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ORIGINAL RESEARCH

Alterations of Gut Microbiota in Pyogenic Liver Abscess Patients with and without Type 2 Diabetes Mellitus

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Purpose: The clinical manifestations of pyogenic liver abscess (PLA) vary between patients with and without diabetes mellitus (DM). However, the relationship between PLA and the gut microbiome remains unknown. This study analyzed the composition of gut microbiota in PLA patients with and without DM and healthy controls (HCs) with the goal of identifying potential reasons for the observed variations in clinical manifestations.

Patients and Methods: Using 16S ribosomal RNA(16S rRNA) gene sequencing, we analyzed the compositions of gut microbiota in 32 PLA patients with DM, 32 PLA patients without DM, and 29 matched HCs.

Results: In PLA patients with DM, the D-dimer level, fibrinogen degradation products, and thrombin time were significantly higher compared to the PLA patients without DM ($P < 0.05$). The abundance and diversity of intestinal flora were reduced in both groups of PLA patients compared with the HCs ($P < 0.05$). Specifically, the PLA patients with DM showed significant decreases in the relative abundances of *Bacteroides, Blautia, Prevotella9*, and *Faecalibacterium*, whereas *Enterococcus* and *Escherichia-Shigella* were relatively more abundant ($P < 0.05$). Compared to PLA patients without DM, those with DM had lower relative abundances of *Lactobacillus* and *Klebsiella* ($P < 0.05$) and showed different bacterial flora, including *Anaerosporobacter* and *Megamonas*.

Conclusion: PLA patients with DM exhibited more severe clinical manifestations of PLA compared to patients without DM. It is important to monitor blood coagulation in PLA patients with DM to prevent the development of thrombotic diseases. Additionally, PLA patients with DM exhibit distinct differences in the composition and diversity of their intestinal flora compared to both PLA patients without DM and HCs.

Keywords: Gut microbiota, Pyogenic liver abscess, type 2 diabetes mellitus, 16S rRNA sequencing

Introduction

Pyogenic liver abscess (PLA) is an infectious disease caused by pyogenic bacteria that invade the liver through various routes and form solitary or multiple collections of pus within the liver.[1,2] In recent years, there has been a noticeable rise in the incidence rate of PLA in adults in China and Korea.[3–5] The incidence of liver abscesses is also on the rise among children in the United States.[6] Patients with PLA do not typically present with specific symptoms. However, if the infection is not effectively managed, it can progress to disseminated infection, sepsis, and potentially death, especially in individuals with type 2 diabetes mellitus (T2DM).[5,7,8] PLA patients with DM tend to experience more severe symptoms compared to PLA patients without DM.[9,10] Over 140 million Chinese adults were estimated to have diabetes in 2021, and this number is projected to increase to over 174 million by 2045.[11] Therefore, effective strategies for PLA prevention and treatment are urgently needed.

The gut microbiota plays a significant role in host metabolism, protection against microbial invasion, and nutrient absorption, thereby exerting a profound effect on human health and disease.[12,13] Gut microbiota dysbiosis can be linked to

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the pathogeneses of chronic liver diseases such as chronic hepatitis B and C, liver cirrhosis, and hepatocellular carcinoma.[14–16] Alterations in the diversity of the gut microbiota have been observed in animal models of liver abscess.[17–19] Changes in the composition of pus (pus collection were as described in a previous study) microbiota are associated with the development of PLA in patients with DM.[20,21] In addition, there are variations in the gut microbiota among individuals from different geographic regions.[22] Hence, we hypothesized that the PLA patients with and without DM show differences in the composition of the gut microbiome. In this study, we analyzed the differences in clinical characteristics between the T2DM +PLA group and the PLA group. Additionally, we utilized 16S rRNA amplicon sequencing to analyze the gut microbiota of PLA patients with DM, PLA patients without DM, and healthy controls (HCs) to better understand the role of gut microbiota in the occurrence of PLA. The ultimate goal is to prevent hospitalization, reduce financial burden, and avoid potential life-threatening complications.

Material and Methods

Study Population

The study was approved by the Medical Ethics Committee of The First People's Hospital of Lianyungang (number KY-20181213001), and all participants provided informed consent.

The diagnostic criteria for PLA included the following: 1) clinical manifestations such as fever, chills, nausea, discomfort in the liver area, fatigue, and tenderness or percussion pain in the liver area; 2) confirmation of liver abscess through imaging examinations such as abdominal Doppler ultrasound, CT, or MRI; 3) positive results from clinical bacteriological examination or effective antimicrobial drug treatment; and 4) confirmation of purulent infection caused by bacteria through percutaneous liver puncture or surgical treatment. To be considered for inclusion, participants had to meet criteria 1 and 2 as well as any one or both of criteria 3 and 4. Diabetes was diagnosed according to the American Diabetes Association criteria.[23]

A cohort of 93 subjects, including 32 PLA patients with DM (T2DM+PLA group) patients, 32 PLA patients without DM (PLA group), and 29 age- and sex-matched HCs (Health Control group), were recruited from The First People's Hospital of Lianyungang in Jiangsu Province, China, between February 2021 and January 2022.

Patient data, including basic demographic information, clinical manifestations, underlying diseases, laboratory test results, and imaging examination results, were obtained from medical records, laboratory information systems, and the Picture Achieving and Communication System at our institution.

Sample Collection and DNA Extraction

Fecal samples were freshly collected from both the PLA groups and the HC group for the analysis of intestinal flora. The samples were processed in the laboratory within 4 h after collection and then stored at −80°C until analysis. DNA was extracted from fecal samples (0.5 g) using the QIAamp PowerFecal DNA kit (QIAGEN, Germany) according to the manufacturer's protocols.

Polymerase Chain Reaction (PCR) and 16S rRNA Amplicon Sequencing

The V3-4 region of the bacterial 16S rRNA gene was amplified by PCR (95°C for 3 min followed by 25 cycles at 95°C for 30s, 55°C for 30s, and 72°C for 30s and a final extension at 72°C for 5 min) using the primers 341F 5′-CCTACGGGNBGCASCAG-3′ and 805R 5′-GACTACNVGGGTATCTAATCC-3′. PCR cleanup was conducted using AMPure XP beads to purify the 16S V3 and V4 amplicon away from the free primers and primer dimer species. The purified product was amplified by PCR (95°C for 3 min followed by eight cycles at 95°C for 30s, 55°C for 30s, and 72°C for 30s and a final extension at 72°C for 5 min) using primers where barcode is an eight-base sequence unique to each sample. The amplicons were subsequently purified by AMPure XP beads to clean up the final library before quantification. Finally, the purified amplicons were pooled in equimolar amounts and paired-end sequenced (2×250) on an Illumina MiSeq platform according to the standard protocols.

Bioinformatics Analysis

Fast Length Adjustment of Short reads (FLASH) was used to merge paired-end reads from next-generation sequencing. Low-quality reads were filtered, and chimera reads were removed. The number of reads for each sample was normalized by random subtraction based on the smallest sample size. Operational taxonomic units (OTUs) were aligned using the UCLUST algorithm with a 97% identity and taxonomically classified using the SILVA 16S rRNA database (v128). The alpha and beta diversities were generated using Quantitative Insights Into Microbial Ecology (QIIME) and calculated based on weighted and unweighted UniFrac distance matrices. We used linear discriminant analysis effect size (LEfSe) method to identify species with statistically significant differences in abundance among the groups.

Statistical Analysis

Normal measurement data were presented as mean ± standard deviation, and statistical comparisons were conducted using the independent *t*-test. Non-normally distribution data were represented by M (P25, P75), and comparisons were performed using the Mann–Whitney *U*-test. Statistical analysis and graphing were performed using SPSS 27.0 and GraphPad Prism9 software. A *P*-value less than 0.05 was considered statistically significant.

Results

Patient Clinical Characteristics

This study included 32 patients each in the T2DM+PLA group and the PLA group. Detailed characteristics of the patients are given in Table 1. The average age of the patients was 56.2 years, and the patients included 43 males (63.19%) and 21 females (32.81%). There were no significant differences in age, gender, or symptoms and signs between these two groups. The rate of hypertension was significantly higher in the T2DM+PLA group ($\chi^2 = 4.267$, $P = 0.039$), while the rate of previous hepatobiliary surgery was significantly higher in patients with PLA ($\chi^2 = 0.7819$, $P = 0.005$). Significant differences were observed in the D-dimer level, content of fibrinogen degradation products (FDP), and thrombin time (TT) between the T2DM+PLA group and the PLA group whereas no significant differences were found in the contents of PCT, C-reactive protein, and alkaline phosphatase, which showed significant increases in the two PLA groups. In terms of treatment, most patients with T2DM+PLA received antibiotics and underwent percutaneous drainage ($\chi^2 = 6.335$, $P = 0.012$). Regarding prognosis, patients with T2DM+PLA experienced a longer duration of hospitalization and drainage tube placement time than patients with PLA ($P < 0.05$).

PLA Decreases Microbial Diversity Both with and without DM

The characteristics of the gut microbiome in the three groups were analyzed based on the 16S rRNA gene sequencing of 93 fecal samples. The α-diversity reflects the abundance and diversity of gut microbes. The gut microbial richness was determined based on the number of observed species, and the Chao1 diversity index and gut microbial diversity were measured by the Shannon and Simpson diversity indexes. The richness and diversity of gut microbiota were significantly lower in the T2DM+PLA and PLA groups than in the HCs ($P < 0.01$; Figures 1A–D). When comparing to the PLA group, there was a decrease in both the richness and diversity of the gut microbiome in T2DM+PLA group. However, the differences were not significant. The β-diversity reflects the composition of gut microbiota. Principal coordinate analysis of the weighted UniFrac distance indicated a non-significant difference in fecal microbiota between the T2DM+PLA and PLA groups. Compared with the PLA group, the fecal microbiota of the T2DM+PLA was more different from the HC group (ANOSIM, $P < 0.01$; Figure 1E). The gut microbiota of the PLA group showed considerable dispersion, indicating significant variations in the composition of the gut microbiota among individuals (Figure 1E).

The Bacteria Differ Among the Three Groups

We assessed the differences in the relative abundances of bacteria at the phylum and genus levels among the three groups. At the phylum level, the relative abundance of *Bacteroidetes*, which contains many beneficial commensal organisms, was lower in the T2DM+PLA and PLA groups compared with the HCs. Conversely, the relative abundance of *Proteobacteria* was significantly higher in the T2DM+PLA and PLA groups ($P < 0.05$). When comparing the T2DM

Table 1 Clinical Characteristics and Laboratory Results of the Study Population

Characteristic	T2DM+PLA (n = 32)	PLA (n = 32)	*P*
Age (years; mean ± SD)	58.03±12.06	54.75±16.53	0.368
Gender (male,%)	22 (68.8)	21 (65.6)	0.79
Hospital stay[a] (d)	24.5±12.02	18.28±7.87	0.017*
Drainage time[b] (d)	20 (13, 27.75)	9 (4, 15.75)	0.001**
Symptoms and signs (n, %)			
Fever	31 (96.9)	28 (87.5)	0.355
Chill	21 (65.6)	19 (59.4)	0.606
Abdominal pain	19 (59.4)	20 (62.5)	0.798
Underlying condition (*n*, %)			
Cholecystitis	11 (34.4)	7 (21.9)	0.266
Cholelithiasis	10 (31.3)	5 (15.6)	0.14
Hypertension	11 (34.4)	4 (12.5)	0.039*
Previous surgical history	2 (6.3)	11 (34.4)	0.005**
Treatment (*n*, %)			
Antibiotics	1 (3.1)	8 (25)	0.012*
Antibiotics+Percutaneous drainage	31 (96.88)	24 (75)	0.012*
Laboratory results			
Leucocytes ($\times10^9$/L)	11.61±4.55	13.23±5.81	0.221
Neutrophils ($\times10^9$/L)	9.29 (7.13, 12.89)	10.33 (7.46, 3.71)	0.386
Platelet count ($\times10^9$/L)	232.16±152.84	229.34±113.94	0.934
PCT (ng/mL)	0.785 (0.11, 14.46)	0.345 (0.13, 5.05)	0.682
CRP (mg/L)	128.69±67.89	105.52±67.74	0.177
D-Dimer (ng/mL)	1209 (794, 2174.94)	633 (391.25, 1205.42)	0.002**
FDP (μg/mL)	8.48 (5.65, 12.55)	5.27 (3.75, 8.14)	0.001**
APTT (s)	29.75 (27.22, 31.3)	30.35 (29.45, 32.8)	0.112
TT (s)	14.05 (12.7, 14.78)	13.2 (12.43, 13.58)	0.03*
PT (s)	13.0 (11.68, 14.10)	13.7 (12.53, 14.85)	0.164
Albumin (g/L)	29.38±5.06	33.15±4.35	0.002**
ALT (U/L)	56 (32.5, 89.5)	42 (20.25, 88.25)	0.133
AST (U/L)	36 (24, 60.5)	28.5 (21.25, 60.75)	0.372
TBIL (μmol/L)	18.3 (10.75, 34.75)	14.9 (10.43, 21.88)	0.298
ALP (U/L)	164 (129.25, 102.5)	130 (102.5, 218.25)	0.145
γ-GGT (U/L)	120 (56.25, 180.5)	134 (55.25, 214.5)	0.559

Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; FDP, fibrinogen degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; ALP, alkaline phosphatase; γ-GGT, gamma-glutamyl transpeptidase. [a]Hospital stay is defined as the duration a patient spends in the hospital from admission to discharge; [b]Drainage time refers to the period between a drainage tube insertion and removal. *$P < 0.05$, **$P < 0.01$.

+PLA group with the PLA group, the relative abundance of *Bacteroidetes* decreased in the T2DM+PLA group, but this difference was not significant (Figures 2A and 2C, P=0.11, Z=1.60). At the genus level, the relative abundances of *Blautia* and *Prevotella9* were significantly decreased in the two PLA groups compared with the HCs ($P < 0.05$). Conversely, the relative abundances of *Enterococcus* and *Escherichia-Shigella* were significantly higher in the two PLA groups compared with the HCs ($P < 0.05$). The relative abundances of *Bacteroides* and *Faecalibacterium* were significantly decreased in the T2DM+PLA group compared with the HCs ($P < 0.05$). Similarly, compared with the PLA group, the relative abundances of *Lactobacillus* and *Klebsiella* were significantly reduced in the T2DM+PLA group (Figure 2B and Table 2).

Differences in Fecal Microbiota Among the Groups

To identify differences in key biomarkers among the groups, we conducted LEfSe analysis to characterize differences in species among the groups. A total of 77 genera showed significant differences between the HC group and the PLA group. Out

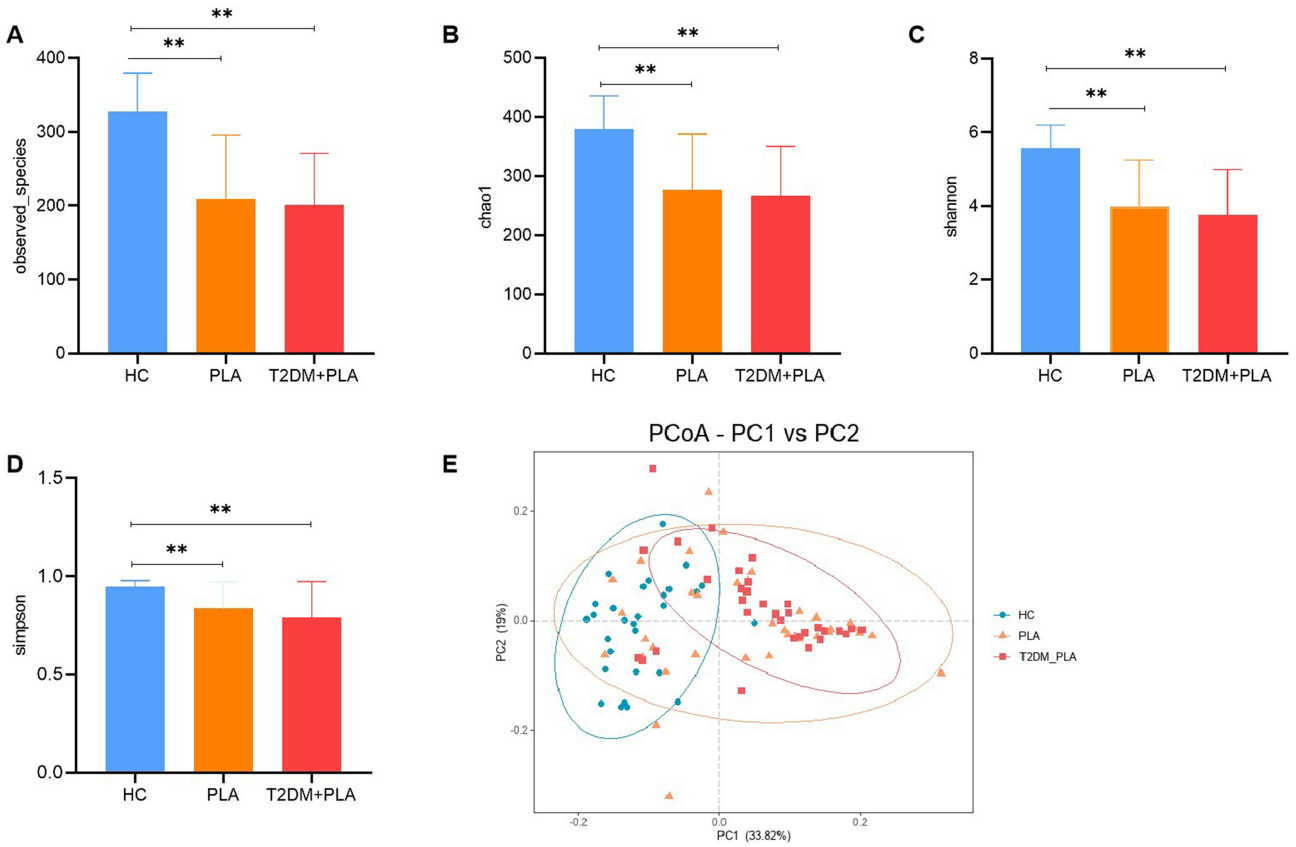

Figure 1 Differences in fecal microbial diversity and community structures in patients with T2DM+PLA (n = 32), patients with PLA (n = 32), and HCs (n = 29). (**A**) Observed species; (**B**) Chao1 diversity index; (**C**) Simpson diversity index; (**D**) Shannon diversity index; and (**E**) β-diversity assessed by principal coordinate analysis of the weighted UniFrac distance. The horizontal and vertical axes in (**E**) represent the first and second principal coordinates in the principal coordinate analysis. $^{**}P < 0.01$.

of these, 60 genera were found in the HC group, and 17 genera were found in the PLA group (Figures 3A and B). Eighty-four genera displayed significant differences between the HC group and the T2DM+PLA group, with 63 genera in the HC group and 21 genera in the T2DM+PLA group (Figures 3C and D). When comparing the two PLA groups, significant differences were observed in 9 genera. In the PLA group, the gut microbiome was dominated by *Lactobacillus, LachnospiraceaeNC2004group, Eubacterium_eligensgroup, Lachnospira, Eisenbergiella, Coprococcus2*, and *Romboutsia*; in contrast, in the T2DM+PLA group, the microbiome was dominated by the *Anaerosporobacter and Megamonas* (Figures 3E and F).

Discussion

We detected inflammatory mediators, liver function indices, and coagulation indicators in this study. In the present study, PLA patients with DM had longer hospital stays and drainage times compared with PLA patients without DM, consistent with previous findings.[20] In the present study, PLA patients with DM had notably elevated levels of D-dimer and FDP compared with PLA patients without DM.Lee et al reported that PLA patients with DM caused by *Klebsiella pneumoniae* displayed platelet hyperreactivity.[24] Furthermore, individuals with liver abscess were found to be susceptible to hepatic venous thrombophlebitis,[25] which can lead to cerebral venous thrombosis[26] and pulmonary embolism.[27] The resolution of venous thrombosis is closely linked to the resolution of PLA.[28] The mechanism by which DM contributes to higher blood coagulation indexes in PLA patients requires further study. Both the present study and past findings highlight the importance of monitoring the coagulation status of PLA patients and implementing timely intervention measures to prevent the development of thrombotic diseases.

In this study, we identified specific signatures of the fecal microbiota in PLA patients with DM, PLA patients without DM, and matched HCs. We found significant differences in the microbiota composition along with decreases in both the

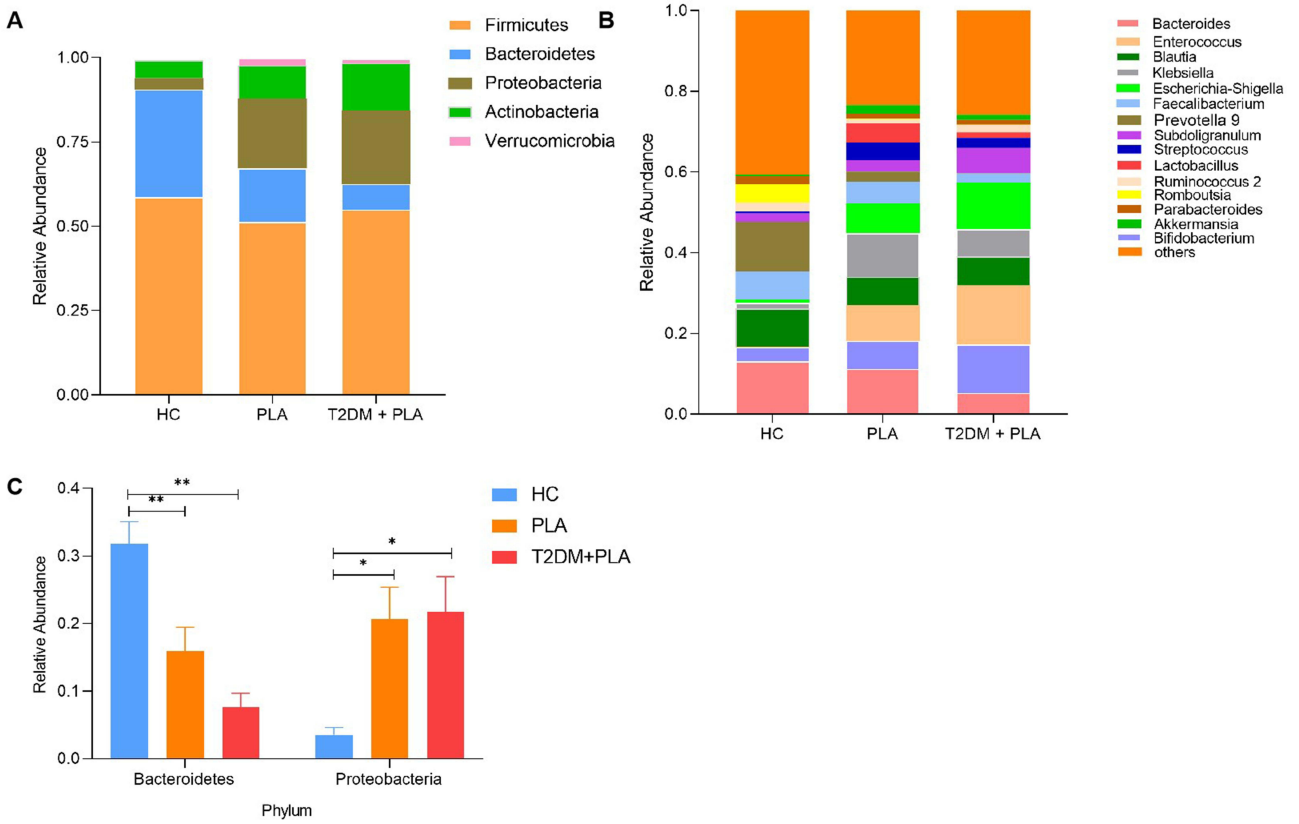

Figure 2 The major gut bacterial phyla and genera in the three groups. (**A**) Bacterial phylum level among three groups. (**B**) Bacterial genus level among three groups. (**C**) Comparison of the relative abundances of gut microbiota at the phylum level. The *P*-values were calculated by Mann–Whitney *U*-test. *$P < 0.05$, **$P < 0.01$.

diversity and abundance of gut microbiota in PLA patients compared to the HCs. These findings are consistent with previous studies demonstrated decreases in gut microbiota diversity in animal models of liver abscess[17,19] and lower microbial diversity in Hepatitis C Virus(HCV) patients compared to HCs.[29] Based on these findings, we speculate that the richness and diversity of the gut microbiome play a role in the pathogenesis of patients with PLA. However, further studies are needed to investigate the specific mechanisms involved.

The gut microbial composition was examined at different phylogenetic levels. At the phylum level, *Proteobacteria* were more abundant than *Bacteroidetes* in both PLA groups compared with the HCs. At the genus level, the relative abundances of the *Blautia* and *Prevotella9* genera were lower in the PLA groups than in the HC group. These genera are responsible for producing short-chain fatty acids and participating in immune response by regulating phagocytosis and chemokines.[30,31] Patients with liver cirrhosis have lower levels of *Bacteroidetes* and higher levels of *Proteobacteria* compared to healthy people.[15,32] The abundance of the *Prevotella* genus was also reduced in patients with severe fever associated with thrombocytopenia syndrome.[33] Wang et al found that the level of *Prevotella* was the same in patients with non-alcoholic fatty liver disease as in healthy individuals.[34] Thus, the alterations in gut microbiota associated with

Table 2 Comparison of the Relative Abundances of Gut Microbiota at the Genus Level Among the Three Groups

Group	HC	T2DM+PLA
HC	–	*Bacteroides, Blautia, Prevotella9, Faecalibacterium* decrease.*Enterococcus,Escherichia-Shigella* increase
PLA	*Blautia,Prevotella9* decrease *Enterococcus, Escherichia-Shigella* increase	*Lactobacillus, Klebsiella* decrease

Note: The term "–" represents that no comparison was made within the same group.

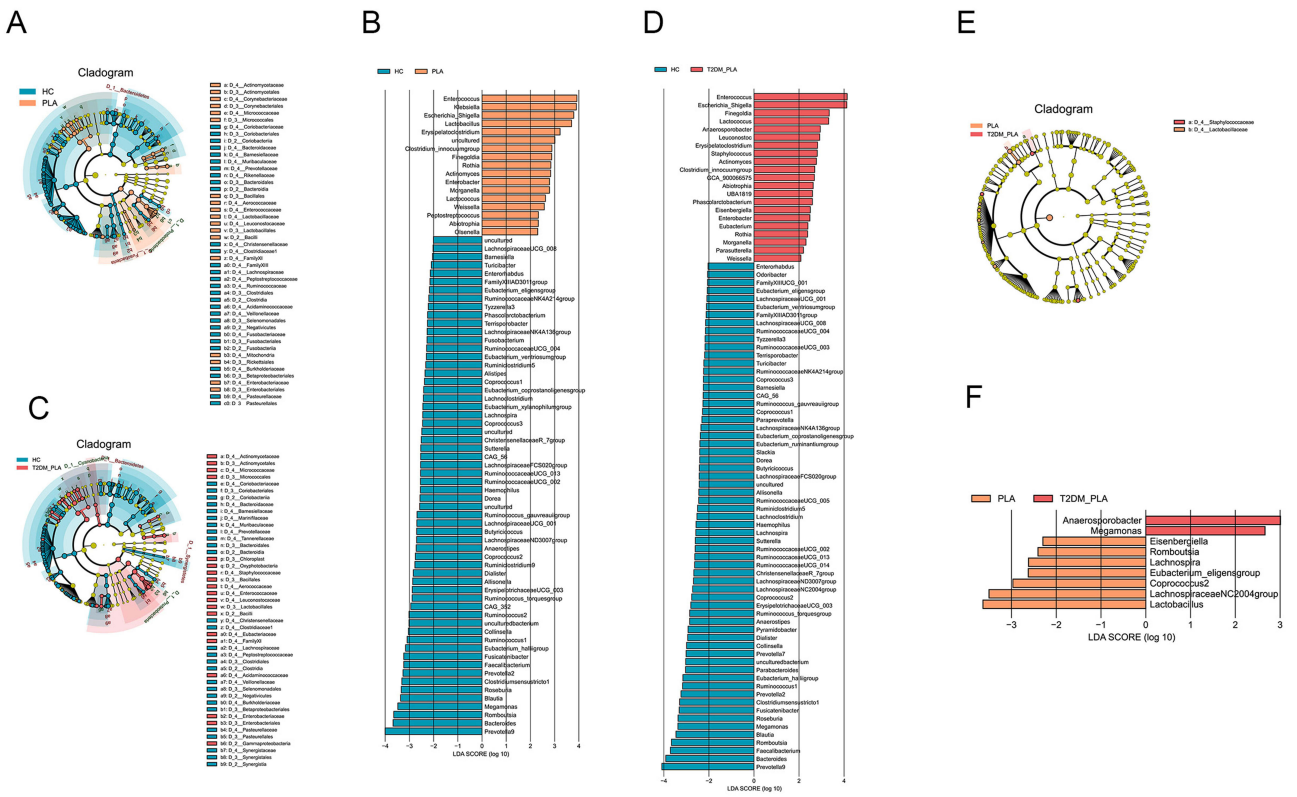

Figure 3 Relative abundances of different species in the three groups identified by LEfSe analysis. The length of the column represents the influence of significantly different species in relative abundance (linear discriminant analysis score > 2). The significantly different species are shown in the cladogram. Each circle represents phylogenetic level from the phylum to genus moving from inside to outside. The diameter of each circle is proportional to the taxon abundance, The PLA, T2DM+PLA, and HC groups are indicated in Orange, red, and blue, respectively. (**A** and **B**) PLA and HC; (**C** and **D**) T2DM+PLA and HC; and (**E** and **F**) PLA and T2DM+PLA.

different diseases have unique characteristics. In the present study, we observed an increase in the abundance of *Enterococcus* and *Escherichia-Shigella* in the PLA patients compared with the HCs. The presence of *Escherichia-Shigella* could potentially impair hepatic lipid metabolism, produce lipopolysaccharides, and contribute to liver injury related to intra-abdominal hypertension.[35,36] Differences in gut microbial may be one reason why PLA patients with DM have more serious clinical manifestations than those without DM.

The abundances of the genera *Lactobacillus* and *Klebsiella* were decreased in the T2DM+PLA group compared with PLA group. The microbiota in T2DM patients is primarily characterized by a reduction in *Roseburia intestinalis* and *Faecalibacterium prausnitzii* along with moderate dysbiosis, a proinflammatory environment, and increased intestinal permeability.[37] The interaction between the changes in bacterial flora in T2DM and PLA requires further study. The pathogenic bacterium *Klebsiella pneumoniae* is commonly found in PLA patients with DM.[10,38] Zhang et al demonstrated that *Klebsiella pneumoniae* liver abscesses are mixed abscesses infected by *Klebsiella pneumoniae* along with other bacteria.[39] Guo et al reported that the relative abundance of *Klebsiella* in the pus cavity of PLA patients with DM was higher than that in PLA patients without DM.[20] This might reflect an increase in the relative abundance of *Klebsiella pneumoniae* within the *Klebsiella genus*; alternatively, bacterial interactions might lead to the enhanced virulence of *Klebsiella pneumoniae*. In an animal model, *Klebsiella pneumoniae* strains were able to cross the intestinal barrier and pass through the portal vein to the liver.[40] Therefore, it is possible that the gut microbial imbalance damaged the intestinal barrier and increased intestinal permeability. As a result, pathogens entered the portal vein and liver, leading to a decrease in *Klebsiella*. Interestingly, changes in the composition of the intestinal flora have been shown to significantly affect the levels of metabolites in the host.[41,42] To understand the underlying mechanism, further investigation using targeted metabolomics is necessary.

Several different probiotic strains, particularly those belonging to *Lactobacillus* and *Bifidobacterium*, have been shown to improve parameters related to T2DM.[37] Future studies could explore the potential of beneficial bacteria to prevent or delay the

progression of PLA in patients with DM through precision medicine. This study identified relevant biomarkers of these diseases, which may play a role in the diagnosis of these diseases.

This study has some limitations. First, it was a single-center study with a limited sample size, and the results are preliminary. Further research is needed to validate the findings in a more diverse population. Second, additional investigation is required to identify the specific mechanisms that connect PLA with changes in the gut microbiota.

Conclusion

In summary, we found that PLA patients with DM exhibited more severe clinical symptoms than those without DM. We also observed significant alterations in the gut microbiota of PLA patients with DM compared with both PLA patients without DM and the HCs. Compared with the HCs, the intestinal microbiomes of PLA patients with DM showed reduced diversity and noticeable changes in composition. These findings establish a theoretical basis for the prevention and treatment of PLA.

Data Sharing Statement

The datasets utilized and/or analyzed during the present study can be obtained from the corresponding author.

Ethics Approval

The research followed the principles of the Declaration of Helsinki. The Ethics Committee of The First People's Hospital of Lianyungang granted approval for this study. The patients/participants provided written informed consent to participate in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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.

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