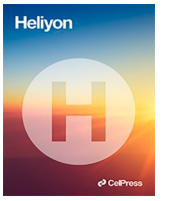
Heliyon 9 (2023) e21662

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Exploring the diversity of blood microbiome during liver diseases: Unveiling Novel diagnostic and therapeutic Avenues

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ARTICLE INFO

Keywords:
Blood microbiome
Liver disease
Microbial components
Microbial translocation
Fecal microbiota transplantation (FMT)

ABSTRACT

Liver diseases are a group of major metabolic and immune or inflammation related diseases caused due to various reasons including infection, abnormalities in immune system, genetic defects, and lifestyle habits. However, the cause-effect relationship is not completely understood in liver disease. The role of microbiome, particularly, the role of gut and oral microbiome in liver diseases has been extensively studied in recent years. More interestingly, the presence of blood microbiome and tissue microbiome has been identified in many liver diseases. The translocation of microbes from the gut into the portal circulation has been attributed to be the major reason for the presence of blood microbial components and its clinical implications in liver disorders. Besides microbial translocation, Pathogen associated Molecular Patterns (PAMPs) derived from gut microbiota might also translocate. The presence of blood microbiome in liver disease has been reviewed earlier. However, the role of blood microbiome as a biomarker and therapeutic target in liver diseases has not been analysed earlier. In this review, we confabulate the origin and physiology of blood microbiome and blood microbial components in relation to the progression and pathogenesis of liver disease. In conclusion, we discuss the translational perspectives targeting the blood microbial components in the diagnosis and therapy of liver disease.

1. Introduction

Liver disease is the fifth leading cause of mortality across the world and accounts for approximately two million deaths per year worldwide. Chronic Liver disease accounted for 2.2 % of deaths and 1.5 % of disability in 2016 [1]. In the United States, Liver diseases were the second leading cause of death amongst all digestive diseases [2].

Over the past years, viral hepatitis has been considered as the leading cause of mortality due to liver disease. However, this rate has decreased over the years due to increased prevention strategies [3]. On the other hand, obesity and alcohol consumption have become key risk factors of liver diseases. They are estimated to drive liver disease epidemiology and account for increased proportions of

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https://doi.org/10.1016/j.heliyon.2023.e21662
Received 6 June 2023; Received in revised form 7 October 2023; Accepted 25 October 2023
Available online 30 October 2023

Glossary of abbreviations

PAMPs	Pathogen Associated Molecular Patterns
FMT	Fecal Microbiota Transplantation
NAFLD	Non-Alcoholic Fatty Liver Disease
NAFL	Non-alcoholic Fatty Liver
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
ALD	Alcoholic Liver Disease
NASH	Non-alcoholic Steatohepatitis
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
HCC	Hepatocellular Carcinoma
LPS	Lipopolysaccharide
LBP	LPS Binding Protein
LTA	Lipoteichoic Acids
16S rDNA	16S ribosomal DNA
M Cells	Microfold Cells
NOD1	Nucleotide-binding oligomerization domain-containing protein 1
TIPS	Transjugular Intrahepatic Portosystemic Shunt
MELD Score	Model for End-stage Liver Disease score
HB-ACLF	Hepatitis B-Acute on Chronic Liver Failure
H_2S	Hydrogen Sulphide
HE	Hepatic Encephalopathy
NHE	Without Hepatic Encephalopathy
LC-HE	Liver Cirrhosis with Hepatic Encephalopathy
LC-NHE	Liver Cirrhosis without Hepatic Encephalopathy
HVPG	Hepatic venous pressure gradient
PH	Portal Hypertension
TLR	Toll-like Receptor
SCFAs	Short Chain Fatty Acids
AAA	Aromatic Amino Acids
TMA	Trimethyl amines
SAH	Severe Alcoholic Hepatitis

mortality due to liver disease in the future. The number of liver disease cases is estimated to be 1.5 billion worldwide. The most common causes of liver disease are non-alcoholic fatty liver disease (NAFLD), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and alcoholic liver disease (ALD) [4]. Some of the common liver diseases are alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD)/Non-alcoholic Steatohepatitis (NASH), Hepatitis B and C virus infections (HBV and HCV), Primary biliary cholangitis (PBC), Primary sclerosing cholangitis (PSC), liver fibrosis, liver cirrhosis and Hepatocellular carcinoma (HCC). The annual mortality rate due to liver cirrhosis has been represented in Fig. 1.

The blood microbiome has been recently identified in liver disease patients. The blood microbiome comprises of the microbial components including PAMPs and microbial metabolites released from the gut due to gut injury or gut leakage. The actual "meaning" of bacteria in blood is the presence of bacterial components and/or bacterial metabolites that are released into the circulation from internal tissues like gut. These bacterial components reach the liver through hepatic circulation.

2. Blood microbiome

Due to the extensive use of antibiotics, vaccines and improved sanitation, the occurrence of infectious diseases has decreased rapidly and this has resulted in the increase in the incidence of metabolic diseases like liver diseases. The blood microbiome identified in liver diseases over the past decade, could be a source of antigens responsible for the onset of liver diseases.

2.1. Blood microbiome in healthy individuals

For centuries together, blood was strongly believed to be a germ-free environment [5]. Very rarely, it has been observed that bacteria could live inside red blood cells [6] and leukocytes [5]. Subsequently, L-forms and Corynebacteria like forms were visualized inside human red blood cells by electron microscope [7,8]. Until the mid- 20th century, microbes in the circulation were identified only in infectious disease cases and hence were considered pathogenic. It was in the beginning of 21st century, Nikkari et al. detected bacterial DNA for the first time in the blood of healthy individuals [9]. Later, bacteria were detected by amplification of the prokaryotic

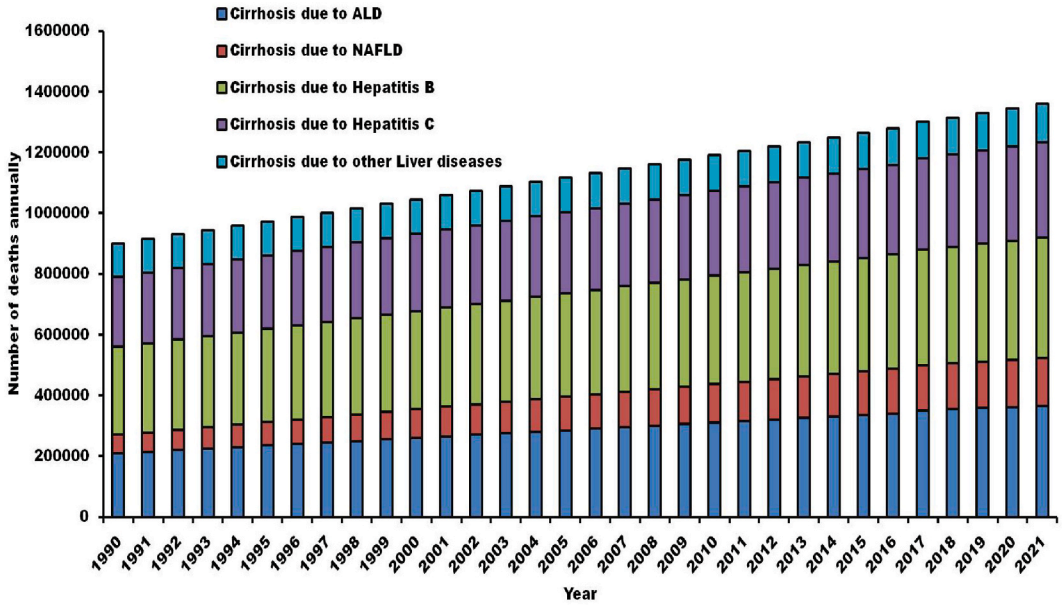

Fig. 1. Number of deaths due to cirrhosis every year globally, by etiology.
Source: References [2–4]. ALD: Alcoholic liver disease, NAFLD: Non-alcoholic fatty liver disease

16S rDNA gene in healthy human blood [10]. In the subsequent years, microbial components were identified in healthy circulation more too often by the availability of next generation sequencing techniques [11,12]. Metagenome shotgun sequencing of the blood has also shown the presence of viral and archaeal DNA in healthy blood [13]. In continuation with the earlier findings, intracellular L-forms or pleomorphic forms of bacteria were detected in healthy human blood [14]. More recently, there was a report on the detection of fungal microbiome in the blood of healthy individuals [15].

The healthy blood microbiota was found to vary from healthy gut microbiota. The healthy gut was found to be dominated by Firmicutes and Bacteroidetes. On the other hand, the healthy blood predominantly contains Proteobacteria [16,17]. The healthy blood microbiota is considered to be dormant because it does not induce clinical complications. However, the dormant state may enable microbes or their components to evade the host immune system. The microbial components remain dormant in blood for many years, either in the living or non-living state [18]. Earlier studies have reported that the dormant state of microbes plays a major role in their ability to sustain antibiotic treatment and causing disease [19]. Dormant bacteria in blood can shed cell membrane components like LPS and LBP during disease conditions to become pathogenic. The genetic material of non-viable bacterial cells may play a vital role in many disease conditions by acting on host cells.

2.2. How do genetic traces of microbes enter the circulation?

The concept of microbial products including microbial metabolites from the gut entering the circulation has been known for many years. This was earlier denoted by many terms such as endotoxemia. Endotoxemia was identified in patients by the detection of lipopolysaccharides (LPS), LPS binding protein (LBP) and lipoteichoic acids (LTA) in the circulation. In recent years, this concept or phenomenon is known by the term called Microbial translocation. Microbial translocation from the gut or the oral tract to the circulation occurs by various mechanisms. Microbial translocation is usually assessed in blood samples by the quantification of PAMPs (LPS, LBP etc.) [20], bacterial DNA or RNA fragments [21], serum CD14 levels [22], endotoxin core antibodies and antiflagellin antibodies [23]. Over the past decades, 16S rDNA gene is detected and quantitated in blood to assess bacterial translocation [21].

2.2.1. Mechanism of microbial translocation across the intestinal barrier

The intestine functions as an effective immunological barrier against intraluminal bacteria from entering the circulation. The gut barrier is formed by a well functioning immune system, properly balanced microflora and an intact mucosa. The innate immune defense system of the intestine is formed by the Peyer's patches in the intestinal crypts, along with lymphocytes and macrophages [24]. A stable ecological balance is maintained in the intestine to prevent bacterial overgrowth and subsequent translocation. When one or more of these defensive mechanisms are impaired, viable microbes or their products such as PAMPs may pass through this barrier and reach the mesenteric lymph nodes or other organs *via* lymphatic drainage and circulation resulting in microbial translocation. These microbes or their components persist in circulation in diseased conditions. Also, practically, PAMPs such as LPS persist in the blood in healthy situation, albeit at a lower concentration.

Many immunological mechanisms are considered responsible for gut leakage. Tight junctions hold the enterocytes together. Bacteria initially adhere to the enterocytes by binding to the receptors on the cell membrane and slowly move to the basal membrane.

The movement of bacterial products occurs either through the paracellular route through tight junctions or the transcellular route through enterocytes [25]. The movement of bacterial and viral components across the gut barrier involves an intricate immunological process. One proven process is by direct cellular uptake through the activation of NOD1 receptors in Microfold cells (M cells) of the Peyer's patches by damage to the gut epithelial cells [26]. Portal vein endotoxemia of gut origin occurs frequently in liver diseases leading to spontaneous bacterial peritonitis [27,21]. The intestinal bacteria are carried to mesenteric lymph nodes by lymphatic drainage from where they spread to other tissues *via* circulation [28]. Interestingly, the process of microbial translocation was also known to occur in the healthy human intestine [29] and appears to begin early in life [30] (Fig. 2).

2.2.2. Mechanism of microbial translocation from the oral cavity

Transient bacteremia is known to occur in patients when exposed to chronic oral infections for a long period. Bacteria have been detected in blood after periodontal surgery, tooth extraction and even after normal tooth brushing [31]. Oral infections like dental caries led to destruction of periodontium, dentin, enamel and the root surfaces of teeth. Translocation of bacteria and their products into the circulation through the oral route has been reported in previous studies [32,33].

Microbial products, virulent components and metabolites are continuously shed into the circulation by disruption of oral biofilms on tooth surface. This disruption may occur because of oral dysbiosis during dental caries, periodontitis, endodontis etc., various dental procedures, daily oral hygiene efforts and even during gentle mastication. In particular, there are innumerable studies on *P. gingivalis*, which is well known to cause oral dysbiosis in many oral diseases [34]. The propinquity of bacteria in the root canal and periapical tissues to the bloodstream can cause bacteremia during clinical dental procedures like tooth extraction, periodontal and endodontic treatments.

3. Microbiota in the pathogenesis of liver disease

The oral-gut-liver-immune system axis plays a significant role in the pathogenesis of liver disease. There are extensive studies on the dysbiosis of gut microbiota in many liver diseases. The healthy gut microbiota harbours a major proportion of Firmicutes and Bacteroidetes and a meagre proportion of Actinobacteria and Proteobacteria [35]. This healthy nature of the human gut is perturbed in liver diseases resulting in dysbiosis of the gut microbiota. Also, perturbed gut microbiota may lead to liver disease complications. It is

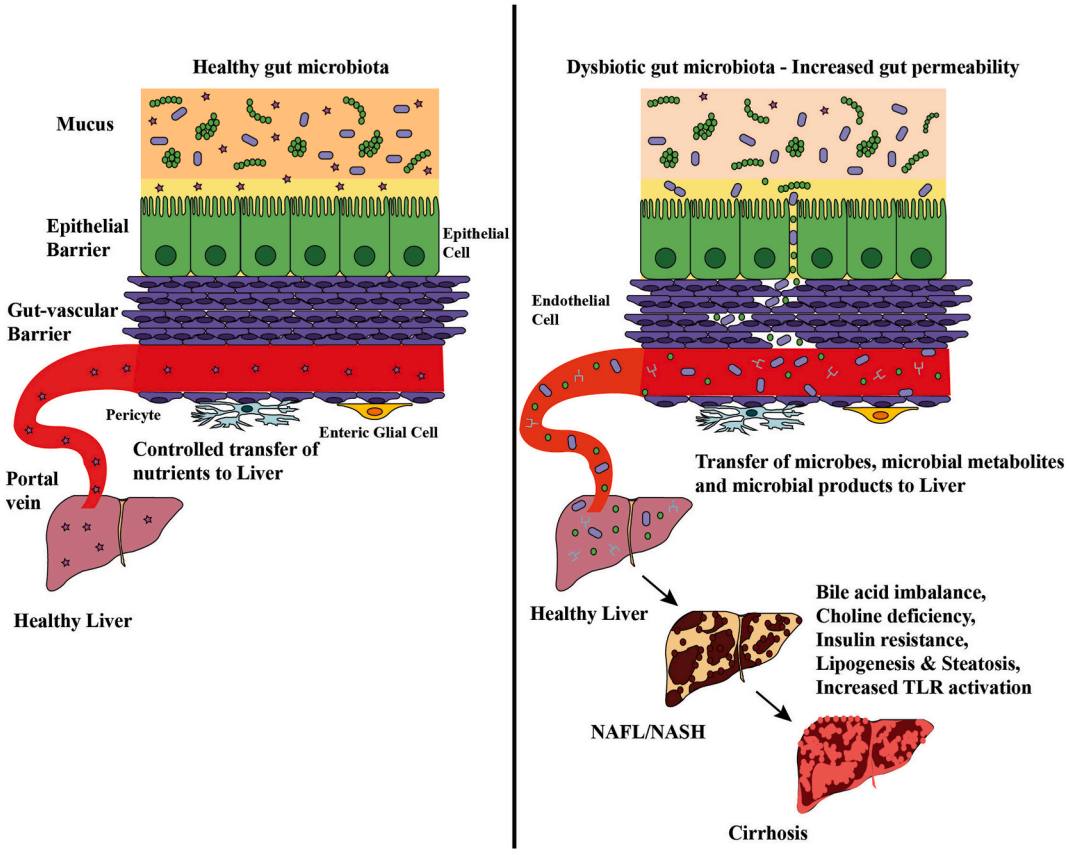

Fig. 2. Schematic representation of an increase in blood microbiota concentration due to gut microbiota dysbiosis in liver disease patients NAFL: Non-alcoholic Fatty Liver, NASH: Non-alcoholic Steatohepatitis, TLR: Toll-like receptor.

Table 1
Studies on blood microbiome in liver disease patients.

Sl. No.	Sample size	Type of Liver disease	Starting material	Methods employed	Key inferences	Reference
1	28 hospitalised patients.	Liver cirrhosis.	Serum	Detection of 16S rRNA sequences by PCR followed by 16S rRNA Sanger sequencing.	Bacterial DNA was detected in the serum of 9 of 28 patients.	Such et al., 2002 [36]
2	17 hospitalised patients.	Liver cirrhosis with ascites.	Serum	Detection of 16S rRNA sequences by qPCR followed by 16S rRNA Sanger sequencing.	*E. coli* was identified in four patients; *C. freundii* was identified in two patients; and *K. pneumoniae* was detected in one patient. In all cases, the same bacterial species were found in the blood and ascitic fluid during admission and in subsequent detections after time.	Frances et al., 2004 [21]
3	258 hospitalised patients.	Liver cirrhosis with ascites.	Blood	Quantification of 16S rRNA sequences by qPCR followed by 16S rRNA Sanger sequencing.	Four species were identified in group II patients (*E. coli* in 41, *Klebsiella* in 10, *S. aureus* in 13, and *E. faecalis* in 13) and group III patients (*E. coli* in 12, *Klebsiella* in 3, *S. aureus* in 4, *S. pneumoniae* in 2, and *E. faecalis* in 1).	Frances et al., 2008 [37]
4	79 hospitalised patients.	Liver cirrhosis.	Blood	Quantification of 16S rRNA sequences by qPCR followed by 16S rRNA Sanger sequencing.	Bacterial DNA was detected in the serum of only patients with ascites (in 38 %; 21/55 patients). Bacterial species identified were: *E. coli* (n = 11), *K. pneumoniae* (n = 5), *E. faecalis* (n = 2), and *S. aureus* (n = 3).	Bellot et al., 2010 [38]
5	Discovery cohort of 50 Spanish obese patients and validation cohort of 71 Italian obese patients.	Liver fibrosis and healthy individuals.	Blood	16S rRNA amplicon Sequencing.	Specific differences were found in the proportion of several bacterial taxa in both blood and feces that correlate with the presence of liver fibrosis. Blood microbiota of obese patients was dominated by Proteobacteria with a meagre concentration of Actinobacteria, Firmicutes and Bactroidetes	Lelouvier et al., 2016 [39]
6	60 patients and 17 healthy controls.	Liver cirrhosis and healthy individuals.	Serum	16S rRNA amplicon Sequencing.	Serum microbiome of patients with ascites presented higher levels of lipopolysaccharide binding protein (LBP), associated with higher diversity and relative abundance of Clostridiales and Cyanobacteria compared to patients without ascites.	Santiago et al., 2016 [40]
7	Cirrhotic patients.	Decompensated Liver cirrhosis.	Blood	Microbial DNA qPCR Array.	Increased blood microbial diversity in conjunction with inflammatory response and systemic hemodynamic parameters was reported in decompensated cirrhotic patients as compared to healthy individuals.	Traykova et al., 2017 [41]
8	35 patients and 14 healthy controls.	Liver cirrhosis and healthy controls.	Serum	16S rRNA amplicon sequencing.	Presence of shared members of Proteobacteria phyla in peripheral and portal circulation of patients with liver cirrhosis.	Lebba et al., 2018 [42]
9	Moderate Alcoholic Hepatitis (MAH) (n = 18), severe Alcoholic Hepatitis (SAH) (n = 19), heavy drinking controls (HDCs) (n = 19) and Non-alcohol consuming controls (NACs) (n = 20).	Alcoholic hepatitis and healthy controls.	Blood	16S rRNA amplicon sequencing.	An increased bacterial concentration in alcoholic hepatitis patients as compared to controls. The alcohol consuming groups (alcoholic hepatitis and heavy drinking controls) had an increased concentration of Fusobacteria and a decreased proportion of Bacteroidetes as	Puri et al., 2018 [43]

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Table 1 (*continued*)

Sl. No.	Sample size	Type of Liver disease	Starting material	Methods employed	Key inferences	Reference
					compared to the non-alcohol consuming controls.	
10	Seven patients.	Decompensated Liver cirrhosis.	Blood	16S rRNA amplicon sequencing.	Identified 65 genera belonging to four phyla, predominantly Proteobacteria, followed by Actinobacteria, Bactroidetes and Firmicutes. Blood microbiota was similar in portal, hepatic, central and peripheral venous circulation.	Schierwagen et al., 2019 [44]
11	76 patients and 192 healthy controls.	Nonalcoholic fatty liver disease (NAFLD) and healthy controls.	Blood	16S rRNA amplicon sequencing.	Obese NAFLD group showed a distinct bacterial community with a lower biodiversity and a far distant phylotype compared with the lean control group. In the blood microbiota alone, Succinivibrionaceae showed opposite correlations in the lean and obese NAFLD groups.	Yun et al., 2019 [45]
12	33 patients.	Decompensated liver cirrhosis.	Blood	16S rRNA amplicon sequencing.	Differences in microbial composition and diversity between ascites and blood were identified. Proteobacteria was the most abundant phylum detected in ascites samples followed by Firmicutes, Actinobacteria, Bacteroidetes, and Gemmatimonadetes. The phylum composition in the blood samples was slightly different, with Proteobacteria accounting for nearly 90 %, while Actinobacteria, Firmicutes, and Bacteroidetes accounted for meager proportions.	Alvarez-Silva et al., 2019 [46]
13	79 patients with Hepatocellular carcinoma (HCC), 83 patients with cirrhosis, and 201 matching healthy controls.	Hepatocellular carcinoma (HCC), Cirrhosis and healthy controls.	Serum	16S rRNA pyrosequencing.	Blood microbial diversity was significantly reduced in HCC, compared with cirrhosis and controls. Blood microbiomes in all the groups were dominated by Firmicutes and Proteobacteria, followed by Actinobacteria and Bacteroidetes in meager concentrations. 5 microbial gene markers were identified which distinguished HCC from controls.	Cho et al., 2019 [47]
14	50 Hepatitis B- Acute on Chronic Liver Failure (HB-ACLF) patients, 25 patients with compensated liver cirrhosis (C-LC) and 23 healthy controls.	Hepatitis B- Acute on Chronic Liver Failure (HB-ACLF), compensated liver cirrhosis and healthy controls.	Plasma	16S rRNA amplicon sequencing.	Circulating bacterial DNA was significantly increased in HB-ACLF patients compared to that in the liver cirrhosis and controls. HB-ACLF patients showed a considerable decrease in circulating microbial diversity. HB-ACLF patients showed an enrichment of Moraxellaceae, Sulfurovum, Comamonas and Burkholderiaceae. But were depleted in Actinobacteria, Deinococcus-Thermus, Alphaproteobacteria, Xanthomonadaceae and Enterobacteriaceae compared to controls.	Zhang et al., 2019 [48]
15	66 patients and 14 healthy individuals.	Liver cirrhosis and healthy individuals.	Blood	16S rRNA amplicon sequencing.	183 genera were identified in cirrhotics as compared to 123 genera in controls. Enterobacteriaceae was significantly higher in cirrhotics	Kajihara et al., 2019 [49]

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Table 1 (*continued*)

Sl. No.	Sample size	Type of Liver disease	Starting material	Methods employed	Key inferences	Reference
					whereas *Akkermansia*, Rikenellaceae and Erysipelotrichales were significantly lower in cirrhotics compared to controls.	
16	30 liver cirrhosis patients with hepatic encephalopathy (LC-HE), 33 liver cirrhosis patients with non-hepatic encephalopathy (LC-NHE) and 26 healthy controls.	Liver cirrhosis with (HE) and without hepatic encephalopathy (NHE) and healthy individuals.	Blood	16S rRNA amplicon sequencing.	*Staphylococcus* and Chloroflexi were increased in the circulation of HE patients. Whereas, *Pseudomonas alcaligenes* was detected in the NHE group.	Jin et al., 2020 [50]
17	32 patients (21 HIV-positive).	HCV-related cirrhosis with clinically significant portal hypertension.	Blood	16S rRNA amplicon sequencing.	Corynebacteriales, Diplorickettsiaceae, Diplorickettsiales, *Corynebacterium*, *Aquicella* and *Undibacterium parvum* had higher relative abundances in patients who reached a decrease in clinically significant portal hypertension (HVPG), while Halomonadaceae, Oceanospirillales, Rhodospirillales and *Massilia* had higher relative abundances in patients who did not show decrease in HVPG. Corynebacteriales and *Massilia* were significantly correlated with the plasma markers of inflammation and metabolites at baseline.	Virseda-Berdices et al., 2022 [51]
18	58 patients and 46 healthy controls.	Liver cirrhosis with portal hypertension and healthy controls.	Plasma	16S rRNA amplicon sequencing.	Cirrhosis patients with portal hypertension had an enrichment of *Comamonas*, *Cnuella*, *Dialister*, *Escherichia*, *Shigella*, and *Prevotella* and the depletion of *Bradyrhizobium*, *Curvibacter*, *Diaphorobacter*, *Pseudarcicella*, and *Pseudomonas*. Enrichment of the genera *Bacteroides*, *Escherichia*, *Shigella*, and *Prevotella* was associated with severe PH (SPH) in both hepatic and peripheral vein compartments. *Escherichia*, *Shigella* and *Prevotella* abundance was correlated with IL-8 levels in the hepatic vein.	Gedgaudas et al., 2022 [52]
19	129 (study cohort) and 58 (validation cohort) acutely decompensated liver cirrhosis patients and 120 non-cirrhosis controls (severe sepsis and haematological malignancies)	Acutely decompensated liver cirrhosis (study and validation cohort) and non-cirrhosis controls	Plasma	Metagenomic shotgun DNA and RNA sequencing.	188 microorganisms were detected in 74.4 % (96/129) patients, including viruses (58.0 %), bacteria (34.1 %), fungi (7.4 %) and chlamydia (0.5 %). Patients with Acutely decompensated liver cirrhosis had a Non Hepatotrophic Virus (NHV) signature and Cytomegalo virus (CMV) was the most frequent NHV. The NHV signature in acute-on-chronic liver failure (ACLF) patients was found to be similar to patients with sepsis and haematological malignancies. The treatable NHV, CMV was detected in 24.1 % (14/58) patients in the validation cohort.	Li et al., 2023 [53]

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Table 1 (*continued*)

Sl. No.	Sample size	Type of Liver disease	Starting material	Methods employed	Key inferences	Reference
20	A total of 223 Severe Alcoholic Hepatitis (SAH) patients, 70 in derivative [50 responders (R) and 20 non-responders (NR)] and 153 in validation cohort [136R, 17NR]	Severe Alcoholic Hepatitis (SAH)	Plasma	Plasma Metabolomics/*meta*-proteomics	Plasma urobilinogen directly correlated with circulating bacterial peptides linked to bilirubin. Increase in plasma Urobilinogen pedals a vicious cycle of bacterial translocation and increase in inflammation and corticosteroid non-response in SAH patients	Yadav et al., 2023 [54]
21	160 patients with liver diseases [Cirrhosis-Sepsis/ Nonsepsis (n = 110); Non-cirrhosis (n = 50)]. Untargeted metaproteomics-metabolomics was performed on a training cohort of 110 patients (Cirrhosis-Sepsis/ Nonsepsis; n = 70 and Non-cirrhosis; n = 40).	Pediatric Cirrhosis and non-cirrhosis controls	Blood and Plasma	Microbial Peptide Sequencing and Plasma Metabolomics/*meta*-proteomics	Increased levels of *Salmonella enterica* and *Escherichia coli* associated peptides were found in cirrhotic patients. Increased levels of *Leifsonia xyli* were found in Pediatric Cirrhosis- Sepsis (PC–S) patients. Increased *Leifsonia xyli*, *Mycoplasma genitalium* and *Hungateiclostridium Thermocellum* were found in PC-S Non-survivors.	Mathew et al., 2023 [55]
22	159 liver disease patients including NAFLD patients (n = 21), Compensated cirrhosis patients (n = 27) and HCC patients (n = 111).	HCC, Cirrhotic and NAFLD patients	Blood	16S rRNA amplicon sequencing.	HCC and cirrhosis patients showed an increased abundance of Ruminococcaceae and Bacteroidaceae in blood as compared to NAFLD patients. The authors were able to prove the translocation of these bacteria from gut to blood in HCC and Cirrhosis patients.	Effenberger et al., 2023 [56]
23	28 liver disease patients including (14 ALD patients and 14 NAFLD patients) and 8 healthy controls.	ALD and NAFLD patients	Blood	16S rRNA amplicon sequencing.	ALD patients showed a significant but temporary increase of microbial DNA quantity in the hepatic and systemic venous blood because of alcohol intervention. But the intervention did not cause a significant change of microbial DNA quantity in the hepatic and systemic venous blood in the healthy controls and NAFLD patients.	Israelsen et al., 2023 [57]
24	12 patients with chronic Hepatitis C Virus infection.	Liver disease patients	Serum	Anellome Sequencing	The presence of the Anello Virus Torque Teno Mini Virus to Torque Teno Midi Virus-expanded anellome was notably more prevalent in individuals experiencing acute liver failure and undergoing liver transplantation, in contrast to other groups of patients with liver diseases.	Zhang et al., 2023 [58]

like the “egg and the chick hypothesis”. The intestinal microbiota and the bacterial products may contribute to liver disease by mechanisms such as intestinal permeability, systemic inflammation, short chain fatty acid production and metabolic changes. Similarly, oral microbiota dysbiosis also plays a role in the pathogenesis of liver disease and augments the concentration of blood microbiome in liver disease patients. The blood microbiome induces the presence of liver tissue microbiome which in turn exacerbates the clinical complications of liver disease.

4. Blood microbiome in liver disease

Blood microbiome in liver diseases originates predominantly due to microbial translocation through the gut-blood-liver axis. One of the clinical complications associated with liver disease and other metabolic diseases is called “the leaky gut phenomenon”, which is the chronic inflammation of intestinal mucosa leading to increased intestinal permeability. This might provoke bacterial translocation leading to a considerable amount and highly divergent bacterial traces in human blood samples. However, blood microbiome and its diagnostic potential has not been investigated in liver diseases until now. The approach employed to gather the comprehensive compilation of studies presented in Table 1 and this section involves utilizing Google Scholar and PubMed search methods. The search

terms utilized include "Blood Microbiome" and "Liver," "Blood Microbiota" and "Liver," "Circulating Microbiome" and "Liver," "Circulating Microbiota" and "Liver," "Blood Virome" and "Liver," as well as "Circulating Virome" and "Liver."

Foot prints of bacteria or rather; bacterial DNA was detected for the first time in the circulation of cirrhosis patients in the year 2002 by PCR amplification and nucleotide sequencing of prokaryotic conserved 16S rRNA gene sequences in the serum of advanced liver cirrhosis patients. Presence of bacterial DNA was detected in the serum of 9 of 28 patients [36]. In the subsequent year, the same group reported the presence of 16S rRNA gene sequences in the serum of cirrhosis patients by quantitative PCR reaction. Seven out of 17 patients showed the presence of bacterial DNA in blood at the time of admission. Also, by 16S rRNA gene nucleotide sequencing, the authors found that bacteria identified during admission were identical to those found in subsequent detections after time [21]. In a similar study, the same group showed the presence of bacterial DNA fragments in the blood of liver cirrhosis patients to prove the concept of bacterial translocation in liver cirrhosis which they have mentioned in their earlier publications [37]. The same group later reported the association of bacterial DNA sequences with inflammatory markers of disease [38].

The concept of blood microbiota in liver disease patients originated for the first time when the group lead by Jacques Amar showed the association of blood microbiota with liver fibrosis in obese patients. The blood microbiota of obese patients was dominated by Proteobacteria with a meagre concentration of Actinobacteria, Firmicutes and Bacteroidetes [39]. Santiago et al. in the same year found difference in the serum microbiome of liver cirrhosis patients as compared to healthy individuals. A complex microbial community was detected in serum of cirrhosis patients as compared to healthy controls. Also, there was difference in the serum microbial diversity in cirrhosis patients with and without ascites. Cirrhotic patients with ascites had a higher concentration of Clostridiales as compared to patients without ascites [40].

In the subsequent year, an increased blood microbial diversity in conjunction with inflammatory response and systemic hemodynamic parameters was reported in decompensated cirrhotic patients as compared to healthy individuals. Intestinal Infections Microbial DNA qPCR Array was used to screen for 53 bacterial DNA from the gut in the blood of both the cirrhotic patients and healthy individuals [41]. Lebba et al. showed the presence of shared members of Proteobacteria phyla in peripheral and portal circulation of patients with liver cirrhosis [42]. They have identified impaired metabolism of short-chain fatty acids (SCFAs) and carbon/methane sources by faecal bacteria in Liver cirrhosis patients as compared to healthy individuals using feces and caecum samples. However, blood samples from healthy individuals were not analysed in this study. In another interesting study, the blood microbiome was compared in alcoholic hepatitis patients, heavy drinking controls and non-alcohol consuming controls. As expected, there was an increased bacterial concentration in alcoholic hepatitis patients as compared to controls. But, both the alcohol consuming groups (alcoholic hepatitis and heavy drinking controls) had an increased concentration of Fusobacteria and a decreased proportion of Bacteroidetes as compared to the non-alcohol consuming controls. This shows the influence of alcohol consumption in the gut and blood microbiome [43].

In a subsequent study, a group in Europe showed that bacteria in the different circulatory compartments were similar in Liver cirrhosis patients which is strong evidence for the concept of bacterial translocation. They characterised the blood microbiome in portal vein (first venous outflow in gut–liver axis), liver outflow, central venous blood and peripheral venous blood from seven patients with decompensated liver cirrhosis receiving transjugular intrahepatic portosystemic shunt (TIPS) for either variceal bleeding (n = 3) or refractory ascites (n = 4). The seven patients had a mean Model for End-stage Liver Disease (MELD) score of 8.4 (range 6–13), Child-Pugh-Score (CHILD A: n = 4, CHILD B: n = 3). They identified 65 genera belonging to four phyla, predominantly Proteobacteria, followed by Actinobacteria, Bactroidetes and Firmicutes [44]. In the same year, the fecal and blood microbiota was studied in obese and lean NAFLD patients. The fecal and blood microbiota profiles were similar among obese and lean NAFLD patients but differed between these two groups, which might serve as potential biomarkers to discriminate these two phenotypes of NAFLD. Obese NAFLD group showed a distinct bacterial community with a lower biodiversity and a far distant phylotype compared with the lean control group. In the blood microbiota alone, Succinivibrionaceae showed opposite correlations in the lean and obese NAFLD groups [45]. In a similar study in decompensated cirrhosis patients, Proteobacteria was identified as the predominant phyla in the blood and ascites samples. Proteobacteria was the most abundant phylum detected in ascites samples followed by Firmicutes, Actinobacteria, Bacteroidetes, and Gemmatimonadetes. The phylum composition in the blood samples was slightly different, with Proteobacteria accounting for nearly 90 %, while Actinobacteria, Firmicutes, and Bacteroidetes accounted for meager proportions [46].

Similar results were obtained in another study performed in the same year in HCC and liver cirrhosis patients. Blood microbial diversity was significantly reduced in HCC patients, compared with cirrhosis patients and controls. Blood microbiomes in all the groups were dominated by Firmicutes and Proteobacteria, followed by Actinobacteria and Bacteroidetes in meager concentrations. 5 microbial gene markers with the potential to distinguish HCC from controls were identified [47]. Comparatively similar results were obtained in Hepatitis B-Acute on Chronic Liver Failure (HB-ACLF) patients as well. HB-ACLF patients showed a significant increase in bacterial DNA compared to that in the liver cirrhosis and controls. HB-ACLF patients showed a considerable decrease in blood microbial diversity. HB-ACLF patients showed an enrichment of Moraxellaceae, Sulfurovum, Comamonas and Burkholderiaceae. But there was a depletion of Actinobacteria, Deinococcus-Thermus, Alphaproteobacteria, Xanthomonadaceae and Enterobacteriaceae in HB-ACLF patients compared to controls [48]. Literally, the same results were obtained in Liver cirrhosis patients in another study performed the same year. Blood microbial diversity was higher in cirrhotics (183 genera) as compared to controls (123 genera). Enterobacteriaceae was found to be significantly higher in cirrhotics whereas *Akkermansia*, Rikenellaceae and Erysipelotrichales were significantly lower in cirrhotics compared to controls [49].

Another study was performed to study the link between microbiota and endogenous Hydrogen Sulphide (H_2S) in the circulation of Liver cirrhosis patients with (HE) and without Hepatic Encephalopathy (NHE). Endogenous H_2S production was found to be significantly associated with different abundances in three taxa between the HE and NHE groups [50]. Another study deals with the work on blood microbiome in HCV related cirrhosis patients. Corynebacteriales, Diplorickettsiaceae, Diplorickettsiales, *Corynebacterium*,

Aquicella and *Undibacterium parvum* had higher relative abundances in patients who reached a decrease in clinically significant portal hypertension (measured by HVPG), while Halomonadaceae, Oceanospirillales, Rhodospirillales and *Massilia* had higher relative abundances in patients who did not show decrease in Hepatic venous pressure gradient (HVPG). Corynebacteriales and *Massilia* were significantly correlated with the plasma markers of inflammation and metabolites at baseline [51].

Another important study is the work on circulating microbiome in cirrhosis patients with portal hypertension. The circulating plasma microbiome profile in cirrhosis patients was different from those of the controls. Cirrhosis patients with portal hypertension (PH) had an enrichment of *Escherichia*, *Shigella*, *Dialister*, *Cnuella*, *Prevotella*, and *Comamonas* and depletion of *Bradyrhizobium*, *Curvibacter*, *Pseudomonas*, *Diaphorobacter*, and *Pseudarcicella*. Enrichment of the genera *Escherichia*, *Prevotella*, *Shigella*, and *Bacteroides* was associated with severe PH in both hepatic and peripheral vein compartments. *Prevotella*, *Escherichia*, and *Shigella* abundance was correlated with IL-8 levels in the hepatic vein [52]. In another study by Li et al., many microorganisms were detected in 74.4 % patients, including viruses, bacteria, fungi and chlamydia [53]. In subsequent plasma metabolomics studies, it was found that plasma urobilinogen was directly correlated with circulating bacterial peptides linked to bilirubin and increased levels of *Salmonella enterica* and *Escherichia coli* associated peptides were found in cirrhotic patients [54,55].

In another recent study, HCC and cirrhosis patients showed an increased abundance of Ruminococcaceae and Bacteroidaceae in blood as compared to NAFLD patients. The authors were able to prove the translocation of these bacteria from gut to blood in HCC and Cirrhosis patients [56]. In the most recent study by Israelsen et al. [57], ALD patients showed a significant but temporary increase of microbial DNA quantity in the hepatic and systemic venous blood because of alcohol intervention. But the intervention did not cause a significant change of microbial DNA quantity in the hepatic and systemic venous blood in the healthy controls and NAFLD patients. In a study on virome sequencing conducted by Zhang et al. [58], it was demonstrated that the occurrence of the expanded anellome from the Anello Virus Torque Teno Mini Virus to Torque Teno Midi Virus was significantly higher among individuals going through acute liver failure and receiving liver transplantation, as opposed to various other patient groups with liver disorders. Taken together, the blood microbiome studies in liver diseases show that the blood microbial diversity increases in liver disease patients as compared to controls. The blood microbiome in liver disease patients is mostly dominated by the phylum Proteobacteria with Actinobacteria, Bactroidetes and Firmicutes in meagre concentrations (Table 1). The methodology for analysis of blood microbiome in liver disease is pictorially represented in Fig. 3.

5. The blood microbiome as diagnostic and therapeutic target in the pathogenesis and treatment of liver disease

At present, many advanced techniques including next-generation sequencing and metabolomics are being employed to detect the

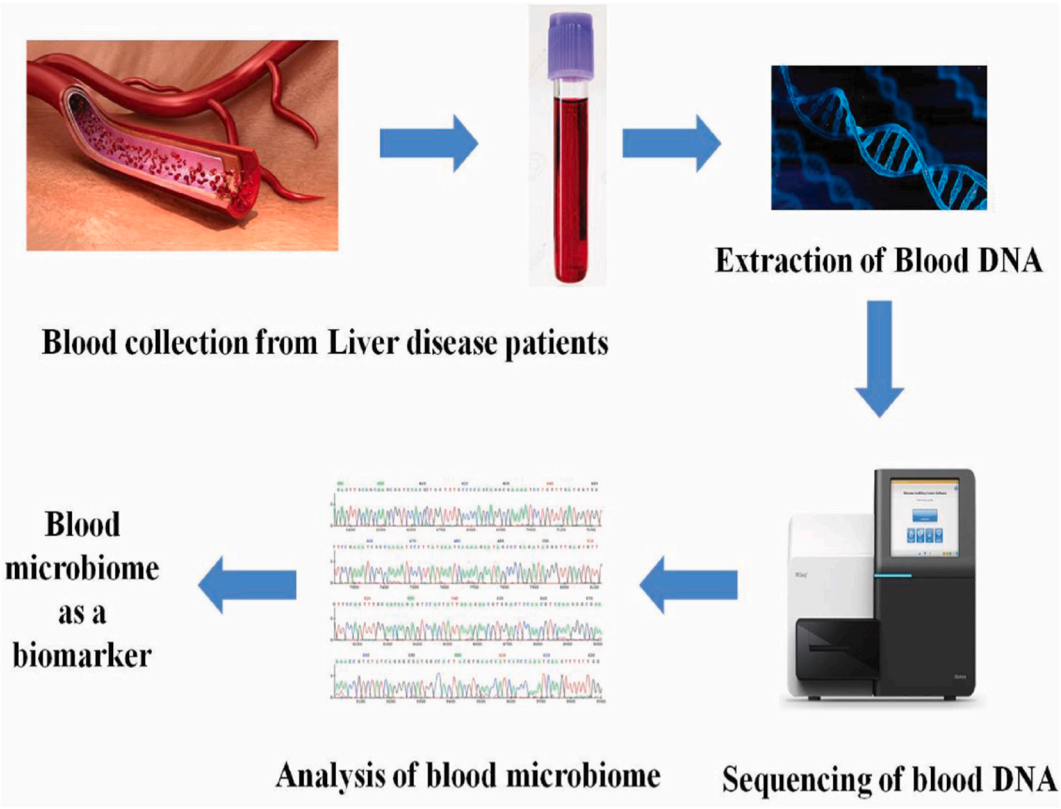

Fig. 3. Methodology for analysis of blood microbiome in Liver disease patients.

presence of blood microbiota and their metabolites. Biosensors and nanosensors can be developed for the detection of specific bacteria or their metabolites both in the gut and blood samples of liver disease patients. The sequencing techniques, metabolomics and biosensors should be incorporated into routine clinical analysis. The concentration of blood microbiota and their metabolites released from the gut into circulation can be decreased by employing different strategies. Antibiotics and drugs have been used to target microbes and their components in systemic and portal circulation earlier [59,60]. Small synthetic chemical molecules are being developed as drugs targeting the microbiota, their metabolites, and some of these molecules are in clinical trials [61,62]. Prebiotics [63], synbiotics and probiotics [64] have been used to restore the perturbed blood microbiota and darn the gut barrier integrity [61, 65]. They can also reduce metabolic endotoxemia (LPS, LBP & LTA in blood), subsequent Toll-like receptor (TLR) activation and insulin resistance. Prebiotics and probiotics restore the normal gut microbiota and thereby reduce the other clinical complications of liver diseases such as diabetes, portal hypertension, cardiomopathy etc.

In addition, fecal microbiota transplantation (FMT) from healthy individuals has been used to restore the gut microbiota in liver disease patients. This will also reduce the release of microbiota derived metabolites like short chain fatty acids (SCFAs), aromatic amino acid (AAA) derived metabolites, trimethyl amines (TMA) and cholines into portal circulation. Fecal microbiota transplantation has the potential to mitigate intestinal permeability and it has been performed earlier in many liver diseases [66–68]. Further, this will reduce bile acid imbalance or dysregulation, lipogenesis and steatosis.

6. Conclusion

It is now recognized that blood microbial components derived from gut microbiome are present in the circulation of liver disease patients. In particular, the presence of microbiome and their metabolites in portal circulation has been clearly studied in liver disease. However, it is also quite important to note that the detection of microbial nucleic acids in the circulation may denote the presence of microbial signatures only and not the presence of live bacteria in the blood. Profound alterations in the blood microbiome and blood metabolome during liver disease indicate that these microbial components may play a role in the etiology and progression of the disease. Further research will lead to understanding of the molecular mechanisms of microbial translocation and their physiology in the development and progression of liver disease. This is also essential to develop the blood microbiome and their metabolites as therapeutic targets and biomarkers in liver disease.

Data availability statement

The authors declare that the data associated with our study has not been deposited into a publicly available repository and no data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Dinakaran Vasudevan: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arulraj Ramakrishnan:** Supervision, Software, Resources, Project administration, Conceptualization. **Ganesan Velmurugan:** Supervision, Software, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest. All the authors have read and accepted the Manuscript.

Acknowledgement

DV thanks the Science and Research Engineering Board (SERB), Government of India for support through the National Postdoctoral Fellowship (File No. PDF/2019/001910). All authors thank the Founding trustees, KMCH Research Foundation for generous research support and research facilities. A special word of thanks to Dr. Krishnan Swaminathan for his constant support and encouragement.

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