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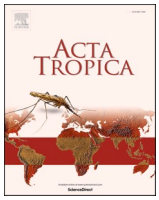

Metabolic alterations in Strongyloidiasis stool samples unveil potential biomarkers of infection

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ABSTRACT

Strongyloidiasis, a parasitosis caused by *Strongyloides stercoralis* in humans, is a very prevalent infection in tropical or subtropical areas. Gaps on public health strategies corroborates to the high global incidence of strongyloidiasis especially due to challenges involved on its diagnosis. Based on the lack of a gold-standard diagnostic tool, we aimed to present a metabolomic study for the assessment of stool metabolic alterations. Stool samples were collected from 25 patients segregated into positive for strongyloidiasis ($n = 10$) and negative control ($n = 15$) and prepared for direct injection high-resolution mass spectrometry analysis. Using metabolomics workflow, 18 metabolites were annotated increased or decreased in strongyloidiasis condition, from which a group of 5 biomarkers comprising caprylic acid, mannitol, glucose, lysophosphatidylinositol and hydroxy-dodecanoic acid demonstrated accuracy over 89% to be explored as potential markers. The observed metabolic alteration in stool samples indicates involvement of microbiota remodeling, parasite constitution, and host response during *S. stercoralis* infection.

1. Introduction

Human strongyloidiasis is a soil-transmitted helminthiasis, quite common in tropical and sub-tropical countries (World Health Organization (WHO) 2015). It is caused by intestinal *Strongyloididae* family nematodes, specially *Strongyloides stercoralis* (Montes et al., 2010). By 2017, strongyloidiasis prevalence was estimated around 8.1% worldwide, corresponding to 613.9 million people infected (Buonfrate et al., 2020). The high prevalence of strongyloidiasis is associated with poor sanitation and hygiene conditions, which are causally linked with parasite larvae transmission through fecal contamination (Schär et al., 2013). Once the infection is installed, the disease can often be asymptomatic, but, in symptomatic cases, the symptoms may vary from mild cutaneous, and/or abdominal symptoms to severe manifestations, known as hyperinfection (Farthing et al., 2020). Intending to avoid infection dissemination and to reduce lethality, improved diagnostic tests are of extreme urgence, since most cases remain underreported (Montes et al., 2010; Farthing et al., 2020; Requena-Méndez et al., 2013; World Health Organization (WHO) 2021). Considering the lack of gold-standard for this disease, strongyloidiasis are usually detected by a combination of coprological concentration techniques such as Hoffmann sedimentation, Baermann-Moraes, Rugai and agar culture (Buonfrate et al., 2020; Farthing et al., 2020; Requena-Méndez et al., 2013). Additional techniques have been developed intending to improve sensitivity, such as: enzyme-linked immunosorbent assay, immunoblotting, immunofluorescence antibody test, polymerase chain reaction and loop mediated isothermal amplification assay (Requena-Méndez et al., 2013; World Health Organization (WHO) 2021; Levenhagen and Costa-Cruz, 2014; Fernández-Soto et al., 2020). When it comes to serological assays, they present considerable sensitivity and potential for scaling, however, antibodies' cross-reactivity culminates with false-positive results (Requena-Méndez et al., 2013). Although

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molecular tests present higher specificity, they potentially fail with sensitivity, once they depend on parasitic load for nucleic acids detection (Buonfrate et al., 2020; Farthing et al., 2020; Requena-Méndez et al., 2013; Levenhagen and Costa-Cruz, 2014). Unfortunately, both direct and indirect abovementioned techniques have their limitations in terms of sensitivity and specificity, making them complementary for each other.

In this scenario, the knowledge about metabolic alterations present on strongyloidiasis could provide new insights into molecules with better sensitivity and specificity to improve diagnosis. Several studies have been addressing metabolomic profiling of worms and biological samples aiming for new biomarkers (MôS Ferreira et al., 2014; MS Ferreira et al., 2014; Kadeschid et al., 2020; Melo et al., 2016; Wang et al., 2020; Mangmee et al., 2020; Yeshi et al., 2020). Untargeted omics previously annotated metabolites of *Schistosoma mansoni* (MS Ferreira et al., 2014; Kadeschid et al., 2020), *Ascaris spp.* (Melo et al., 2016; Wang et al., 2020), *Trichinella papuae* (Mangmee et al., 2020), *Nippostrongylus brasiliensis* and *Trichuris muris* (Yeshi et al., 2020). To date, besides genomic (Hunt et al., 2017) and transcriptomic (Marcilla et al., 2012), metabolomics information of strongyloidiasis infection is quite scarce (Machado et al., 2005; Pace et al., 2018; Jenkins et al., 2018). Therefore, this work presents an untargeted metabolomic analysis of stool samples from patients with strongyloidiasis through high-resolution mass spectrometry intending to annotate metabolites related to this parasitic disease, and then, open opportunities to the development of improved detection methods.

2. Materials and methods

2.1. Study design and sample processing

This study was approved by University of Campinas ethics committee (CAAE 39598214.5.0000.5404) and followed the ethical principles of the Declaration of Helsinki. Stool samples were obtained from routine analysis exceeded samples of the clinical pathology department of University of Campinas Clinics Hospital (HC UNICAMP), in Brazil. Admitted patients had stool collected within 48 h; Controls were completely negative for parasitic infection and positive samples for strongyloidiasis were diagnosed by analysis of fresh stool samples, within 2 to 3 h from collection, through direct microscopic analysis (Hoffman et al., 1934) and Rugai methodologies (Rugai et al., 1954). Patients diagnosed for more than one pathogen were excluded. Control ($n = 15$) group was represented by 66.7% females and mean age (SD) of 48.5 years (±14.2), while positive group for strongyloidiasis ($n = 10$) were represented by 30.0% females and median age (SD) of 53.4 years (±11.7). Prior storage, stool samples (1 g) were resuspended in 10 mL of distilled water followed by centrifugation at 3000 rpm, for 5 min at 15 °C. The stool pellet was resuspended in 30 mL of distilled water repeating the centrifugation step until a clear supernatant was obtained. An aliquot of 1 mL of supernatant was segregated and stored at −80 °C until mass spectrometry analysis.

2.2. Mass spectrometry analysis

An aliquot of 10 μL of the washed stool samples was diluted in 990 μL of methanol: water (1:1) solution, homogenized and ionized with formic acid (0.1% final concentration) prior infusion in an ESI-LTQ-XL Orbitrap Discovery (Thermo Scientific, Bremen, Germany) with nominal resolution of 30,000 FWHM. Spectral data were acquired in triplicate for each sample using the *m/z* range of 100–400 and 400–800. The experiment was optimized using the following parameters: flow rate of 10 μL.min^{-1}, capillary temperature of 280 °C, spray voltage 5 kV and sheath gas 10 (arbitrary units). XCalibur software (v. 2.4, Thermo Scientific, San Jose, CA) was used to visualize mass spectra.

2.3. Statistical analysis and biomarker selection

Relative intensities present in spectral data for each *m/z* feature were extracted, aligned, filtered with interquantile range, normalized (quantile) and tranformed (logaritmic) prior multivariate statistical analysis. Using MetaboAnalyst 5.0 (www.metaboanalyst.ca) online software, we compared *Strongyloides stercoralis* positive group with controls using PLS-DA (Partial Least Square Discriminant Analysis) to determine discriminant features through a Variable Importance in Projection score list higher than 1.7. Metabolites were proposed using an online database, METLIN (Scripps Center for Metabolomics, La Jolla, CA), with mass accuracy < 5 ppm. Metabolites distribution is highlighted by a heat map using Ward's method with Euclidean distance measure. A PCA (Principal Component Analysis) and a new PLS-DA score plots were used to verify similarities within groups and samples. The PLS-DA model was validated through permutation tests (100). Through biomarker analysis package, the most significant ones with AUC (Area Under Curve) higher than 0.80 were selected to build a ROC (Receiver Operating Characteristic) curve for sensitivity and specificity metrics calculation. The ROC curve was validated using permutation tests.

3. Results

Using untargeted metabolomics approach, we acquired high-resolution mass spectrometric data from stool samples of non-infected and *Strongyloides stercoralis* infected patients. The PLS-DA multivariate statistical analysis demonstrated discrimination among control and strongyloidiasis groups on both 100–400 and 400–800 *m/z* ranges (Fig. 1a and b). Most important features were evaluated and annotated as detailed in Table 1. From 18 annotated metabolites, 4 were found decreased on Strongyloidiasis condition (increased in Control group), being those keto-caproic acid (FA 6:1;O), hydroxy-dodecanoic acid (FA 12:0;O), a lysophosphatidylinositol (LPI 20:4) and glucose (hexose). Moreover, 14 metabolites were found enhanced upon infection, being those representants of bilirubin, fatty acids, glycerophospholipids, phospholipids and sugar classes. This last one is represented by mannitol, which was detected in two *m/z* signals, *m/z* 183.0859 $[M + H]^+$ and *m/z* 205.0677 [M+Na]+. A heat map (Fig. 1c) highlighted the metabolites distribution within all samples, where the redder the area, the higher biomarker relative intensity in comparison to the bluer areas, representative of lower intensities. Sample similarity and grouping were projected using PCA and PLS-DA with the annotated metabolites (Supplementary file Fig. S1), and validated through permutation tests (Supplementary file Fig. S2).

To evaluate metabolites significance and potential for diagnostic purposes, a ROC curve was projected with those molecules that showed AUC > 0.8, which, in descending order, were: LPI 20:4, mannitol $[M + H]^+$, glucose, mannitol $[M+Na]^+$, caprylic acid (FA 8:0) and hydroxy-dodecanoic acid (FA 12:0;O). The final obtained AUC corresponded to 0.965, with confidence interval ranging from 0.874 to 1 (see Fig. 2a). Permutation test applied to the AUC using Linear SVM algorithm demonstrated a *p*- value < 0.001. Considering the number of false positive and false negative predictions, the metrics were calculated for the model, which reached specificity of 88.9%, sensitivity of 90.0%, accuracy of 89.3%, positive predictive value of 84.4% and negative predictive value of 93.0% (Fig. 2b and c). Overall, the metrics demonstrated that the annotated metabolites have potential to be further used as infection biomarkers.

4. Discussion and conclusion

Parasitic infection affects millions of people worldwide, where *Strongyloides stercoralis* represents one of these human intestinal parasites (Siddiqui et al., 2011). However, the knowledge about metabolic alterations in stool samples of patients with strongyloidiasis is quite

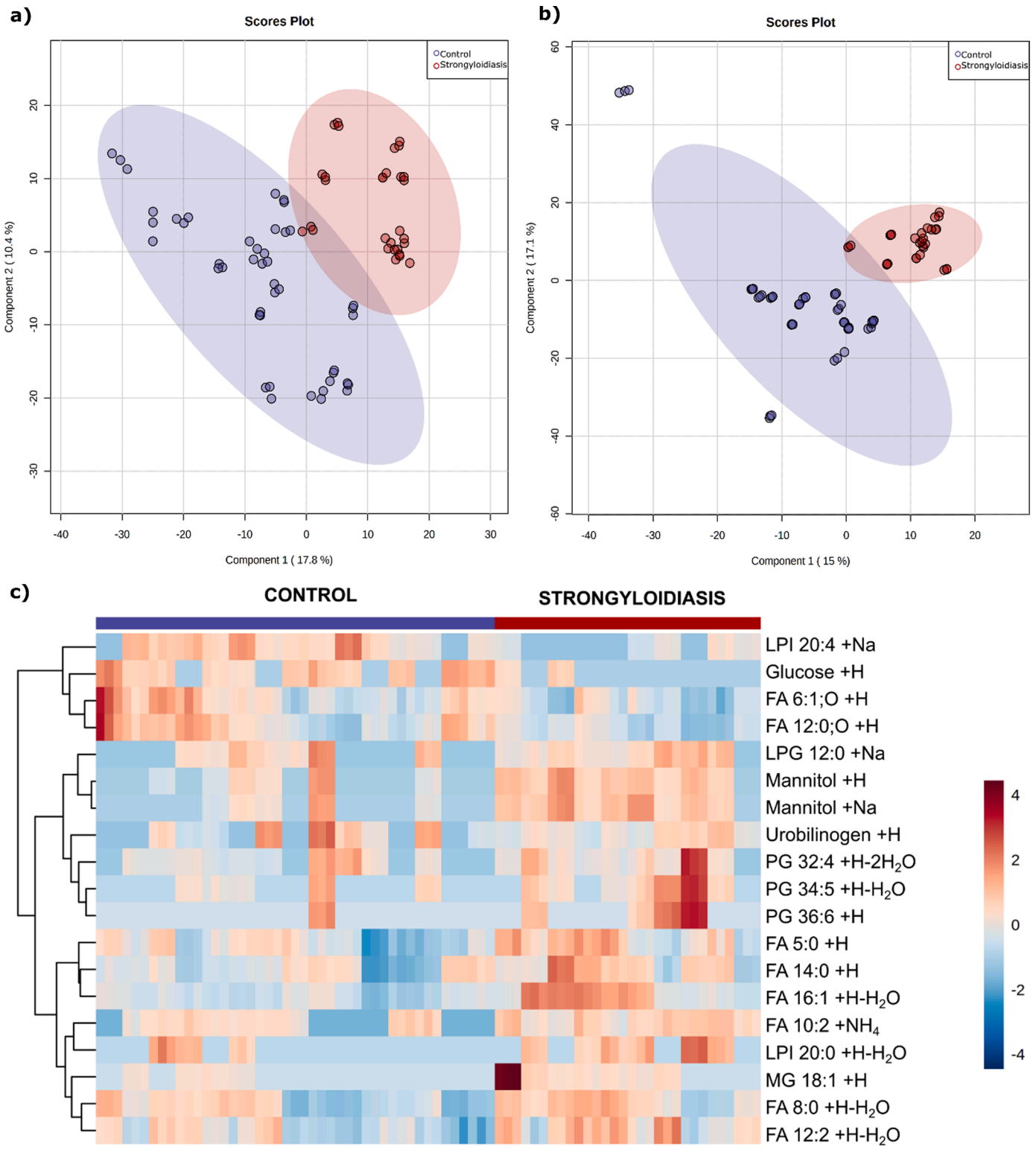

Fig. 1. Multivariate statistical analysis using PLS-DA of mass spectrometry data acquired in *m/z* 100–400 (a) and *m/z* 400–800 (b) ranges in the positive ion mode for the Controls (blue) and Strongyloidiasis (red) groups. Proposed markers distribution within samples are highlighted using heat map analysis (c), on which a scale from red to blue determine markers' level intensities from higher to lower, respectively. Abbreviations: FA – Fatty acid; LPI – Lysophosphatidylinositol; LPG – Lysophosphatidylglycerol; MG – Monoacylglycerol; PG – Phosphatidylglycerol.

scarce (Machado et al., 2005; Pace et al., 2018; Jenkins et al., 2018). Recently, metabolomics approaches appeared as tools for the annotation of potential disease biomarkers. On a study with fecal samples, a connection between metabolomic profile of strongyloidiasis and microbiome analysis was established; metabolites such as short-chain fatty acids and amino acids present in altered abundances in infected subjects supported the maintenance of specific bacteria classes (Jenkins et al., 2018). In this context, the modulation of microbiome can be inferred in the present study by the annotation of mannitol as increased marker, which is not produced by mammal cells. Heterofermentative

Table 1
Decreased and increased proposed markers for Strongyloidiasis.

Strongyloidiasis	Category	Exact *m/z*	Molecule	Adduct	Molecular Formula	Error (ppm)
Decreased	Fatty acids	131.0702	FA 6:1;O	$[M+H]^+$	$C_6H_{10}O_3$	1.11
		217.1794	FA 12:0;O	$[M+H]^+$	$C_{12}H_{24}O_3$	1.76
	Phospholipids	643.2885	LPI 20:4	$[M+Na]^+$	$C_{29}H_{49}O_{12}P$	−4.81
	Sugar	181.0712	Glucose	$[M+H]^+$	$C_6H_{12}O_6$	−2.95
Increased	Bilirubin	593.3344	Urobilinogen	$[M+H]^+$	$C_{33}H_{44}N_4O_6$	−1.70
	Fatty acid	103.0753	FA 5:0	$[M+H]^+$	$C_5H_{10}O_2$	1.37
		145.1221	FA 8:0	$[M+H\text{-}H_2O]^+$	$C_8H_{16}O_2$	1.23
		179.1427	FA 12:2	$[M+H\text{-}H_2O]^+$	$C_{12}H_{20}O_2$	4.78
		186.1485	FA 10:2	$[M+NH_4]^+$	$C_{10}H_{16}O_2$	1.83
		229.2158	FA 14:0	$[M+H]^+$	$C_{14}H_{28}O_2$	1.94
		237.2208	FA 16:1	$[M+H\text{-}H_2O]^+$	$C_{16}H_{30}O_2$	4.23
	Glycerolipids	357.2989	MG 18:1	$[M+H]^+$	$C_{21}H_{40}O_4$	2.87
	Phospholipids	451.2085	LPG 12:0	$[M+Na]^+$	$C_{18}H_{37}O_9P$	−4.06
		611.3558	LPI 20:0	$[M+H\text{-}H_2O]^+$	$C_{29}H_{57}O_{12}P$	0.27
		679.4370	PG 32:4	$[M+H\text{-}2H_2O]^+$	$C_{38}H_{67}O_{10}P$	−3.82
		723.4627	PG 34:5	$[M+H\text{-}H_2O]^+$	$C_{40}H_{69}O_{10}P$	−3.54
		767.4872	PG 36:6	$[M+H]^+$	$C_{42}H_{71}O_{10}P$	−1.84
	Sugar	183.0859	Mannitol	$[M+H]^+$	$C_6H_{14}O_6$	1.98
		205.0677	Mannitol	$[M+Na]^+$	$C_6H_{14}O_6$	2.75

Metabolites considering structural and geometric isomers. Lipids represented by class, carbon number: double bond. Abbreviations: FA – Fatty acid; LPI – Lysophosphatidylinositol; LPG – Lysophosphatidylglycerol; MG – Monoacylglycerol; PG – Phosphatidylglycerol.

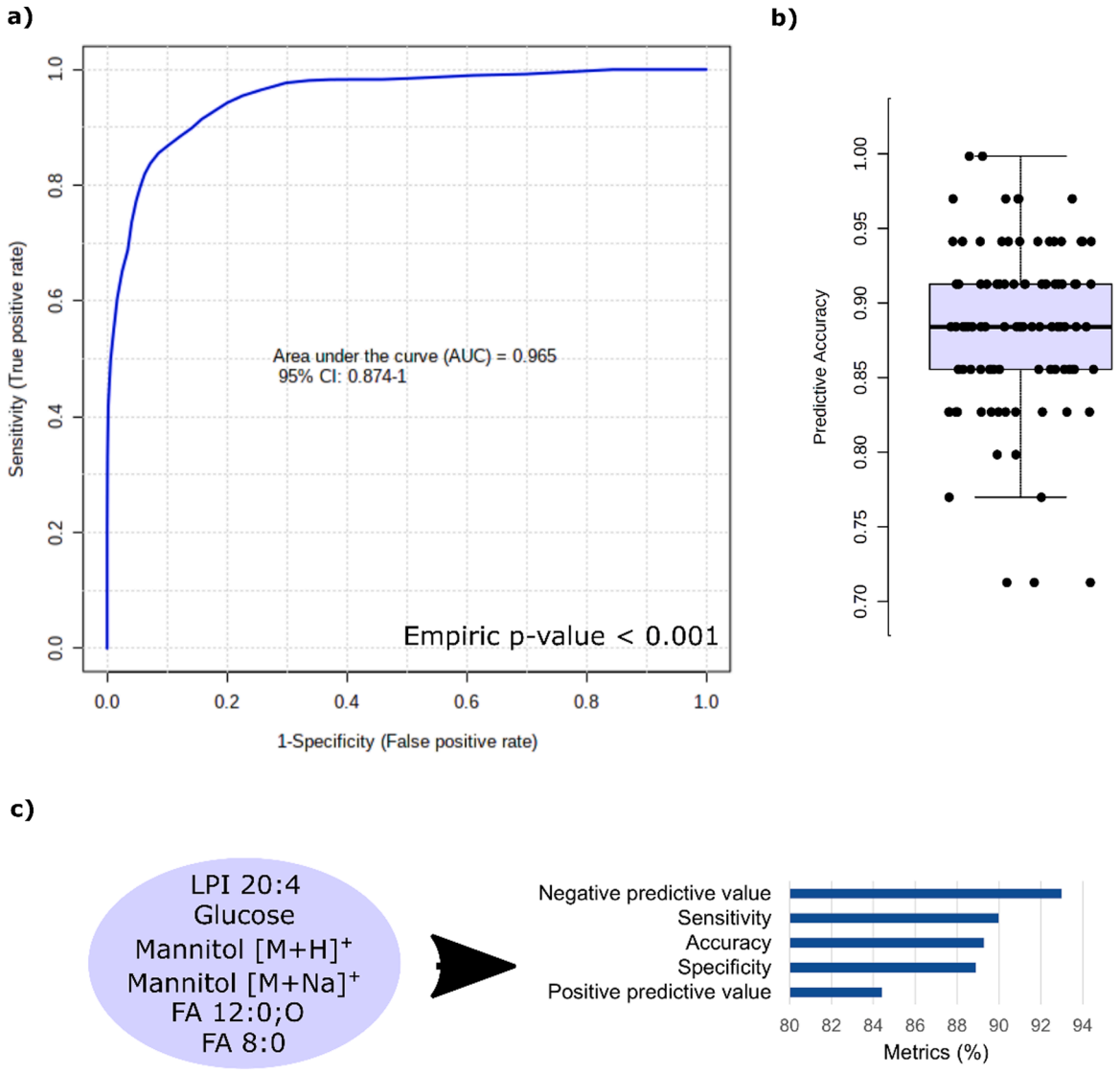

Fig. 2. Use of 6 annotated biomarkers for ROC curve projection (a) and permutation (1000). Predicted accuracy (b) and performance metrics (c) were used to assess the selected markers impact for diagnostic purposes.

lactobacilli, such as *Lactobacillus brevis* present in human gastrointestinal tract, have been reported to produce mannitol, using especially fructose as carbohydrate source (Wisselink et al., 2002). In addition, mannitol has been reported to protect microorganisms and accumulate under stress conditions (Chaturvedi et al., 1997). Besides the increase of mannitol, our analysis identified reduced levels of fecal glucose, an energy source for fermentative bacteria (Thompson, 1987), and increased levels of urobilinogen, which is synthesized from bilirubin deconjugation promoted by intestinal bacterial β-glucuronidases (Saxerholt et al., 1986; Fahmy et al., 1972). As an infection, strongyloidiasis might modulate intestinal environment and induce significant changes in the microbiota (Jenkins et al., 2018), which may explain the disrupted levels of these metabolites.

Besides sugar and bilirubin constituents, phospholipids were other main metabolites found increased in infected individuals, especially phosphatidylglycerol (PG). Still, phospholipids are important cell membrane constituent and have been observed altered during life cycle of *Caenorhabditis elegans* (Lam et al., 2017) and *Schistossoma mansoni* (Ferreira et al., 2014a). In addition, we reported three lysophospholipids (LPLs) species, both increased and decreased in strongyloidiasis. Scientific literature has been shown that LPLs effects over immune response are not completely clear. Some studies present proinflammatory effects induced by LPLs, such as production of IL-1β and IL-6 cytokines (Vladykovskaya et al., 2011; Zhao et al., 2008), in contrast to observed anti-inflammatory response (Hung and Kim, 2011; Nishikawa et al., 2015), which demonstrate the complexity of LPLs biochemical signaling pathways. Considering immune modulation, *Strongyloides spp.* infection have been reported to increase humoral response through the activation of Th2 lymphocytes and induction of eosinophils differentiation and activation (Iriemenam et al., 2010). In this context, further studies are required to clarify the role of LPLs in *S. stercoralis* infection and their real effects within the disease.

Monoacylglycerol (MG) represents another increased metabolite present in stool samples infected with *S. stercoralis*. A study observed that some parasitic nematodes, including *S. stercoralis*, show synthetic enzymes for MG, such as the diacylglycerol lipase (DAGL); increased DAGL activity is involved with monoacylglycerol synthesis as well as with synthetic endocannabinoid pathways (Batugedara et al., 2018). Interestingly, endocannabinoids have been reported as immune regulators, even in intestinal epithelial cells (DiPatrizio. et al., 2011), associated with improved host immunity, where high levels of endocannabinoids activate cannabinoid receptors and induce Th2 immune response (Batugedara et al., 2018). Moreover, decreased and increased levels of fatty acids were annotated. Alterations on nutrients absorption by the host and acquisition by the parasite may influence the fecal biochemical composition profile (Mondal et al., 2016). When lipids are evaluated, they are essential for cell membrane constitution, such as parasite cuticle assembly (Lee, 2010)() and larvae development, such as palmitic acid (C16) (Minematsu et al., 1989). Therefore, the annotation of phospholipids, lysophospholipids, monoacylglycerol and fatty acids may be associated with altered microbiota profile under parasitic infection, be a reflect of host immune response as well as part of the parasitic structural constitution.

Conversely, the annotated metabolites should be further investigated prior to clinical translation, considering that our study presented as limitations the small number of recruited patients, the absence of co-infected and/or positive samples for other parasitic diseases, that could improve metabolites specificity to *S. stercoralis* infection and the elimination of confounding factors for differential diagnosis, as well as the absence of information regarding parasite load in the samples. Although the sensitivity of the proposed method cannot be directly associated with detection on low parasitic load, the methodology was based on a highly diluted solution, regardless of the presence of the parasite on the metabolomic stool sample, which even in these circumstances enabled the annotation of relevant metabolites of strongyloidiasis. Hence, our work brought to light some fecal metabolic alterations due to human strongyloidiasis, which might be valuable assets in defining new tools for diagnosis. Considering the involvement of the annotated metabolites with microbiota modeling, parasite constitution, and host response, the results are promising as preliminary measurements of *S. stercoralis* infection metabolites.

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Data availability

Pre-processed mass spectrometry data is available at Zenodo: https://doi.org/10.5281/zenodo.5807588.

CRediT authorship contribution statement

Allan Daniel Ribeiro Sotelo Montanhaur: Formal analysis, Writing – original draft. **Estela de Oliveira Lima:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft. **Jeany Delafiori:** Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Cibele Zanardi Esteves:** Conceptualization, Methodology. **César Corat Ribeiro Prado:** . **Silmara Marques Allegretti:** Conceptualization, Resources, Writing – review & editing. **Marlene Tiduko Ueta:** Conceptualization, Resources, Writing – review & editing. **Carlos Emílio Levy:** Conceptualization, Resources, Writing – review & editing. **Rodrigo Ramos Catharino:** Conceptualization, Resources, Writing – review & editing, Supervision.

Declarations of Competing Interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actatropica.2021.106279.

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