figure 2. Direct influences of *Leishmania* spp. and ancylostomatid single infections, coinfection and body condition in health indicators of 77 adult southern coatis (*Nasua nasua*) captured from March 2018 to March 2019 in Campo Grande, Mato Grosso do Sul, Brazil. RBCI: Red blood cell indicator; CDI: Cardiac damage indicator; KDI: Kidney damage indicator; LDI: Liver damage indicator; SMDI: Skeletal muscle damage indicator; NPI: Nutritional profile indicator; PPI: Protein profile indicator.

DISCUSSION

Studies on the physiological response to parasite infection are vital for the development of effective strategies to wildlife conservation and to monitor ecosystem health. The present study provides for the first-time information regarding the outcomes of *Leishmania* spp. and ancylostomatid infections in the hematological and biochemical parameters of a common wild carnivore species that inhabits urban forested fragments at Brazilian Midwest.

Our results showed that leishmaniasis in sampled coatis resulted in hepatocyte damage since we observed a positive correlation between *Leishmania* spp. single infection and ALT

(Figure 1), and LI group presented significantly higher ALT values (Table 3). This correlation was evident in coatis sampled at AFBV because we detected a significant difference in ALT means (Table 3), and greater occurrence rates of *Leishmania* spp. in this area (Table 1). The hepatic injury is a common finding in human and canine leishmaniasis [47-52], and high levels of ALT may be a common laboratory finding because such enzyme is found inside the hepatocytes and is released into the blood stream upon hepatocyte damage [53].

Ancylostomatid infections are commonly related to anemia due to its hematophagous behavior and bleeding as a result of attachment to the small intestine [54]. However, our analysis did not show any influence of ancylostomatid infection on decrease of anemia parameters such as RBC, Hg and PCV, and this may be related to the fact that we only sampled adult animals. Indeed, it is well known that prevalence and severity of ancylostomatid infections tend to be lower in adult animals because the infective third-stage larvae (L3) tend to become encysted in somatic tissues instead of performing tracheal migration, resulting in less L4 and adult worms attached to the small intestine mucosa [54]. In fact, it has been reported that the anemia due to ancylostomatid infection is most found in juveniles than in adults individuals [55-60]. Undoubtedly, adult animals tend to have higher acquired immunity after continued exposure to hookworms than young animals, as immunity becomes stronger and more specific with increasing age; for example, increased concentration of circulating interleukins that mediate the Th2 response to helminths [61]. In this sense, adult coatis, as observed in other mammal species, tend to develop chronic asymptomatic ancylostomatid infections.

Although ancylostomatid infections usually result in microcytosis due to the iron deficiency caused by hematophagy [62-65], we detected a positive correlation between ancylostomatid single infection and MCV. Macrocytosis (high MCV) was already reported in domestic dogs parasitized by *Ancylostoma caninum* [66]. Possibly, the infection by

ancylostomatids may go along with a dysfunction in intestinal mucosa, resulting in low absorption of vitamin B12 and folic acid, nutrients involved in the maturation of erythrocytes at the bone marrow [67], and consequent high MCV regardless of anemia. Such findings demonstrate that MCV should be investigated in ancylostomatid infected coatis even in absence of RBC, Hgb and PCV alterations.

To date, five genera of ancylostomatids are reported parasitizing procyonids (*Ancylostoma*, *Arthrocephalus*, *Arthrostoma*, *Necator* and *Uncinaria*) [68]. Although it was not possible to distinguish the ancylostomatid species in the present study because of the absence of diagnostic characters in eggs, it is most likely that the sampled animals were parasitized either by *Ancylostoma* spp. or/and by *Uncinaria* spp., the only two genera reported in southern coatis in Brazil [69]. Considering these two genera have been reported parasitizing domestic dogs and cats worldwide [70-74], stray and household pets that inhabit/access the studied areas are certainly contributing to the environmental contamination and consequent infection of southern coatis. For instance, the occurrence of *Ancylostoma* spp. eggs in dog faeces recovered from public squares in Campo Grande was already reported in all regions of the city [75].

Coinfection by *Leishmania* spp. and ancylostomatids in sampled coatis may be resulting in kidney damage because we found a positive correlation with urea (Figure 2). Glomerular filtration impairment is a common event in LV due to the deposition of immune complexes [76-78], leading to a raise in serum urea levels. On the other hand, serum urea is an important predictor of gastrointestinal bleeding [79, 80], which may be a result of anchoring of hookworms in the enteric mucosa. Nevertheless, increase of serum urea levels could be also attributed to (i) a high protein intake, assured by the occurrence of vertebrate preys at forested fragments in Campo Grande/MS [29, 38, 39], and to (ii) *D. renale* parasitism, which eggs were accidentally detected in fecal examinations. In fact, southern coatis may constitute an

important host of *D. renale* in urban forest fragments, where high prevalence of infection was reported [30].

Our results showed that protein profile was positively influenced by both *Leishmania* spp. single infection, coinfection, and BC, since we observed a positive correlation with TSP and albumin levels (Figure 2). Hyperproteinemia may be related to dehydration, but it is usually accompanied by an increase in PCV [81], which was not seen in our results, neither dehydration was observed in sampled coatis during the capture events. The positive association between serum albumin and muscle mass [82-84] may explain the positive correlation with BC found in our study. The observed hyperproteinemia in LI and CI groups seems to be related to serum albumin rather than immune globulins, since we observed significant differences only in albumin levels (Table 2). In the case of coinfection, the observed positive correlation with albumin (Figure 2) may be attributed to the immunomodulatory characteristic of ancylostomatids because they secret bioproducts that inhibit the pro-inflammatory interleukins TNF-α and IL-6 [85], responsible for suppressing albumin synthesis [86, 87]. Moreover, hookworms induce a Th2 response not mediated by IL-6 [54]. Also, since *Leishmania* spp. single infection and coinfection correlated positively to HDL cholesterol, and HDL cholesterol is capable of attenuate the expression of TNF-α and IL-6 [88], the albumin synthesis would not be compromised in the parasitized coatis.

Regarding the nutritional profile, *Leishmania* spp. single and coinfection were positively correlated to HDL cholesterol and glucose (Figure 2). Such findings are intriguing because the attachment and internalization of *Leishmania* spp. into macrophages are dependent upon the content of sphingolipids and total cholesterol in the lipid rafts [89, 90]. Once inside the cell, *Leishmania* spp. depletes the cholesterol content in lipid rafts, impairing interleukin signaling and the immune response [91,92]. However, this mechanism can be overcome by an increase in serum lipid and lipoproteins, promoting protection against the

parasite, as described by Ghosh and co-workers [93]. In fact, HDL cholesterol is reported to (i) promote the cholesterol reverse transport, which could impair *Leishmania* spp. internalization across macrophage plasma membrane [94-96], (ii) to correlate positively with gamma-interferon (IFN-γ) and negatively with IL-10, cytokines related to protection and progression of leishmaniasis, respectively [97, 98], and (iii) to correlate negatively with amastigote burden in lymphoid tissue [99,100]. In this sense, the high HDL cholesterol in *Leishmania*-infected coatis, associated to the absence of clinical signs, suggests that this species, although parasitized, does not present the clinical form of the disease, at least in endemic areas. Moreover, the high HDL cholesterol observed in LI group (Table 2) may be a result of compensatory synthesis at the enterocytes [101], as a result of liver damage, as discussed above. Additionally, the access to a high-fat diet from human food waste (de Macedo Personal Communication) would be contributing to the increase of serum lipids and lipoproteins.

Furthermore, as we observed significant higher HDL cholesterol and albumin in LI (Table 2), and in the early stages of *Leishmania* spp. infections low serum HDL cholesterol and albumin has been observed in dogs and humans [102-110], we assume that the southern coatis were chronically infected by *Leishmania* spp. at the time of the captures. In fact, low serum concentration of albumin and cholesterol HDL related to acute phase of infections has been widely reported [111,112]. In addition, the high HDL cholesterol observed in *Leishmania*-infected animals in the present study suggest a chronic phase of infection because in acute symptomatic infections, IL-10 is expressed and IFN-γ production is reduced [97,113,114].

The direct influence of BC in the nutritional profile through a positive correlation with glucose may be explained by the release of glucose into blood stream induced by glucocorticoid during stress events, as trapping and handling. However, the correlation of BC

with glucose and HDL cholesterol together was unexpected because it has been reported that HDL cholesterol reduces blood glucose levels by stimulating β-cell insulin secretion [115], as well as being inversely correlated to body mass index [116, 117]. In addition, a positive correlation between glucose and body mass index has been observed in insulin-resistance condition [118, 119], but this does not appear to be the case of sampled coatis, since insulin resistance condition is associated with significantly lower levels of HDL cholesterol [120,121].

The positive correlation between *Leishmania* spp. and ancylostomatid single infections with serum CKMB (Figure 2) may suggest a possible alteration of the cardiac function or even skeletal muscle damage. Indeed, the isoenzyme CKMB represents approximately 30% and 7% of total creatine kinase present in the cytosol of cardiomyocytes and skeletal muscles, respectively, being released into bloodstream in heart disease and strong physical activity conditions [122, 123]. However, in our study, high CKMB concentrations may not indicate cardiac abnormalities because the CKMB/CK ratio was above 20% for all the sampled coatis (Table 2). It seems that CKMB rates found in the present study are related to the presence of macro-CK, an enzyme-antibody complex with a high molecular weight composed by one CK isoenzyme and an immunoglobulin (mostly IgG) [124]. To the author's knowledge, there are no reports of ancylostomatids leading to cardiac abnormalities that could induce a high level of serum CKMB. On the other hand, ancylostomatid infections are characterized by an immune response Th2 [54] that can result in circulating IgG, consequently favoring serum macro-CK formation. The same can be suggested in the case of *Leishmania* spp. infection, which is characterized by a polyclonal activation of B cells with high IgG production [125-127]. By the exposed, we suggest that CKMB measure in coatis may not be an efficient tool for cardiac evaluation. In fact, it must be considered that free-ranging mammals are certainly exposed to several infectious agents, more than humans and domestic animals, and the

immune responses triggered by chronic subclinical infections or coinfections result in a strong immunoglobulin production.

We observed the influence of *Leishmania* spp. single infection in the SMDI through a positive correlation with CK (Figure 2). The presence of amastigote forms within macrophages and myofibers and the consequent infiltration of mononuclear cells and deposition of immune complexes certainly contribute to skeletal muscle tissue injury [128, 129]. Inflammatory muscle diseases have been recorded in dogs naturally parasitized by *L. infantum* [128, 129].

The analysis also showed that BC directly influenced the SMDI through a positive correlation with CK (Figure 2). CK is an indirect marker related to muscle membrane disruption and inflammatory response in consequence to metabolic demands during physical effort [130]. Skeletal muscle is the most important CK source and a higher body mass is related to an increase in susceptibility to mechanical load-induced muscle membrane damage [130, 131]. Furthermore, it has been demonstrated that free-living animals are likely to present higher levels of CK as consequence of handling and trapping events [132-136]. In this sense, it is reasonable that the sampled coatis may suffer capture stress with consequent skeletal muscle effort, regardless of parasitism and BC.

Interestingly, the variance analysis revealed specific differences regarding sex and area (Table 3). Firstly, we observed that males of PSP presented lower means of HDL cholesterol and higher means of monocyte counts. Since monocytes are pro-inflammatory cells playing important roles in atherosclerosis progression, and HDL cholesterol plays a role in inhibition of the pro-inflammatory and pro-oxidant effects of the monocytes [137], PSP males may be experiencing arterial diseases. Secondly, it was demonstrated that males from AFBV presented higher levels of neutrophils and lower levels of lymphocytes (Table 3). This leukogram profile may indicate a stress-induced condition, since glucocorticoids are related to

alterations in cell trafficking and redistribution, specifically the transmigration of lymphocytes from bloodstream to various tissues, and neutrophils from bone marrow to bloodstream [138, 139]. We predict that some events acting together may be responsible for a boost in stress-related leukocyte changes in males from AFBV, such as stress situations due to agonistic encounters with domestic dogs, human presence in this area (de Macedo personal communication), and the intra-specific mate competition [140, 141].

The significant high AP in coatis from PSP (Table 3) may be associated to less habituation to anthropogenic stressors (interactions with domestic animals and human beings, trash cans and vehicles) in comparison to AFBV animals (de Macedo, personal communication), since corticosteroids induces the increase in serum AP. Under stress condition, the hypothalamus produces and releases corticotropin-releasing hormone (CRH), which induces the secretion of adrenocorticotropin hormone (ACTH) from pituitary gland [142]. Subsequently, ACTH stimulates the release of AP to the extracellular environment [143]. Since coatis from PSP did not present high levels of ALT, as observed in AFBV animals (Table 3), the significant increase of AP probably is not related to hepatic disease. Moreover, as we sampled only adult animals, the observed increase of AP is not related to osteoblast activity and bone maturation that occur mainly in young animals [144].

CONCLUSION

To the best of our knowledge, the present work demonstrates for the first time the pathophysiological consequences of *Leishmania* spp. and ancylostomatid single infections, and coinfection in southern coatis that inhabit forest urban fragments. We highlight the importance of our results for the conservation of one of the most common wild carnivore species inhabiting urban forest fragments at Brazil.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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APÊNDICE

Apêndice 1A: Supplementary material 1. Clinical findings of Southern coatis (*Nasua nasua*) sampled from March 2018 to April 2019 in two forested fragments at Campo Grande, Mato Grosso do Sul.

	Prosa State Park (PSP)		Air Force Base Village (AFBV)		Total (77)
	Males (21)	Females (18)	Males (19)	Females (19)	
Paw pad hyperkeratosis	7 (33.3%)	7 (38.8%)	8 (42.1%)	4 (21%)	26 (33.7%)
Fight-like wounds	10 (47.6%)	3 (16.6%)	6 (31.5%)	6 (31.5%)	25 (32.4%)
Scars	7 (33.3%)	4 (22.2%)	6 (31.5%)	7 (36.8%)	24 (31.1%)
Linfadenopathy	2 (9.5%)	2 (11.1%)	2 (10.5%)	1 (5.2%)	7 (9.1%)
Sialorrhea	-	-	5 (26.3%)	1 (5.2%)	6 (7.8%)
Bone fracture	1 (4.7%)	1 (5.5%	-	2 (10.5%)	4 (5.2%)
Vaginal swelling	-	1 (5.5%	-	3 (15.7%)	4 (5.2%)
Alopecia	2 (9.5%)	-	-	1 (5.2%)	3 (3.9%)
Desquamation	2 (9.5%)	-	-	1 (5.2%)	3 (3.9%)
Obesity	-	-	3 (15.7%)	-	3 (3.9%)
Preputial swelling	2 (9.5%)	-	-	-	2 (2.6%)
Cryptorchid	-	-	1 (5.2%)	-	1 (1.3%)
Diarrhea	1 (4.7%)	-	-	-	1 (1.3%)
Limb swelling	-	1 (5.5%	-	-	1 (1.3%)
Nipple nodule	-	-	1 (5.2%)	-	1 (1.3%)
Nipple swelling	-	-	1 (5.2%)	-	1 (1.3%)
No clinical signs	5 (23.8%)	4 (22.2%)	2 (10.5%)	5 (26.3%)	16 (20.8%)

NORMAS DAS REVISTAS