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Characteristics of the gut microbiome and associated metabolites of tuberculosis patients in Xinjiang, China as determined by microbiome and metabolomics analyses

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Abstract

Objective: Integrated microbiome and metabolome analyses were conducted to describe the diversity, composition, function, and metabolite profiles of the intestinal microbiota of Uygur populations with active pulmonary tuberculosis (PTB) and latent tuberculosis infection (LTBI) to elucidate the mechanisms underlying microbiome-host interactions.

Methods: In this case-control study, fecal samples were collected from patients with PTB and LTBI, as well as healthy controls (HC). Then, 16S ribosomal RNA (rRNA) sequencing was performed to assess the diversity and composition of the gut microbiota. Metagenomics functional analysis, liquid chromatography-tandem mass spectrometry untargeted metabolomics, and Lasso regression model were used to identify metabolites as potential diagnostic biomarkers. Finally, correlation analysis was performed to assess associations between microbial metabolites and disease.

Results: In total, 170 samples were collected. The results of 16S rRNA sequencing revealed changes to the diversity and composition of the gut microbiota in the PTB group. Metagenomics analysis of 58 samples showed functional differences among the three groups. Pathways associated with valine, leucine, and isoleucine biosynthesis, mismatch repair, and streptomycin biosynthesis were significantly enriched in the PTB, LTBI, and HC groups, respectively. Metabolomics analysis of 90 samples found unique differential metabolites between the PTB/HC, LTBI/HC, and PTB/LTBI groups, which were screened by Lasso regression analysis as potential biomarkers. The single metabolites with the highest diagnostic efficiency among the three comparison groups were nicotinamide (area under the curve [AUC] = 0.90; 95% confidence interval [CI] = 0.82–0.98), adenine (AUC = 0.83; 95% CI = 0.73–0.94), and pyocyanin (AUC = 0.97; 95% CI = 0.94–1.00). The results of Spearman correlation analysis revealed that the three metabolites had the highest correlations with microbes, especially the correlation between pyocyanin and *Oscillospira* species in the PTB vs. LTBI group ($R = 0.80, p < 0.001$).

Conclusion: Multi-omics analysis found that microbe and metabolite levels changed in response to the state of MTB infection and microbe-associated metabolites were

effective diagnostic biomarkers. These findings provide clues for exploring the interactions between microbes and host and to elucidate the underlying mechanisms.

Keywords: Tuberculosis; Latent tuberculosis infection; 16S rRNA; Metagenomics; Metabolomics;

Introduction

Tuberculosis (TB) is a chronic infectious disease mainly affecting the lungs that is caused by *Mycobacterium tuberculosis* (MTB). The Global Tuberculosis Report 2025 issued by the World Health Organization (WHO) identified 10.7 million new cases of TB worldwide, with an incidence of 131 per 100,000 population. In China, the estimated number of new cases is 696,000, with an incidence of 49 per 100,000 population, accounting for 6.5% of the global burden. This figure is lower than that of India (25%), Indonesia (10%), and the Philippines (6.8%) [1]. TB develops relatively slowly, as about 25% of cases globally (~2 billion) are diagnosed with latent TB infection (LTBI), including 5%–10% likely to develop active disease [2]. The state of MTB infection is co-regulated by the host immune response and pathogenic potential of the bacteria through a variety of factors, which may include the host microbial community [3]. The microbiota is a dynamic ecosystem that plays important roles in human health, especially the gut microbiota [4], which is closely related to immune function.

There is a growing body of evidence of a relationship between MTB infection and the gut microbiota. Studies using mouse models have found that the diversity of the gut microbiota decreased after MTB infection [5] and following treatment with antibiotics [6]. In patients with PTB, an increase in the abundance of *Bacteroides* is related to systemic inflammation [7]. As compared to the healthy control (HC) and LTBI groups, there were significant differences in the composition of the gut microbiota of patients with PTB treated with antibiotics [8]. However, most previous studies investigated the composition and diversity of the gut microbiota. Hence,

metagenomic studies on the function of gut microbiota are needed to further understand the pathogenesis of MTB infection.

As an intracellular parasitic bacterium, MTB relies on the host cell for most nutrients, thereby disrupting metabolism [9]. The widespread application of metabolomics studies of MTB infection can comprehensively investigate changes to the endogenous metabolites and phenotype of the host cell [10]. The results of previous metabolomics studies of sputum, blood, breath, and urine samples have been notably heterogeneous [11-14]. The fecal metabolome can serve as an intermediate phenotype reflecting host-microbiome interactions and is a powerful tool to complement microbiome studies [15].

Xinjiang is an autonomous territory in northwest China populated by multiple ethnicities with a relatively high burden of MTB infection, and Uyghur has the highest population proportion. Therefore, Uyghur populations with PTB, LTBI, and HCs residing in Xinjiang were selected to systematically characterize differences in fecal microbial communities, functions, and metabolic profiles of the different states of MTB infection using 16S ribosomal RNA (rRNA) sequencing, metagenomics and metabolomics, respectively, to provide new directions for TB prevention and control.

Materials and methods

Study Design and Sample Collection

A case-control study was carried out in the present investigation. The case inclusion criteria and fecal sample collection method are as described in a previous article [16]. The study cohort of 170 subjects who met the inclusion criteria, included 69 with PTB, 51 with LTBI, and 50 with HCs. Age, gender, and body mass index were still comparable among the three groups. At least three fecal samples from each subject were collected and stored in sterile collection tubes and containers for later use.

DNA Extraction and Metabolite Extraction

Total microbial genomic DNA samples were extracted using the the QIAamp DNA Stool Mini kit (QIAGEN, Inc., Netherlands), following the instructions of the manufacturer and stored at -20°C prior to further assessment. The quantity and quality of extracted DNAs were measured using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and agarose gel electrophoresis, respectively.

Samples were slowly thawed at 4°C , 100-mg fecal samples were accurately weighed, 1 mL precooled methyl alcohol/acetonitrile/water (2:2:1, v/v) was added and adequately vortexed. After ultrasonic decomposition at low temperature for 30 min, the samples are incubated for 10min at -20°C to precipitate the protein, and then centrifuged (14000g, 4°C , 20 min). The supernatants were collected and dried under vacuum, and then stored at -80°C standby. Redissolve the sample in 100 μL acetonitrile/water (1:1, v/v) and adequately vortexed, and then centrifuged (14000rpm, 4°C , 15 min). The supernatants were collected for LC-MS/MS analysis.

16S rRNA Gene Sequencing Analysis

The 16S rRNA sequencing analysis approach was performed as described in our previous study [17]. Briefly, target fragment PCR amplification, sequencing library preparation and sequencing, the raw data was analyzed.

Metagenomic Shotgun Sequencing Analysis

The extracted microbial DNA was processed to construct metagenome shotgun sequencing libraries with insert sizes of 400 bp by using Illumina TruSeq Nano DNA LT Library Preparation Kit. Each library was sequenced by Illumina NovaSeq platform (Illumina, USA) with PE150 strategy at Personal Biotechnology Co., Ltd. (Shanghai, China). Raw sequencing reads were processed to obtain quality-filtered reads for further analysis. The clean data of each sample were assembled, and the generated contigs (longer than 200bp) were then pooled together and clustered using mmseqs2. MetaGeneMark was used to predict the genes in the contigs. The functionality of the non-redundant genes were obtained by annotated using mmseqs2 against the protein databases of Kyoto Encyclopedia of Genes and Genomes (KEGG).

Fecal Metabolic Analysis

Sample separation was performed using an ultra-high-performance liquid chromatography (UHPLC, 1290 Infinity LC, Agilent Technologies). The mobile phase of chromatography was composed of buffer A (Water +25 mM ammonium acetate +25 mM ammonium hydroxide) and buffer B (Acetonitrile). The gradient was 95% B for 1 min and was linearly reduced to 65% in 13 min, and then was reduced to 40% in 2 min and kept at 40% for 2 min, and then increased to 95% in 0.1 min, with a 5 min re-equilibration period employed. Analyses were performed using an UHPLC coupled to a quadrupole time-of-flight (AB SCIEX Triple TOF 6600). The electrospray ionization (ESI) source conditions following HILIC separation were set as follows: Ion Source Gas1 (Gas1) as 60, Ion Source Gas2 (Gas2) as 60, curtain gas (CUR) as 30, source temperature: 600°C, Ion Spray Voltage Floating (ISVF) 5500 V in positive mode, and -5500 V in negative mode. In MS only acquisition, the instrument was set to acquire over the m/z range 60-1000 Da, product ion scan m/z range 25-1000 Da, TOF MS scan accumulation time 0.20 s/spectra, product ion scan accumulation time 0.05 s/spectra. The product ion scan is acquired using information dependent acquisition (IDA). The collision energy (CE) was fixed at 35 eV with $\pm$ 15eV. Declustering potential (DP) was set as $\pm$ 60 V. IDA was set as follows: Exclude isotopes within 4 Da, Candidate ions to monitor per cycle:6.

Bioinformatics and Statistical Analysis

The 16S rRNA sequencing data, alpha diversity indices, and Kruskal–Wallis H test were used to assess differences among the three groups. Dunn's test was used for post-hoc pairwise comparisons. Beta diversity was described by nonmetric multidimensional scaling using UniFrac distance metrics. Analysis of similarities was used to examine differences between groups, while correlation network analysis was used to explore and visualize associations among microbial communities. After removal of unidentified, unclassified, and unassigned organisms, the top 100 genera were selected for Spearman correlation analysis and correlation networks of the three groups were constructed (correlation coefficient > 0.6 and $p < 0.05$).

For metagenomic analysis, 58 samples for sequencing were selected based on the results of metabolomics analysis, which included 20 patients with PTB 20 with LTBI, and 18 HCs. Principal component analysis (PCA) was performed to identify the functional units of the samples. The biological functions of selected genes were determined in reference to the KEGG database. The Kruskal–Wallis H test was used to assess differences among the three groups. Finally, linear discriminant analysis effect size (LEfSe) was used to identify signature metabolic pathways among the three groups, where significantly enriched pathways were based on linear discriminant analysis (LDA) values > 3.0 and $p < 0.05$. Histogram of LDA scores and cladogram illustrating the functional taxa exhibiting significant differences between groups.

Metabolomics analysis, based on the 16S rRNA sequencing data, was performed using 30 samples with good reproducibility within the group and large differences among the groups. The raw mass spectrometry (MS) data were converted to MzXML files using ProteoWizard msConvert (<https://proteowizard.sourceforge.io/>) and processed using XCMS software (<https://xcmsonline.scripps.edu/>) for feature detection, retention time correction, and alignment. The metabolites were identified by accurate measurement of the mass (<25 ppm) and matching of the MS/MS data to a standard database. PCA of the peaks extracted from all experimental and quality control samples was performed to assess the quality of experimental data. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to visually compare metabolite profiles. The model evaluation parameters R^2 and Q^2 obtained through seven-fold cross-validation were used to evaluate the reliability and stability of the model. The OPLS-DA algorithm with Variable Importance in Projection (VIP) scores > 1 and $p < 0.05$ were used as the screening criteria to identify significant differences in metabolites among the groups. A Venn diagram was generated to visualize both shared and unique metabolites obtained by pairwise comparisons. Lasso regression analysis was performed to identify potential signature metabolites. The area under the receiving operating characteristic (ROC) curve (AUC) of the

201 filtered variables and the 95% confidence interval (CI) were calculated. The ROC
202 curves of single metabolites in each group were evaluated.

203 The Mann–Whitney U Test was used to compare the abundances of the top 50
204 amplicon sequence variants (ASVs). Spearman correlation analysis was performed to
205 identify differences in the abundances of the ASVs and metabolites screened by
206 Lassos regression analysis among the groups. The results are presented as a heatmap.
207 A p value of < 0.05 was considered statistically significant. Statistical analyses were
208 conducted using IBM SPSS Statistics for Windows, version 21.0. (IBM Corporation,
209 Armonk, NY, USA) and R software (V4.0.2; <https://cran.r-project.org/>).

211 Results

212 16S rRNA sequencing

213 A total of 170 participants were enrolled in this study, including 69 patients with PTB,
214 51 individuals with LTBI, and 50 HC. No statistically significant differences were
215 observed among the three groups in terms of age, gender, BMI, smoking status, or
216 alcohol consumption (Table S1A).

217 After quality filtering, denoising, merged, and non chimeric, a total of 8,130,425
218 high-quality reads were obtained from all subjects. On average, 47,826 reads were
219 generated per sample. Taxonomic annotation revealed a total of 23 phyla, 81 classes,
220 151 orders, 277 families, 598 genera, and 834 species (Table S2). There were notable
221 differences in the alpha and beta diversity indices among the groups ($p < 0.001$)
222 (Figure 1A and 1B, respectively).

223 Putative key genera were identified to determine whether MTB infection and the
224 incidence of TB altered the structure and interactions of the gut microbiota. The
225 results found significant correlations in the HC group as compared to the PTB and
226 LTBI groups. In the HC group, there were significant correlations among the genera
227 *Erysipelothrix*, *Gallicola*, *Vagococcus*, *Facklamia*, *Tissierella_Soehngenia*,
228 *Trichococcus*, and *Alcaligenes* and others. In the LTBI and PTB groups, three genera
229 were most associated with others (Figure S1A–C). In general, there were differences
230 in the diversity and composition of the microbiota among the three groups.

Metagenomics analysis

As shown in Table S1B, a total of 58 participants (20 PTB, 20 LTBI, and 18 HC) were recruited. There were also no statistically significant differences among the three groups regarding age, sex, BMI, smoking status, or alcohol consumption.

To further understand the function of the gut microbiota, metagenomics analysis of all samples was conducted. The PCA results revealed significant functional differences among the three groups ($p < 0.001$) (Figure 2A). At level I pathways, the relative abundance of the metabolic pathway was the highest across all groups, followed by Genetic Information Processing. (Figure 2B). In total, 41 level II pathways were annotated (Figure 2C), which included 17 with significant differences among the groups (Figure 2D). The LEfSe results found that at level III, enriched pathways of the PTB, LTBI, and HC groups included “valine, leucine, and isoleucine biosynthesis”, “mismatch repair”, and “streptomycin biosynthesis”, respectively (Figure 2E,2F). The distribution of the three pathways in each group is shown in Figure 2G.

Metabolomics analysis

The metabolomes of 90 samples (30/group) were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). No significant differences were observed in baseline characteristics except for occupational type (Table S1C). The PCA results showed that quality control samples were tightly clustered, indicating reliability of the data (Figure 3A). The results of OPLS-DA showed clear separation of the metabolites among the three groups (Figure 3B, 3C, and 3D, respectively).

In total, 1564 metabolites were identified. The unique and common metabolites among the three groups are presented as a Venn diagram (Figure 3E). Lasso regression analysis of 35 unique metabolites between the PTB and HC groups, 35 between the LTBI and HC groups, and 59 between the PTB and LTBI groups, identified 16, 19, and 14 metabolites, respectively, as potential biomarkers (TableS3A-C). Single metabolites with the largest AUC values between the PTB/HC, LTBI/HC, and PTB/LTBI groups included nicotinamide (AUC = 0.90; 95% CI = 0.82–0.98) adenine (AUC = 0.83; 95% CI = 0.73–0.94), and pyocyanin (AUC = 0.92;

95% CI = 0.74–1.00), respectively. Notably, the diagnostic efficacy of combined metabolites was greater than that of single metabolites (Figure 3F–H; Table S3A–C).

Correlation between gut microbiota and metabolites

Based on the results of 16S rRNA sequencing, differences in the most abundant 50 ASVs were analyzed. The results identified 28 differential ASVs between the PTB and HC groups, 19 between the LTBI and HC groups, and 30 between the PTB and LTBI groups. The results of Spearman correlation analysis and the differential metabolites identified by Lasso regression analysis showed that ASV_38093 (nicotinamide) had the strongest correlation in the PTB vs. HC groups ($R = -0.53$, $p < 0.001$), which was annotated as *f_Lachnospiraceae* and *g_Ruminococcus*. In the LTBI vs. HC groups, ASV_83244 was positively correlated with adenine ($R = 0.55$, $p < 0.001$) and annotated as *f_Prevotellaceae* and *g_Prevotella*. In the PTB vs. LTBI groups, ASV_94592 ($R = 0.80$, $p < 0.001$) and ASV_56035 ($R = 0.79$, $p < 0.001$) were positively correlated with pyocyanin and annotated as *f_Ruminococcaceae* and *g_Oscillospira* (Figure 4A, B, and C, respectively). The single metabolites with the highest diagnostic efficacy were also the most relevant to microbes.

Discussion

This study is the first to characterize the fecal microbiome of patients with MTB infection and disease in the Uyghur population of Xinjiang by integrating 16S rRNA gene sequencing, metagenomic sequencing, and LC–MS/MS-based metabolomics. The results showed that the diversity, composition, and function of the gut microbiota, and fecal metabolic phenotype were significantly altered by the state of MTB infection, demonstrating that microbe-associated metabolites can be used as diagnostic biomarkers.

Our previous study, based on 16S rRNA gene sequencing, identified differences in microbial composition and diversity between patients with active-TB and latent MTB infection in the Uyghur[16] and Han[17] populations. In the present study with an expanded sample size of 170 Uyghur participants, these differences still existed. The

289 results of correlation network analysis indicated perturbations to the gut microbiota
290 interaction network in the PTB and LTBI groups as compared to the HC group.

291 Metagenomics analysis was performed to further explore the impact of altered
292 microbial function on disease. In the three groups, most (~70%) of the enriched
293 pathways were associated with metabolism, while about 20% were associated with
294 genetic information processing. The results of LEfSe analysis showed that pathways
295 associated with amino acid metabolism and valine, leucine, and isoleucine
296 biosynthesis were significantly enriched in the PTB group. Amino acid balance is
297 especially important to maintain cell regulation and metabolism, including
298 gluconeogenesis, proteolysis, and oxidative catabolism [18]. Some amino acids,
299 including leucine, isoleucine, valine, phenylalanine, aspartate, and glutamate, were
300 found to be at higher levels in TB patients[19], which is in close agreement with our
301 observations. In addition, the pathways of metabolism of cofactors and vitamin was
302 only secondary to amino acid metabolism in portance, previous study of HU et al [20].
303 and Song et al [21]. also confirmed this pathway was representative in TB. In the
304 LTBI group, the mismatch repair pathway, which is essential to maintain genomic
305 stability, was enriched. Hypermutable bacterial pathogens are often associated with
306 defects in mismatch repair and increased risks of clinical infections, such as MTB [22,
307 23]. The streptomycin biosynthesis pathway, which was enriched in the HC group, is
308 associated with resistance to infection and pathogenesis of MTB.

309 Microbiome studies based on high-throughput gene sequencing have greatly
310 enhanced the understanding of the roles of microbes in health and disease. However, a
311 single method is insufficient to comprehensively assess the pathogenesis of MTB,
312 thus integrated multi-omics analysis is imperative. Fecal metabolome characterization
313 can improve current understanding of the responses of the gut microbiota to
314 perturbations [24]. In the present study, untargeted metabolomics of stool samples and
315 Lasso regression analysis were employed to identify metabolites as potential
316 biomarkers of MTB infection. The results found that nicotinamide, adenine, and
317 pyocyanin had the highest diagnostic efficacy.

Nicotinamide is an amide form of vitamin B3 with anti-inflammatory effects that has been implicated in diseases of the respiratory tract, immune system, and metabolism [25-29]. In a mouse model of lung inflammation, nicotinamide was found to promote apoptosis of neutrophils in response to neutrophilic inflammation of the lungs [29]. Adenine, formally known as vitamin B4, was identified as novel allosteric activator of MTB pyruvate kinase [30], which senses changes to energy and sugar levels during MTB infection [31]. In addition, MTB replication in macrophages results in necroptosis and bacterial dissemination. Necrosis of the infected macrophages is caused by tuberculosis necrotizing toxin via hydrolysis of nicotinamide adenine dinucleotide (NAD⁺). In general, NAD⁺ depletion triggers macrophage necroptosis [32, 33]. Nicotinamide is the precursor of NAD⁺ and adenine is involved in the synthesis of NAD⁺, thereby providing a mechanistic explanation for the identification of both metabolites. A previous study found that MTB infection increased the content of NAD⁺ in macrophages [34]. In the present study, nicotinamide content was increased in the PTB group and adenine was increased in the LTBI group as compared to the HC group. Pyocyanin, a main phenazine produced by *Pseudomonas aeruginosa* [35], is an electrochemically active metabolite with antibacterial properties [36] and antagonistic activities against pathogenic bacteria, including like *Salmonella paratyphi*, *Klebsiella pneumonia*, *Escherichia coli*, and *Staphylococcus aureus* [37]. In addition, pyocyanin was reported to downregulate levels of interleukin-1 β , tumor necrosis factor- α , and nitric oxide, which exerts anti-inflammatory effects in mouse peritoneal macrophages [38]. However, it remains unclear whether pyocyanin has antagonistic activities against MTB or modulates inflammation. The content of pyocyanin was significantly higher in the LTBI group than the PTB group, suggesting that higher content of pyocyanin can prevent progression of LTBI to PTB.

When describing the correlation between microbes and metabolites, the single metabolite with the highest diagnostic efficacy among the three comparison groups also had the strongest correlation with the genera *Ruminococcus*, *Prevotella*, and *Oscillospira*, respectively. *Ruminococcus*, the first genus of bacteria identified in the

stomach, obtains nutrients by breaking down cellulose in the digestive system of the host and degrades resistant starch [39]. A prior study found that an increase in the content of *Ruminococcus* is correlated with respiratory allergy in infants [40]. A cohort study of the bacillus Calmette–Guérin vaccine found that the specific response, measured by interferon- γ production upon MTB stimulation, was negatively associated with the abundance of *Ruminococcus*, indicating that an increase in MTB is related to a decrease in *Ruminococcus* [41]. In the present study, the abundance of *Ruminococcus* was significantly reduced in the PTB group as compared to the HC group. *Prevotella*, a dominant bacterial genus colonizing both the intestinal and respiratory tracts[42], was significantly depleted in the PTB group in our Han-Chinese cohort. Although there is no consensus on the relationship with TB [43], Dillon et al. showed that the abundance of *Prevotella* was positively correlated with the number of CD4+ and CD8+ immune cells, indicating that *Prevotella* is a potential biomarker of immune function [44]. Dysregulation of the gut microbiota in TB patients is specifically characterized by a decrease in the abundance of *Prevotella* [45]. In the present study, bacteria content was generally higher in the LTBI group than the PTB and HC groups. *Oscillospira* species, which are difficult to culture and grow slowly, account for a large proportion of intestinal microorganisms. *Oscillospira* species, as producers of butyrate and short-chain fatty acids, play important roles in human health and disease [46]. Inflammatory diseases characterized by reduced abundance of *Oscillospira* species [47], include Crohn's disease [48], nonalcoholic fatty liver disease [49], and aging (a low-grade chronic inflammation characterized by elevated circulating levels of inflammatory mediators) [50]. In the present study, the abundance of *Oscillospira* species was also decreased by MTB infection.

Interestingly, we found *Ruminococcus*, *Prevotella* were the strongest correlated with metabolites of vitamins B in PTB/HC and LTBI/HC groups, respectively. Vitamin metabolism pathways were proved to be important by LEfSe analysis, therefore, we hypothesized that both bacteria affect the MTB infection and the pathogenesis of TB by regulating vitamin metabolism pathways. However, the interaction mechanism between the probiotic *Oscillospira* and the metabolite

Pyocyanin need to be studied more closely. In general, the results of correlation analysis confirmed that microbe-derived metabolites can be used as diagnostic biomarkers and preliminarily explored the possible mechanisms.

Conclusion

Fecal samples were collected from the Uygur population of Xinjiang, China with PTB and LTBI for 16S rRNA sequencing and metagenomics analysis. The results found notable differences in the diversity, composition, and function of intestinal microbiota between the PTB and LTBI groups. In addition, microbe-associated metabolites were identified as potential biomarkers of the onset and progression of pulmonary TB. These findings also provide clues for study the mechanisms underlying the state of microbial diseases.

Ethics Statement

All research subjects provided signed informed consent before sample collection and the protocol was approved by the Ethics Committee of First Affiliated Hospital of Xinjiang Medical University (20180223-159). The patients/participants provided their written informed consent to participate in this study.

Data availability statement

The sequence data of this study have been deposited in the GenBank Sequence Read Archive (SRA) of NCBI under the accession code BioProject: PRJNA795263 and PRJNA879909 for 16S rRNA sequencing, PRJNA881732 for Metagenomic data.

Author contributions

YW: Conceptualization, Investigation, Formal analysis, Data curation, Visualization, Writing-original draft, Writing-review & editing. JG: Data curation, Visualization, Writing-review & editing. ZL: Writing-original draft, Investigation. YC: Investigation, Formal analysis, Visualization. YX: Conceptualization, Supervision, Funding acquisition, Project administration. XP: Writing-review & editing, Resources, Funding

acquisition; All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Figure 1. 16SrRNA results of the three groups (A) Alpha diversity indices. (B) Beta diversity represent by nonmetric multidimensional scaling.

Figure 2. Metagenomics results of the three groups (A) PCA of microbial function. (B) The distribution of KEGG pathways at level I. (C) The distribution of KEGG pathways at level II. (D) Differential metabolic pathways at level II. (E) Cladogram of the LEfSe results for microbial function. (F) Distribution of LDA scores for significantly differential pathways. (G) Distribution of the abundance of three enriched pathways.

Figure 3. Untargeted metabolomics results (A) PCA score plots of the three groups. OPLS-DA score plots for comparison of the (B) PTB vs. HC groups ($R^2 X = 0.172$,

$R^2 Y = 0.991$, $Q^2 = 0.773$), (C) LTBI vs. HC groups ($R^2 X = 0.154$, $R^2 Y = 0.933$, $Q^2 = 0.249$), and (D) PTB vs. LTBI groups ($R^2 X = 0.132$, $R^2 Y = 0.972$, $Q^2 = 0.790$).

(E) A Venn diagrams showing different disease states and the abundance of metabolites ($VIP \geq 1$ and $p < 0.05$) among the three groups. ROC curves of metabolites as potential biomarkers determined by comparisons of the (F) PTB vs. HC groups, (G) LTBI vs. HC groups, (H) and PTB vs. LTBI groups.

Figure 4. Correlation analysis between different ASVs and potential metabolic biomarkers. Significant correlation identified by comparisons between the (A) PTB vs. HC groups, (B) LTBI vs. HC groups, and (C) PTB vs. LTBI groups. The depth of the color in the heatmap signifies the strength of the correlation. Blue represents a positive correlation, whereas red indicates a negative correlation. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Table S1. Baseline distribution of the three groups of subjects. (A) 16S rRNA sequencing, (B) Metagenomics analysis, and (C) Metabolomics analysis

Table S2. Microbial taxonomic annotation at different levels.

Table S3. Coefficients for Lasso regression analysis and ROC curve analyses of metabolites as potential biomarkers. (A) PTB vs. HC groups, (B) LTBI vs. HC groups, and (C) PTB vs. LTBI groups.

Figure S1. Correlation network analysis of the top 100 abundant genera of (A) LTBI, (B) PTB, and (C) HC groups. The lines between nodes indicate the Spearman correlation. All correlations are positive and indicated by red lines. $R > 0.6$. Colors assigned to the genera are based on phylum affiliation.

Metabolite abbreviations:

Docosahexaenoic acid, (4Z,7Z,10Z,13Z,16Z,19Z)-4,7,10,13,16,19-Docosahexaenoic acid;

Phosphorylcholine, 1-o-octyl-2-o-(n-methylcarbamoyl)-sn-glyceryl-3-phosphorylcholine;
 octadecadienoic acid, 13-hydroxy-9z,11e-octadecadienoic acid;
 octadecenamide, N-[(1r)-2-hydroxy-1-methylethyl-9z-octadecenamide;
 eicosatetraenoic acid, 8(9)-epoxy-5z,11z,14z,17z-eicosatetraenoic acid;
 3-phosphoserine, 2-oleoyl-1-palmitoyl-sn-glycero-3-phosphoserine

Reference

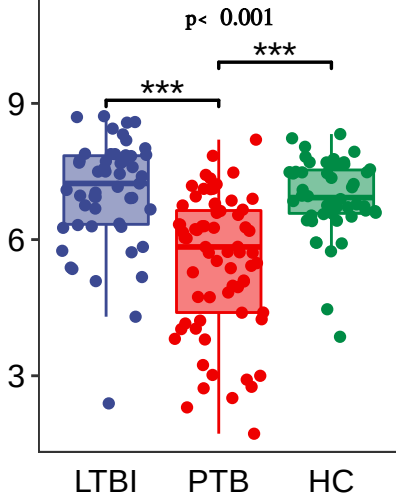
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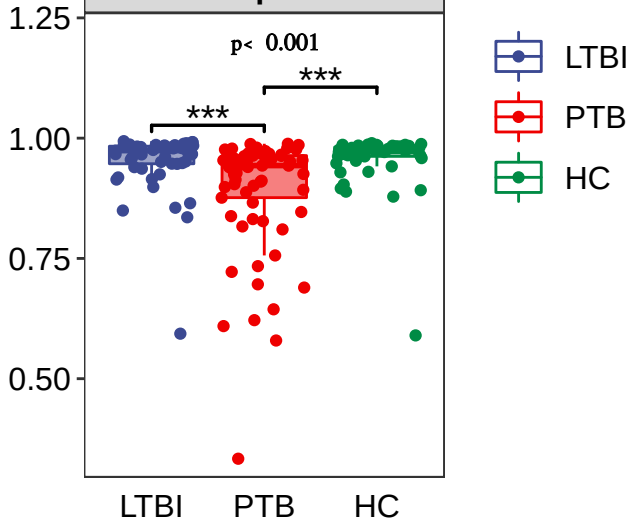
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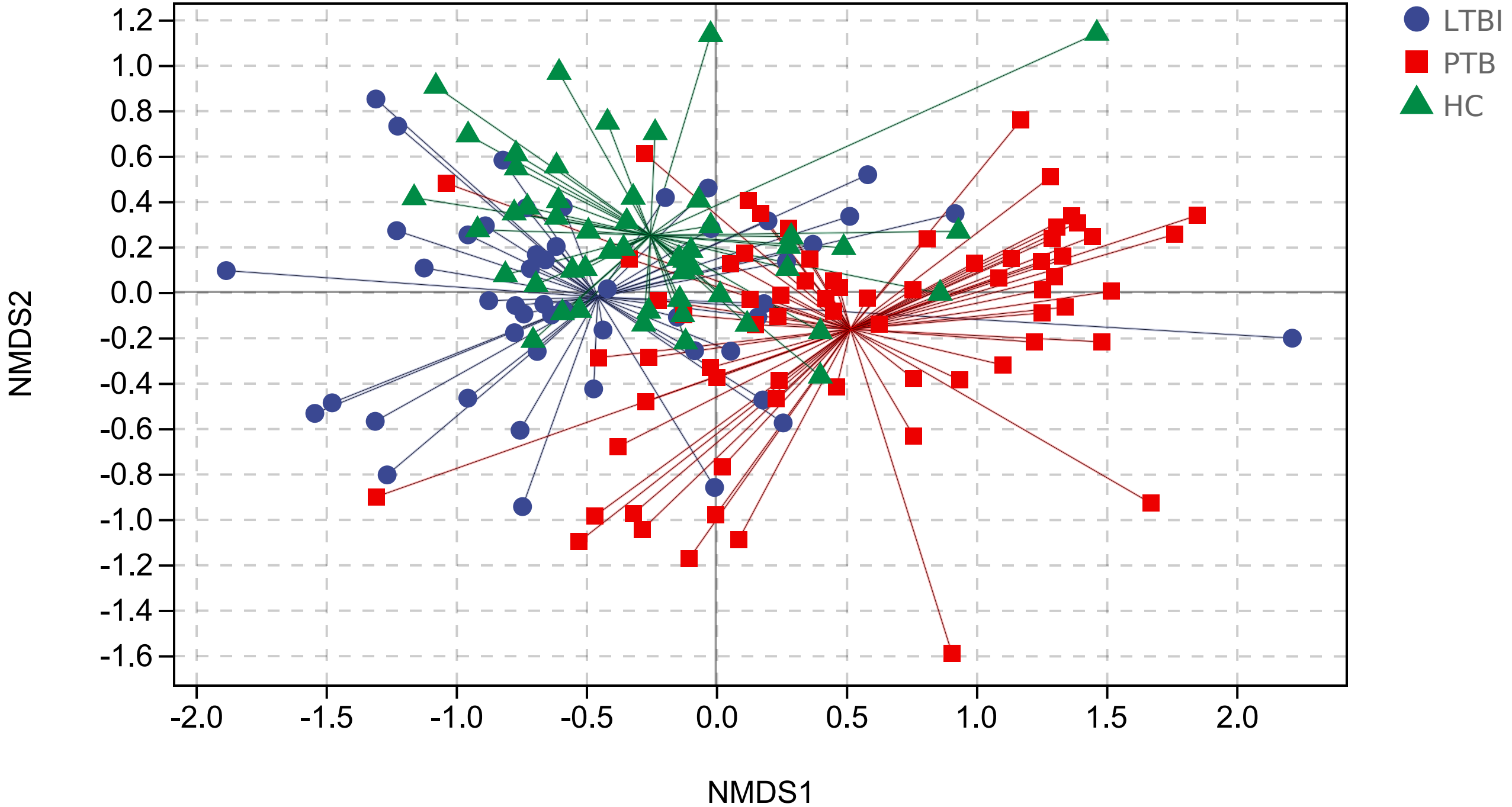
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Shannon

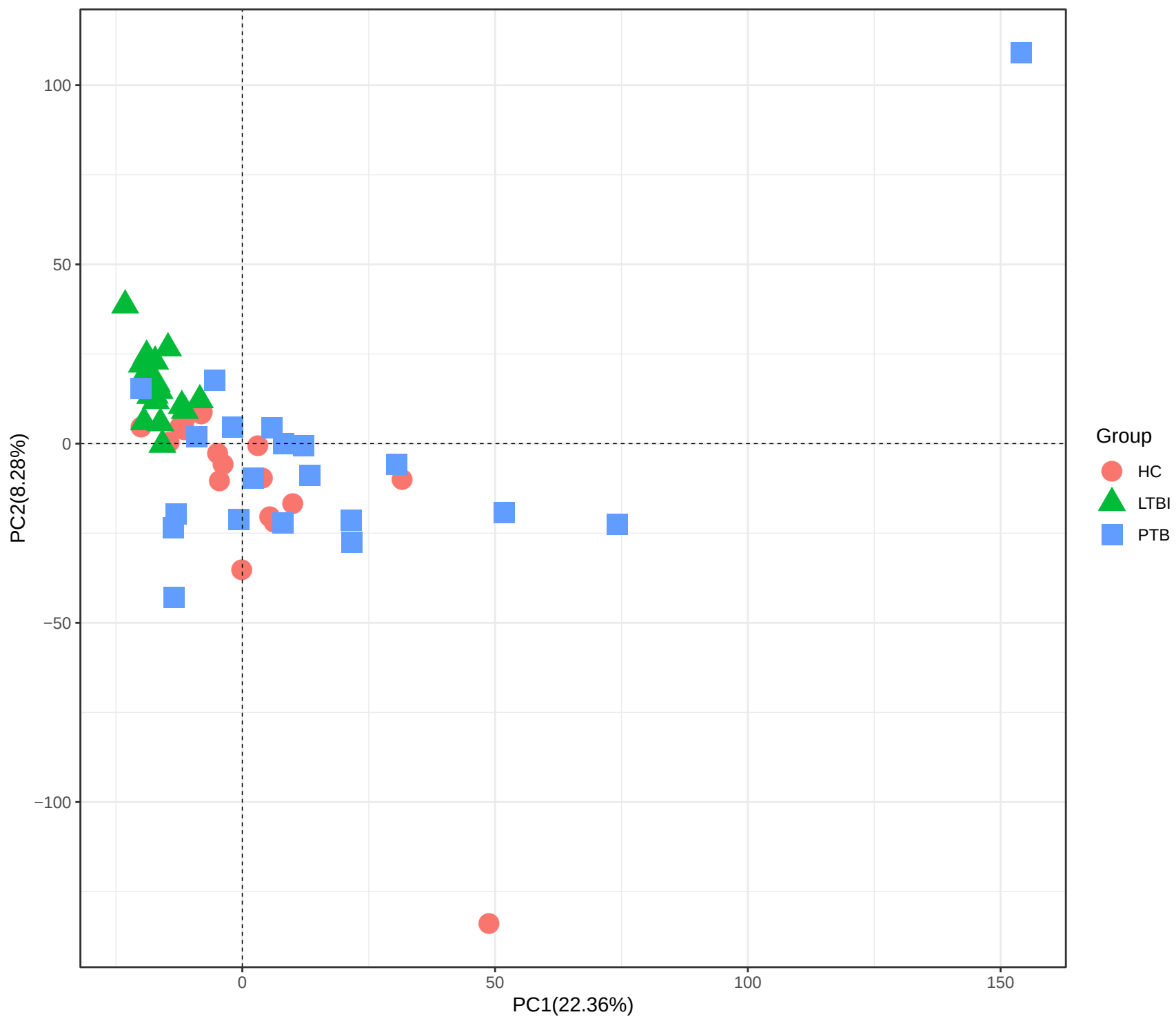


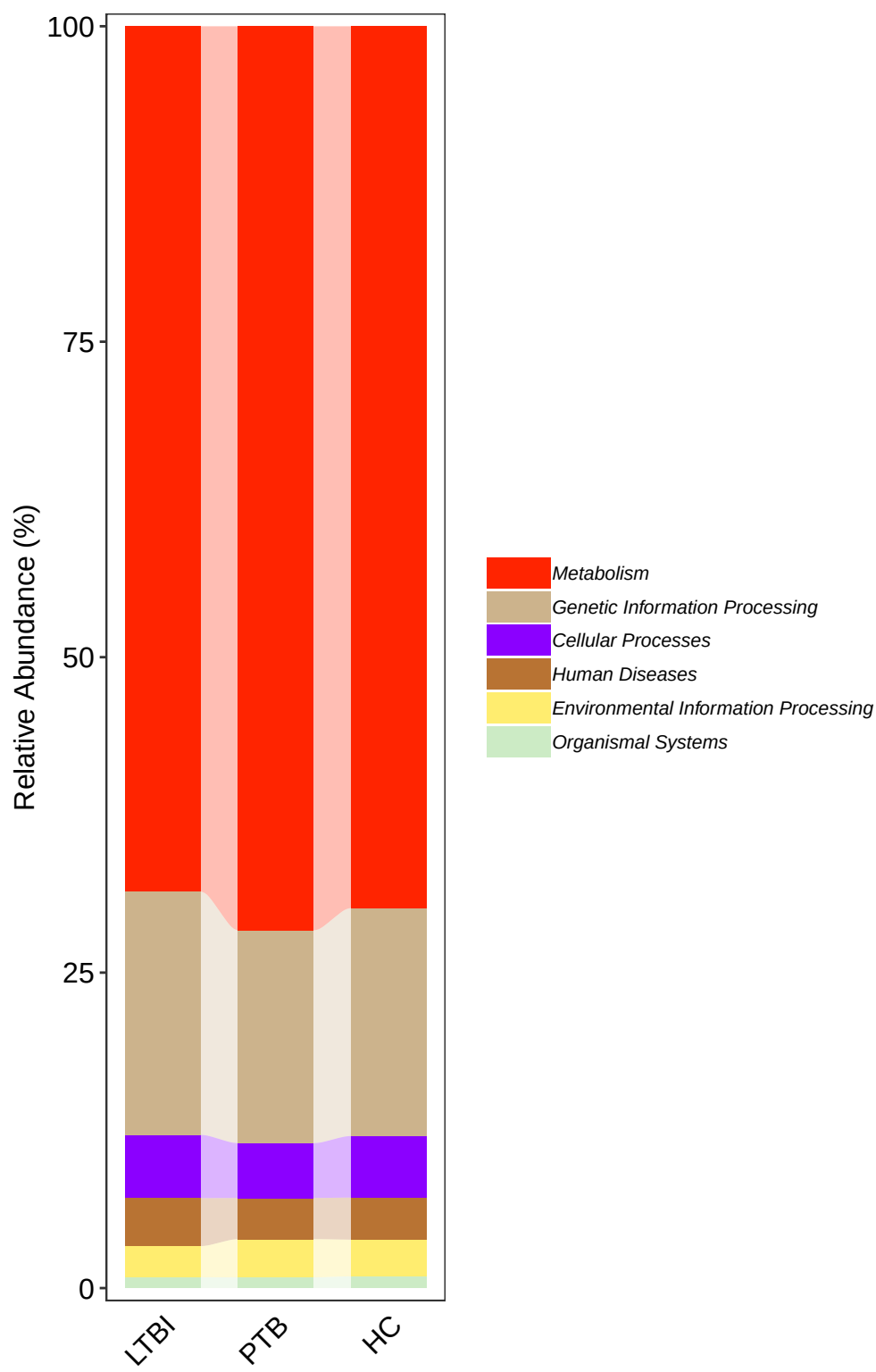
Simpson

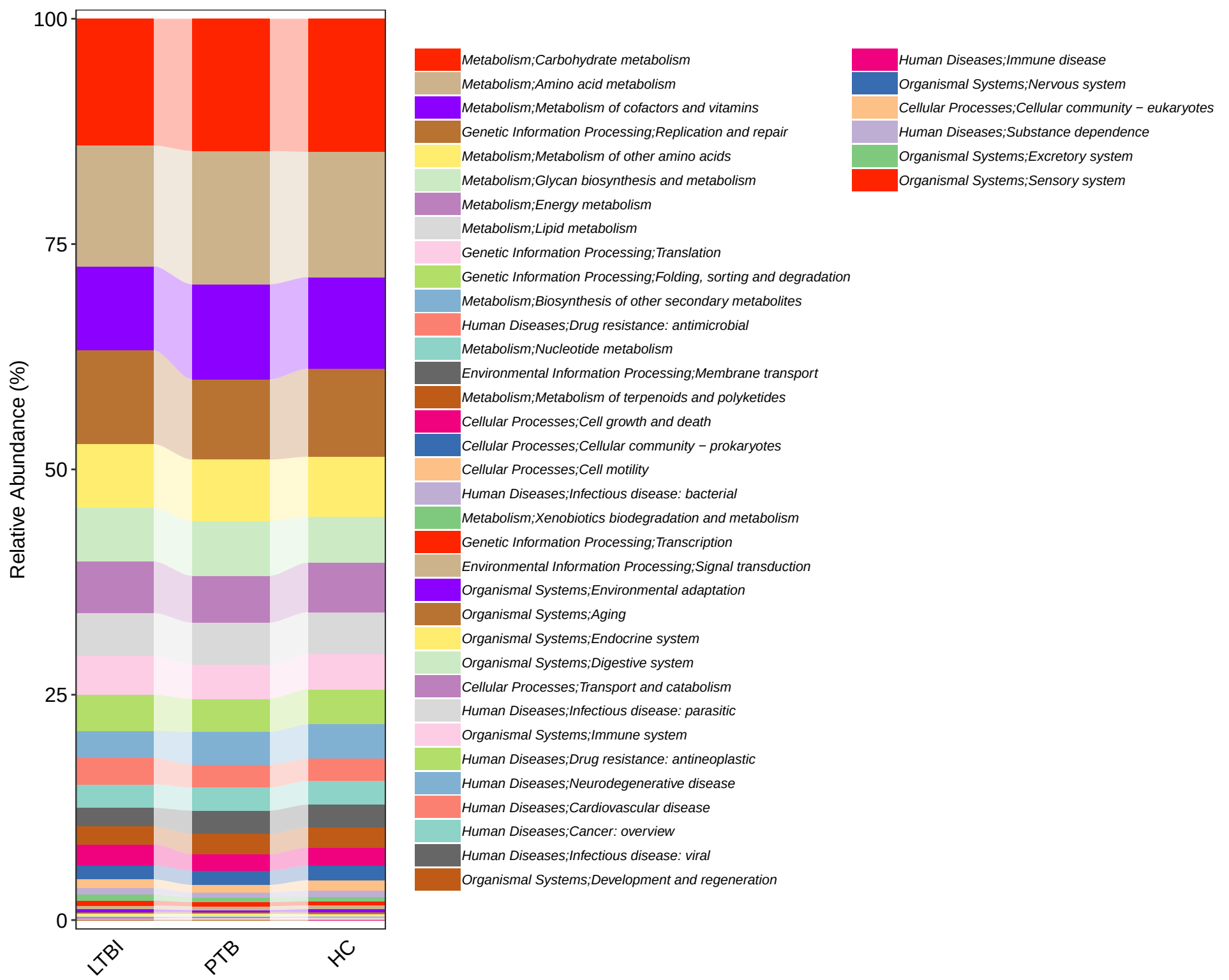


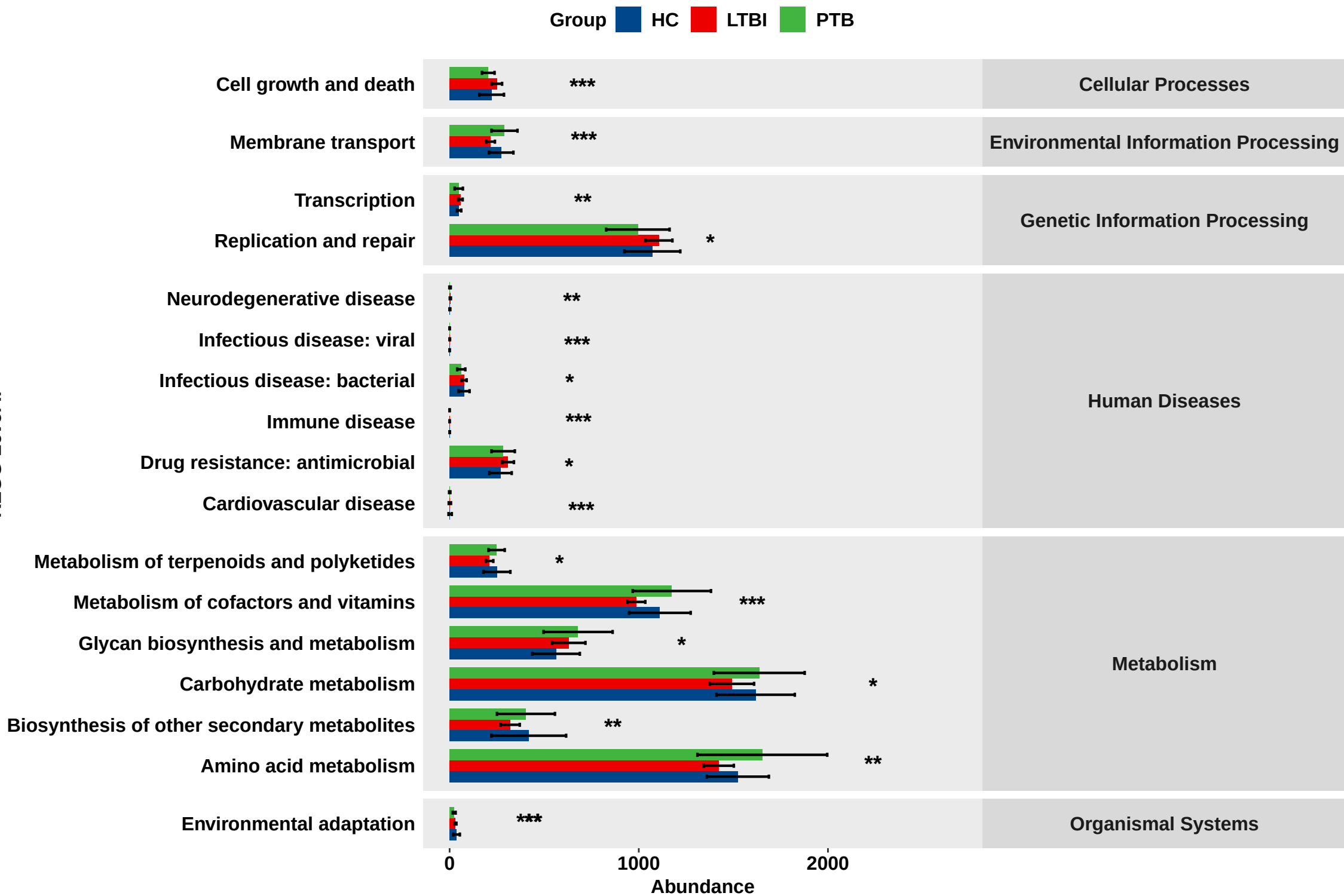


PCA



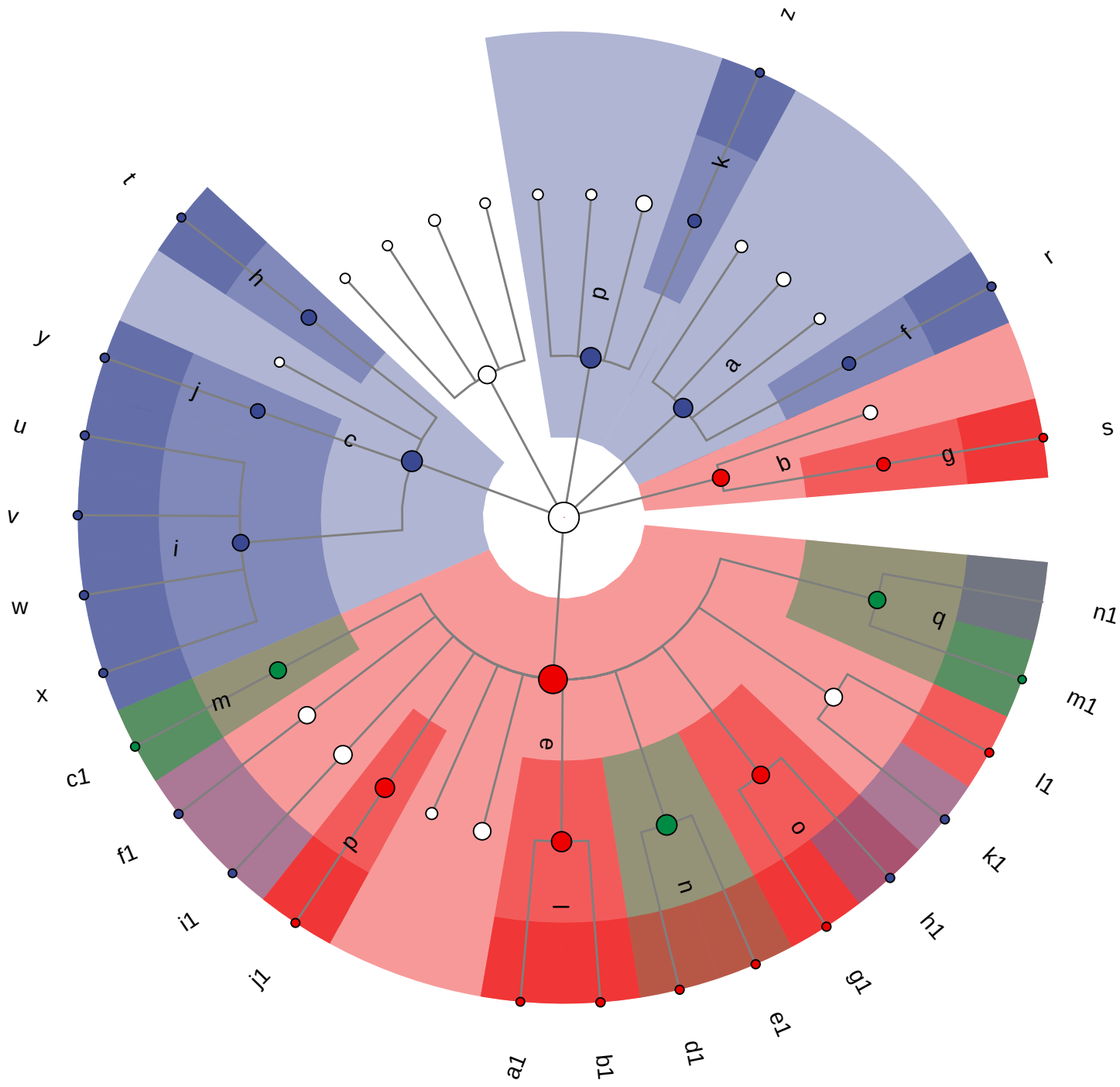






LEfSe analysis
The current LDA threshold is 3

Groups ■ LTBI ■ PTB ■ HC

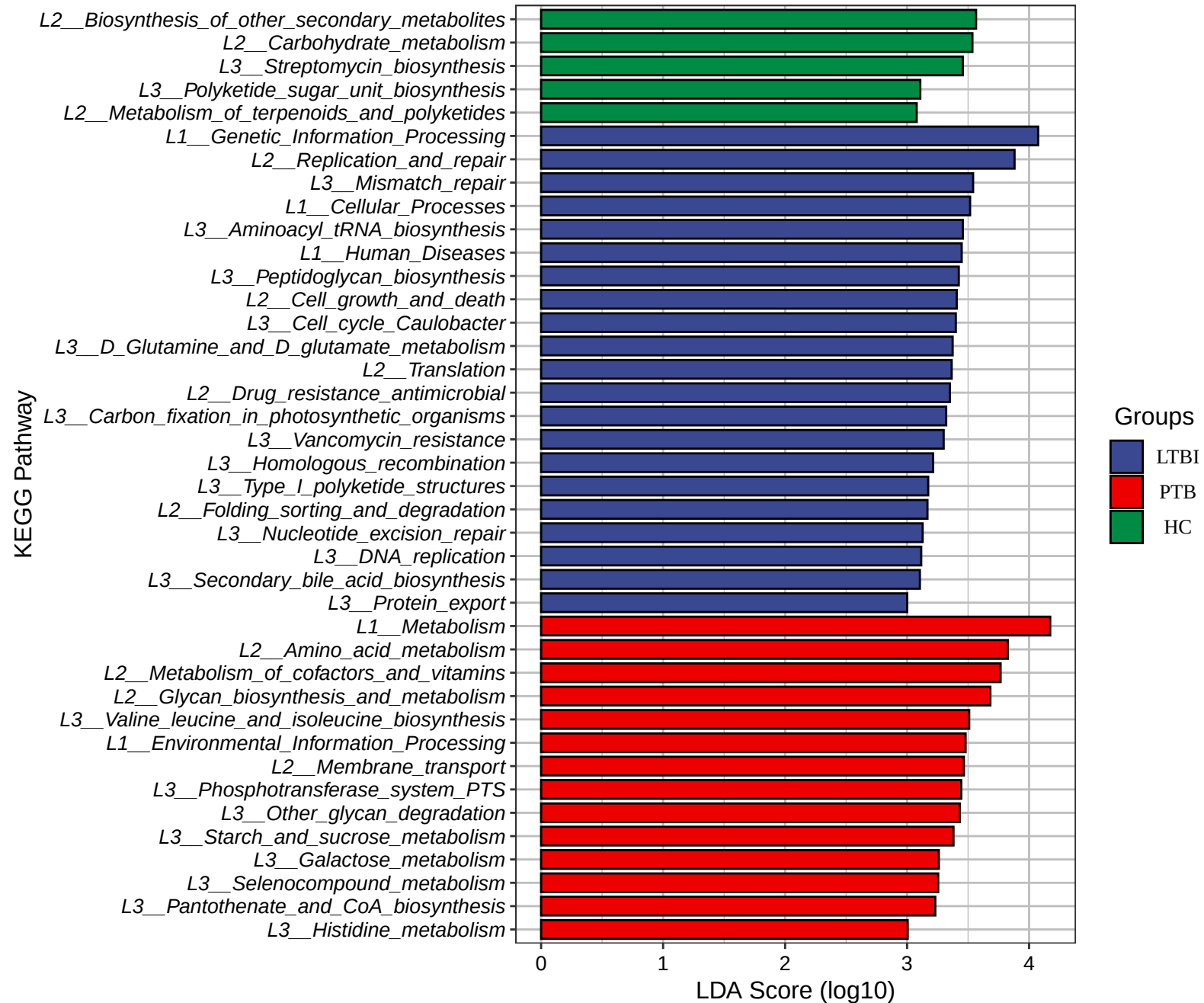


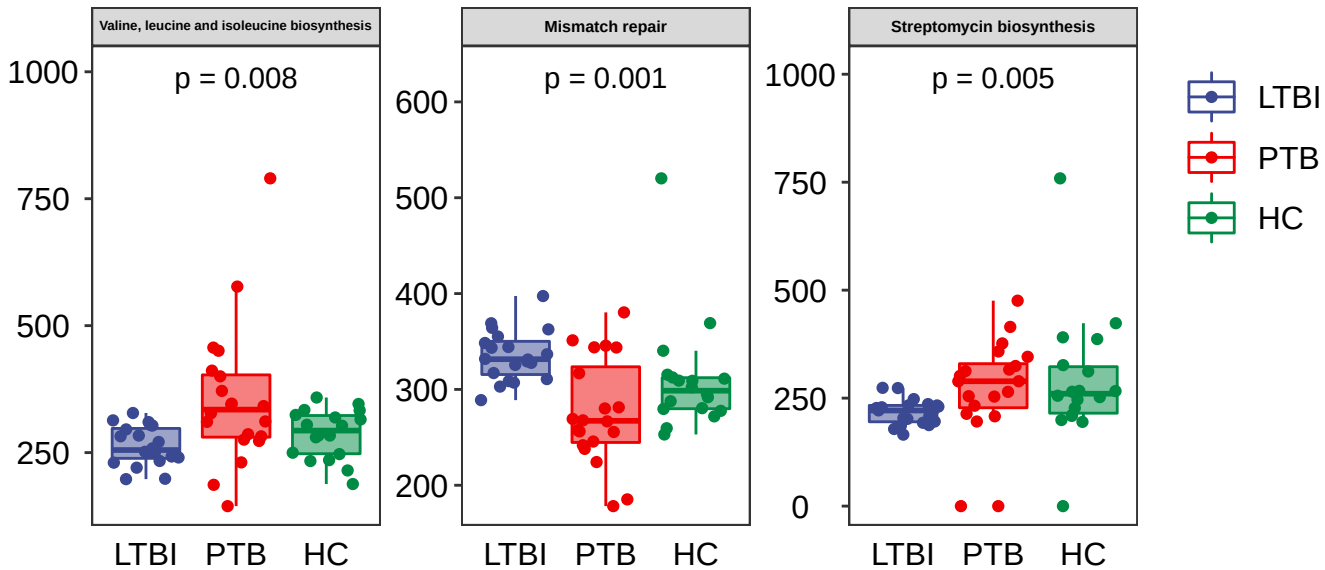
KEGG Pathway

- | | |
|---|---|
| ■ a: L1__Cellular_Processes | ■ z: L3__Vancomycin_resistance |
| ■ b: L1__Environmental_Information_Processing | ■ a1: L3__Histidine_metabolism |
| ■ c: L1__Genetic_Information_Processing | ■ b1: L3__Valine_leucine_and_isoleucine_biosynthesis |
| ■ d: L1__Human_Diseases | ■ c1: L3__Streptomycin_biosynthesis |
| ■ e: L1__Metabolism | ■ d1: L3__Galactose_metabolism |
| ■ f: L2__Cell_growth_and_death | ■ e1: L3__Starch_and_sucrose_metabolism |
| ■ g: L2__Membrane_transport | ■ f1: L3__Carbon_fixation_in_photosynthetic_organisms |
| ■ h: L2__Folding_sorting_and_degradation | ■ g1: L3__Other_glycan_degradation |
| ■ i: L2__Replication_and_repair | ■ h1: L3__Peptidoglycan_biosynthesis |
| ■ j: L2__Translation | ■ i1: L3__Secondary_bile_acid_biosynthesis |
| ■ k: L2__Drug_resistance_antimicrobial | ■ j1: L3__Pantothenate_and_CoA_biosynthesis |
| ■ l: L2__Amino_acid_metabolism | ■ k1: L3__D_Glutamine_and_D_glutamate_metabolism |
| ■ m: L2__Biosynthesis_of_other_secondary_metabolites | ■ l1: L3__Selenocompound_metabolism |
| ■ n: L2__Carbohydrate_metabolism | ■ m1: L3__Polyketide_sugar_unit_biosynthesis |
| ■ o: L2__Glycan_biosynthesis_and_metabolism | ■ n1: L3__Type_I_polyketide_structures |
| ■ p: L2__Metabolism_of_cofactors_and_vitamins | |
| ■ q: L2__Metabolism_of_terpenoids_and_polyketides | |
| ■ r: L3__Cell_cycle_Caulobacter | |
| ■ s: L3__Phosphotransferase_system_PTS | |
| ■ t: L3__Protein_export | |
| ■ u: L3__DNA_replication | |
| ■ v: L3__Homologous_recombination | |
| ■ w: L3__Mismatch_repair | |
| ■ x: L3__Nucleotide_excision_repair | |
| ■ y: L3__Aminoacyl_tRNA_biosynthesis | |

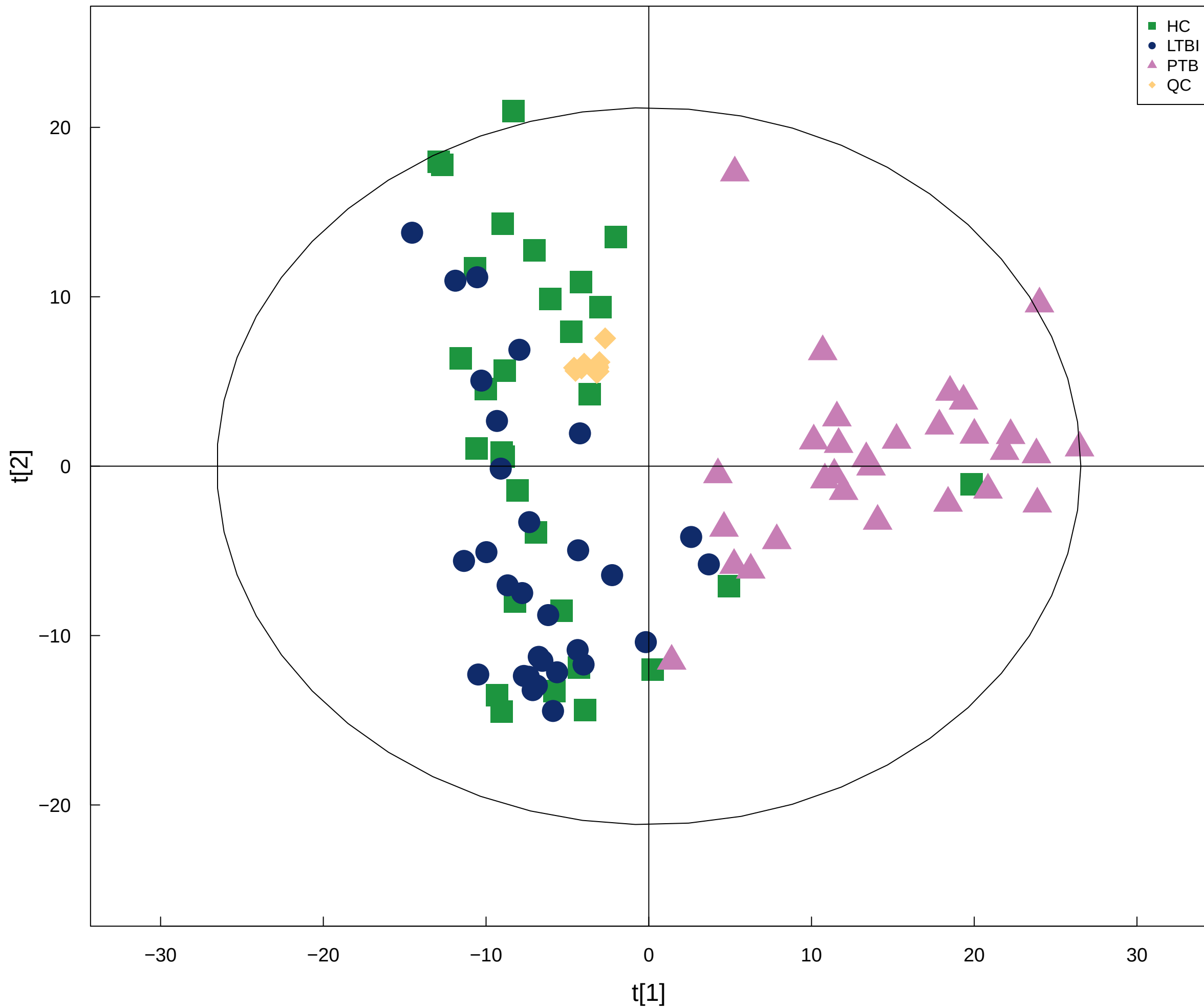
LEfSe analysis

The current LDA threshold is 3

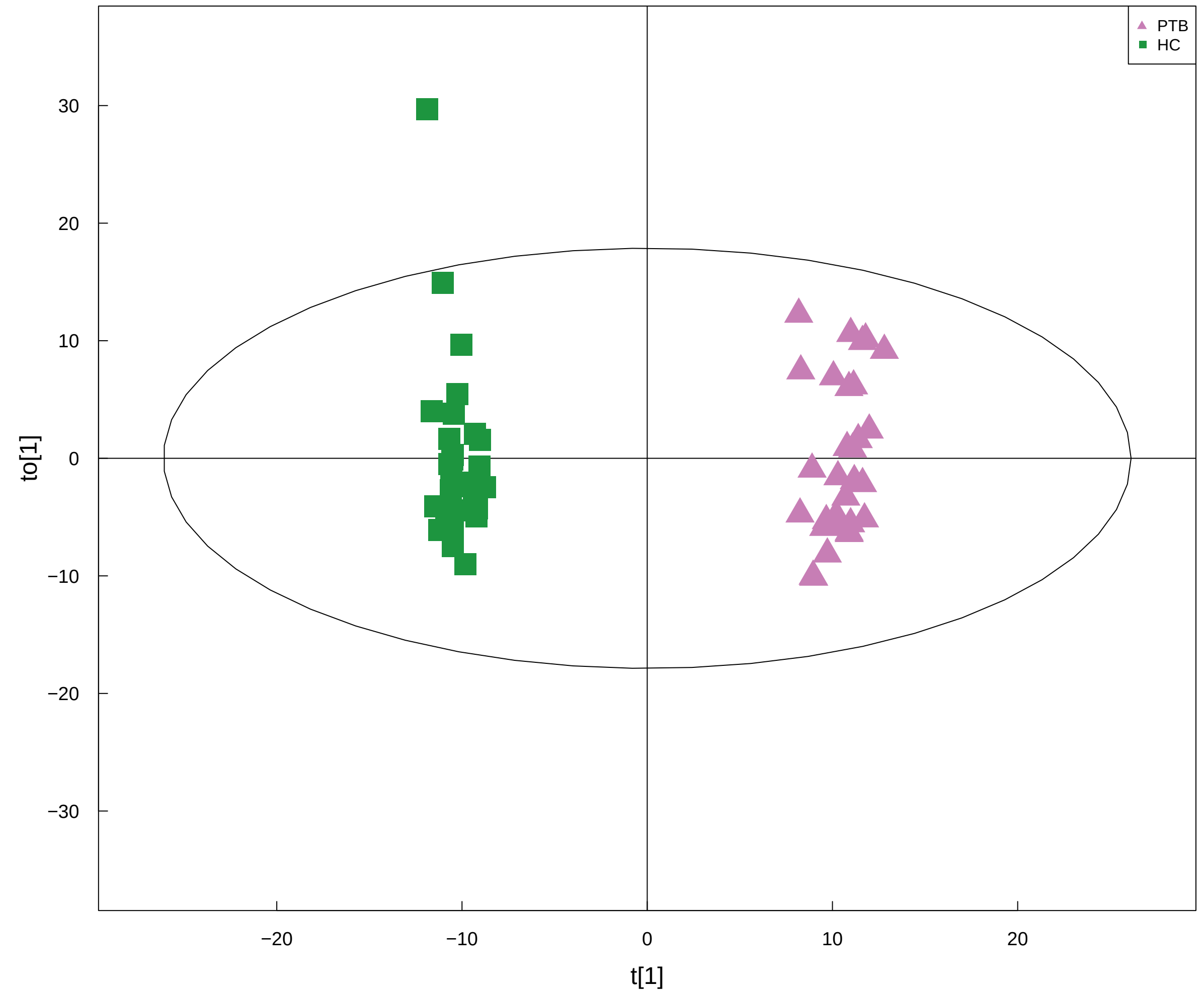




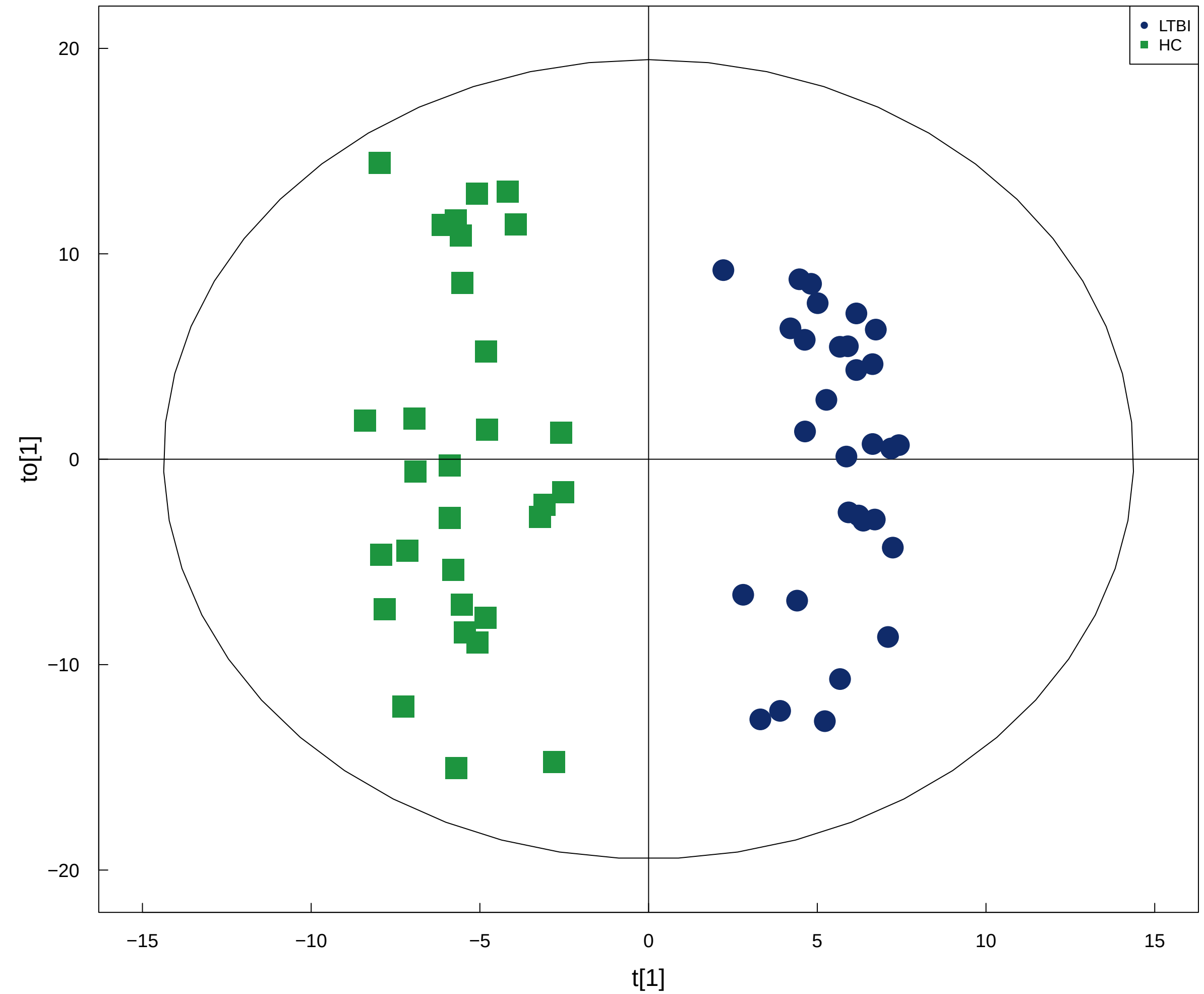
Scores (PCA)



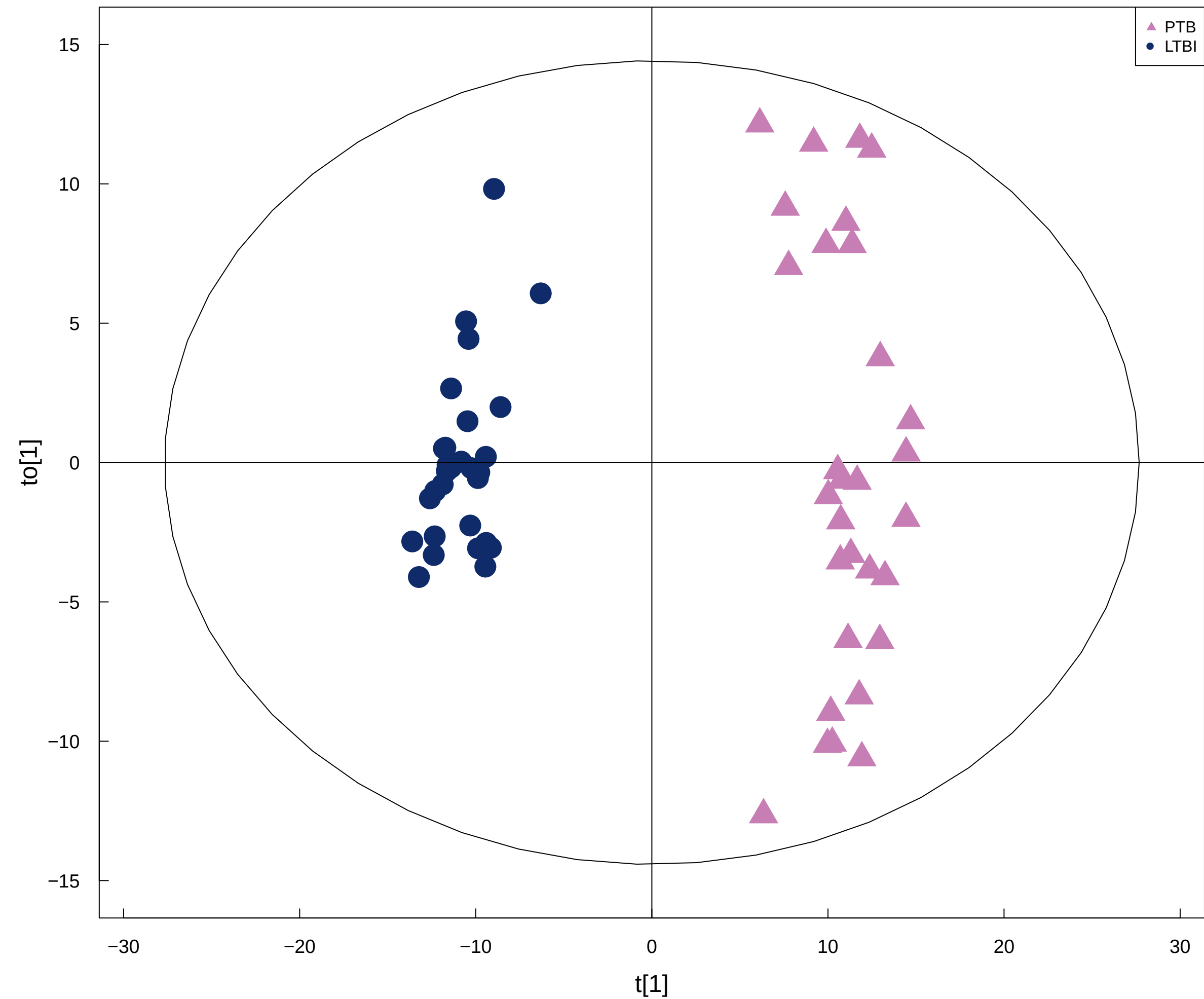
Scores (OPLS-DA)



Scores (OPLS-DA)

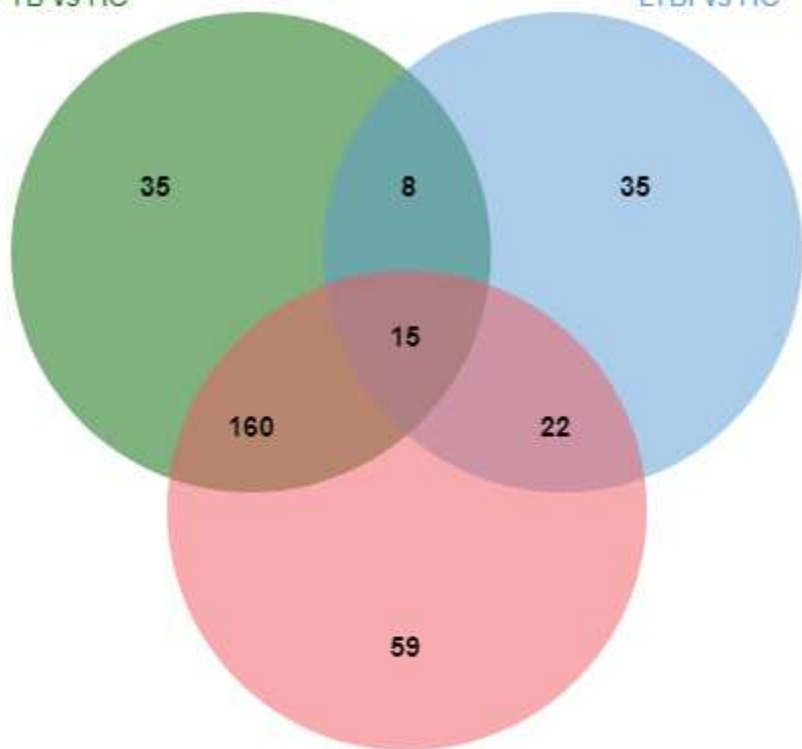


Scores (OPLS-DA)



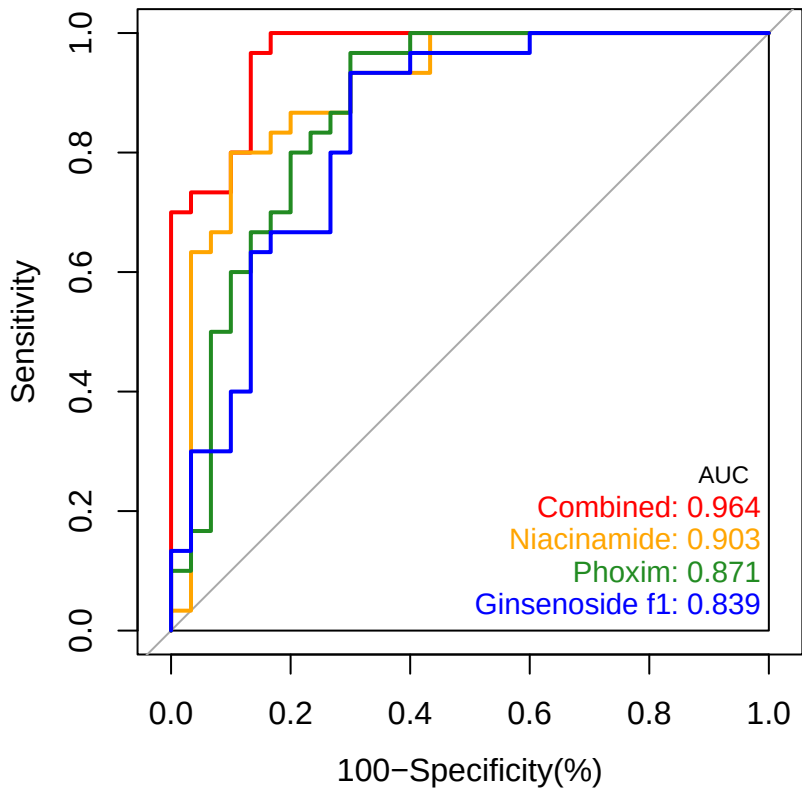
PTB vs HC

LTBI vs HC

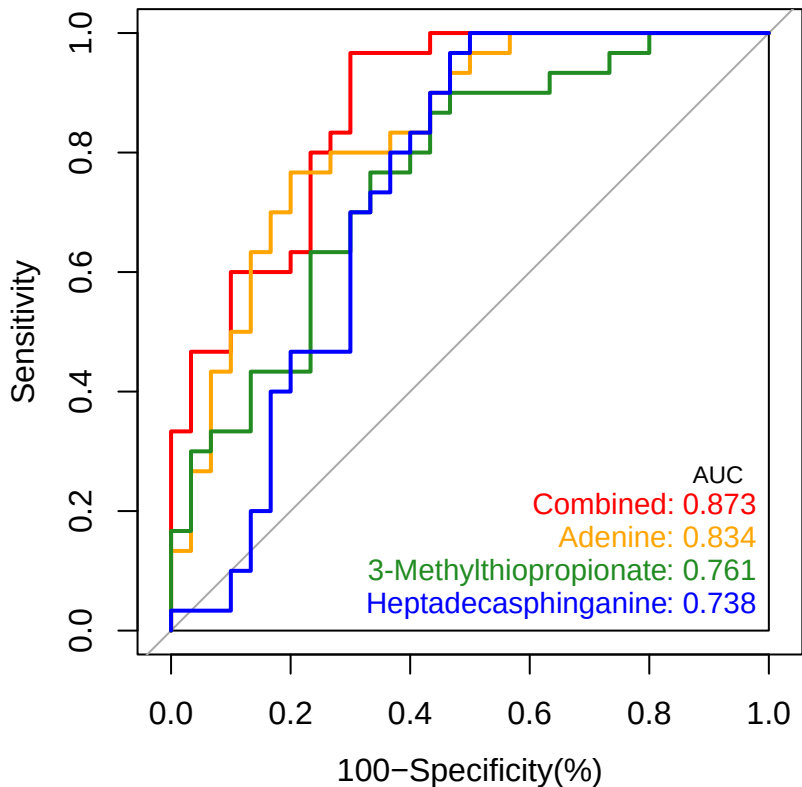


PTB vs LTBI

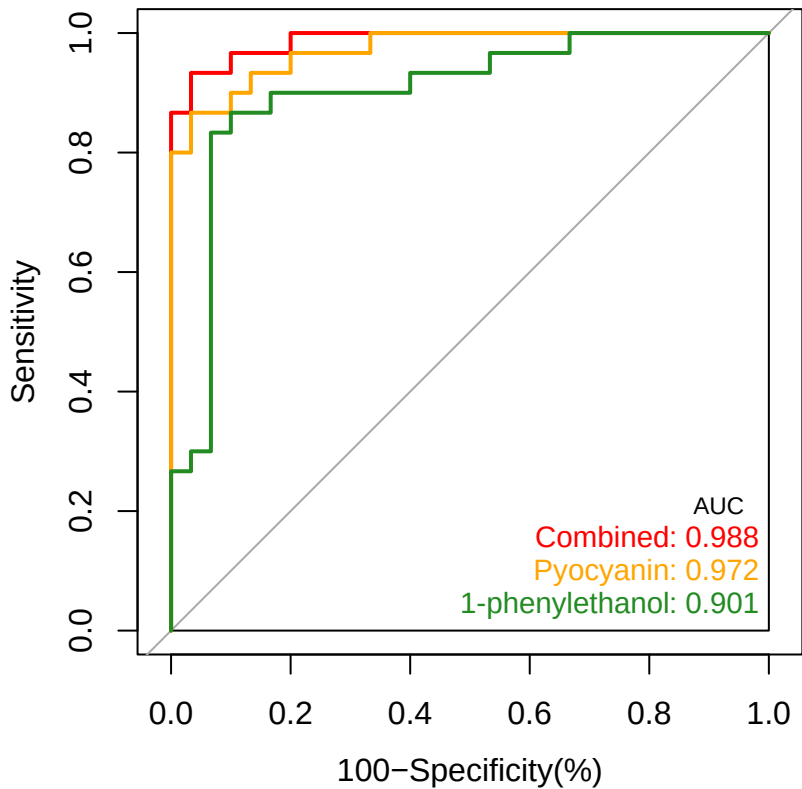
ROC curve of PTB and HC

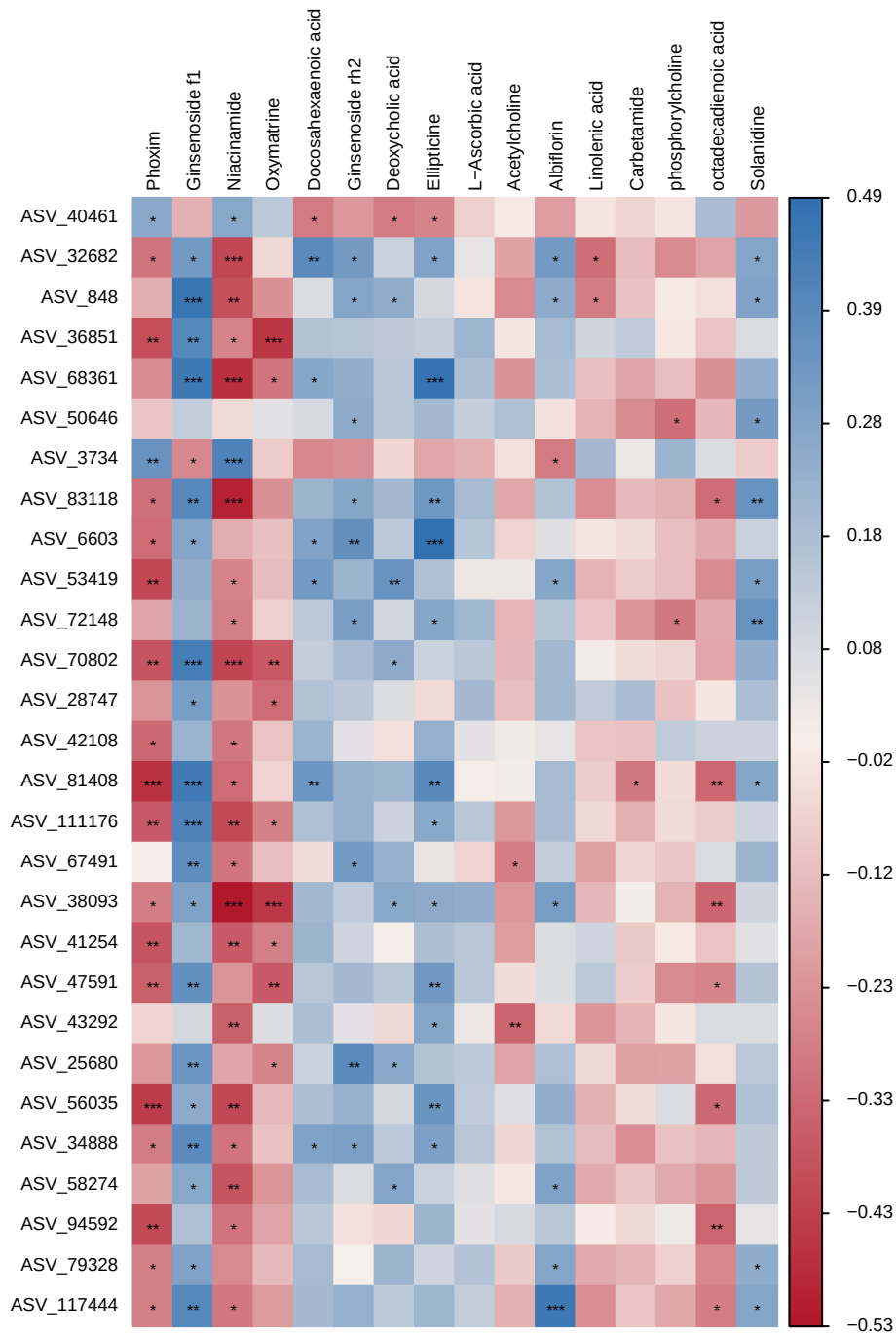


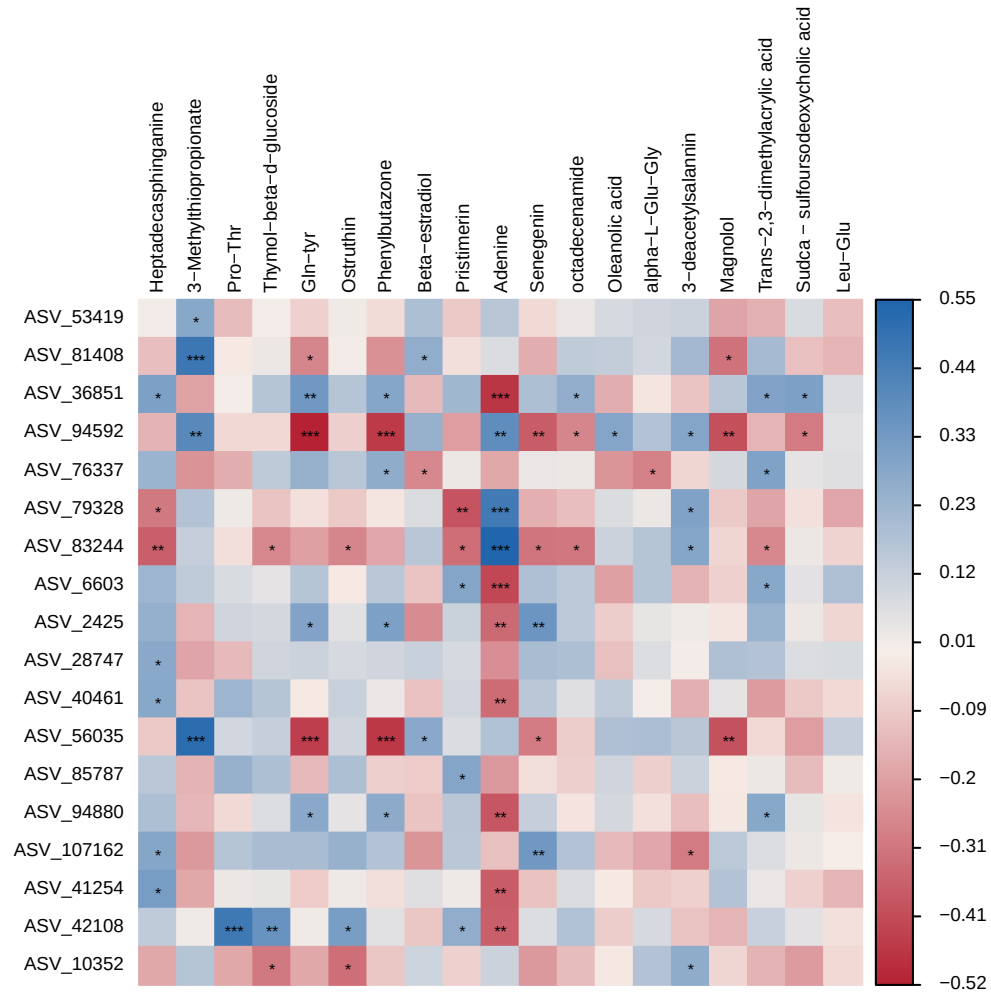
ROC curve of LTBI and HC

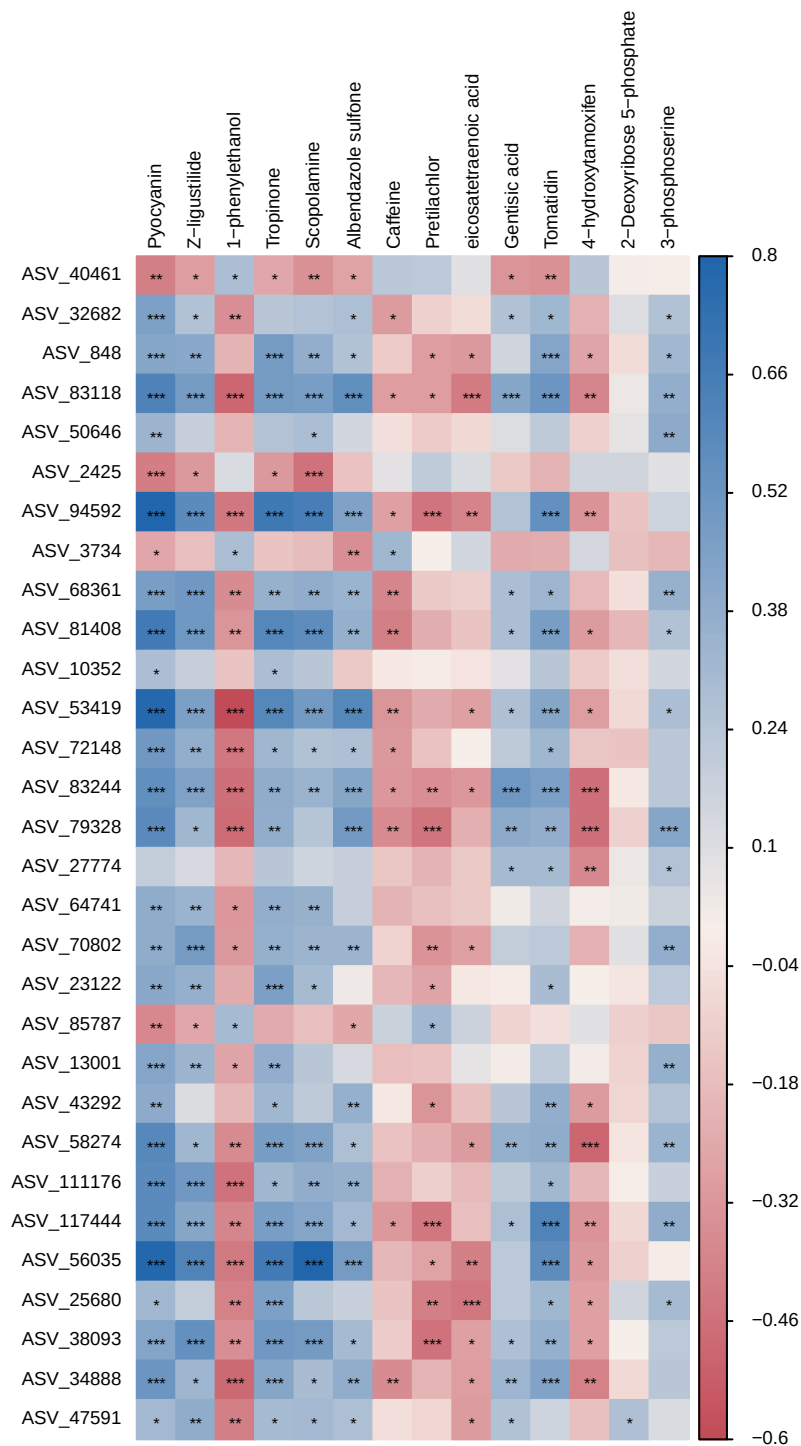


ROC curve of PTB and LTBI









Supplementary Files

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