SYSTEMATIC REVIEW

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The Gut Microbiota Profile in Heart Failure Patients: A Systematic Review

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ABSTRACT

Background & Aims: Traditional cardiovascular risk factors are established predictors of heart failure (HF). However, the human gut microbiota is suggested to potentially interact with the cardiovascular system through the "gut-heart axis", which induces inflammation and contributes to HF pathogenesis. This systematic review aims to confirm the interconnection between the gut microbiome in HF patients.
Methods: Peer-reviewed human studies comparing the gut microbiota profile in adult patients with HF and healthy controls (HCs) up to April 18, 2022, were searched in Ovid MEDLINE, Ovid EMBASE, SCOPUS, and the Cochrane Library. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS).
Results: A total of nine studies, including 317 HF patients and 510 HCs, were included in the review. Decreased gut microbiota richness and similar microbial diversity (alpha diversity), and significantly different gut microbiota composition (beta diversity) were observed between HF patients and HCs. In comparison to HCs, HF patients had a greater abundance of *Actinobacteria*, *Proteobacteria*, and *Synergistetes* phyla; E*nterococcus, Escherichia, Klebsiella, Lactobacillus, Streptococcus*, and *Veilonella* genera and *Ruminococcus gnavus, Streptococcus sp.*, and *Veilonella sp*. species. In contrast, there was decreased abundance of *Firmicutes* phylum; *Blautia, Eubacterium, Faecalibacterium,* and *Lachnospiraceae FCS020* genera; and D*orea longicatena, Eubacterium rectale, Faecalibacterium prausnitzii, Oscillibacter sp*., and *Sutterella wadsworthensis* species in HF patients.
Conclusions: Gut microbiota diversity, richness, and composition in HF patients differ significantly from the healthy population. Overall, short-chain fatty acid (SCFA)-producing gut microbiota was depleted in HF patients. However, different underlying comorbidities, environments, lifestyles, and dietary choices could affect gut microbiota heterogeneity.

Key words: gut microbiota – dysbiosis – heart failure – short-chain fatty acid – SCFA- *Firmicutes*.

Abbreviations: BMI: body mass index; HC: healthy control; HF: heart failure; HfpEF: HF patients with preserved ejection fraction; HfrEF: HF patients with reduced ejection fraction; LPS: lipopolysaccharides; NOS: Newcastle-Ottawa Scale; NYHA: New York Heart Association; SCFA: short-chain fatty acid.

INTRODUCTION

Heart Failure (HF) is a prevalent problem worldwide, with an estimated prevalence of 63.7 million in 2017, presenting a significant burden of disease and cost of patient care (an estimated cost of US $ 3000 per patient for HF-related care) [1]. Various predisposing conditions have been established as risk factors for HF, including traditional cardiovascular risk factors such as hypertension, obesity, dyslipidemia, smoking, and a sedentary lifestyle, among others [2]. Although these traditional cardiovascular risk factors are well established, the human gut microbiota has been increasingly suggested to be associated with the occurrence of HF.

The gut microbiota plays a significant role in supporting the regulation of intestinal barriers, digestion, and metabolism, as well as providing immunological support for the gut. The gut also interacts with distant organs through various signaling molecules and metabolites produced by its microbiome, altering the functions and affecting the homeostasis of distant organs [3]. The "gut-heart axis", a newly conceived phenomenon, attempts to describe the interconnection between the dysbiosis of the gut microbiome and the occurrence of cardiovascular diseases, focusing on the proinflammatory signals produced

by the underlying conditions that contribute to chronic cardiovascular diseases, including HF. On the contrary, the impaired cardiac output and congestive states found in HF may play a role in the induction of bacterial and endotoxin translocation [3, 4]. Establishing a connection between the "gut-heart axis" opens various possibilities for the future of HF patients, such as using specific gut microbes from fecal samples as a clinical biomarker to monitor HF and its progression, similar to existing biomarkers. It also opens the possibility for a more targeted HF therapy that focuses on personalized alterations in the gut microbiome with the use of probiotics or antibiotics targeted towards maintaining a favorable microbiome for HF patients [3, 5].

There is growing evidence about the variation in the gut microbiota of HF patients, with previous studies suggesting notable differences in gut microbiota composition of HF patients compared to the average population independent of demographic characteristics [6-8]. In this systematic review, we aim to summarize available knowledge on gut microbiota composition in HF and define the baseline gut microbiota characteristics observed in HF patients.

METHODS

Protocol Registration and PRISMA Guideline

A systematic review protocol was developed and prospectively registered with PROSPERO (CRD42022326568). The writing of this systematic review was compliant with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Supplementary file, Table I) [9].

Search Strategy and Eligibility Criteria

On April 18, 2022, peer-reviewed papers were searched from database inception from four online databases: MEDLINE (OVID interface), EMBASE (OVID interface), SCOPUS, and CENTRAL (the Cochrane Library). The search strategy consisted of a combination of the following Medical Subject Heading (MeSH) terms and keywords along with their synonyms: "gut microbiota" and "heart failure". The complete search strategy is reported in Supplementary file (Supplementary method). Human studies that compared the gut microbiota profile in adult (18 years or older) patients with HF (regardless of the subtype) to healthy controls (HCs) were eligible for study inclusion. Any observational studies and/or randomized trials with preintervention baseline data were sought. Exclusion criteria of the studies were intervention studies investigating the effects of gut-modulating substances such as, but not limited to, probiotics, dietary interventions, and any drugs or antibiotics usage known to influence the gut microbiota.

Study Selection and Data Extraction

Articles retrieved from the online database searches were imported and compiled into Endnote 20 (Clarivate, USA) for study selection. The study selection, data extraction, and quality assessment were performed in pairs by three independent reviewers (S.A., P.A.W., A.D.W.). In situations where there were discrepancies between the initial reviewers, another reviewer (D.M.S.) performed an independent review without prior knowledge of the results from the initial review, and the result was taken as final. The study selection process included deduplication, screening titles and abstracts according to the eligibility criteria, and a full-text review of eligible studies prior to inclusion in the overall analysis. A data extraction form was used to extract important data from the studies, such as the first author and publication date, location of the study, study design, available baseline characteristics of HF patients and HCs (precisely the number of samples, age, gender, body mass index (BMI), and health statuses such as hypertension, diabetes, New York Heart Association (NYHA) Functional Classification, subtype of HF, antibiotics/probiotics status, and dietary information), outcome measurement details (sample collection and handling, sequencing methods not limited to the microbiome approach, pipeline and reference database) and the outcome results (gut microbiota richness and/or diversity, composition and relative abundance of gut microbiome taxonomy).

Quality Assessment

The quality assessment was done by assessing each study according to the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. The overall NOS scores were classified into three categories: low/poor quality (0-3), moderate quality (4-6), and high quality (7-9).

Data Analysis

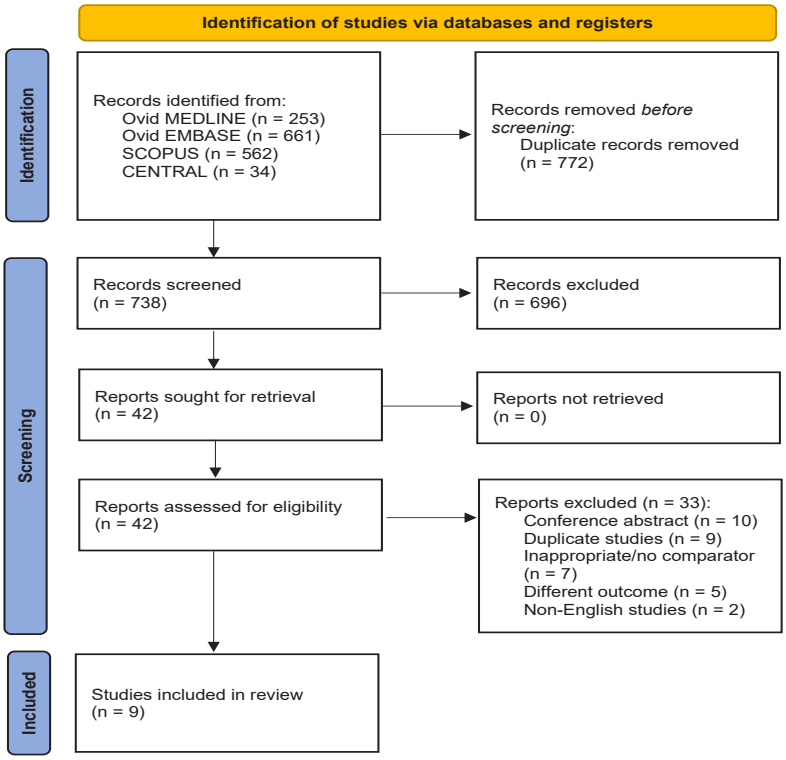
The data obtained were summarized narratively and presented in tables. The gut microbiota characteristics data were collated according to their reported alpha diversity, beta diversity, and the change in the relative abundance of the gut microbiota taxonomy in HF patients compared to HCs. The alpha diversity compared the gut microbiota richness and diversity, while the beta diversity compared the inter-group dissimilarity of gut microbiota composition between HF patients and HCs. Gut microbiota richness refers to the overall number of bacterial species or taxa while diversity refers to the amount of each individual bacterial species present in the gut. The changes in the relative abundance of gut microbiota taxonomy in HF patients relative to HCs were categorized as increased (↑), no change (=), and decreased (↓), and data from the phylum, genus, and species levels were collected and summarized.

RESULTS

Study Selection and Study Characteristics

The electronic database search yielded 1,510 studies, of which 772 were duplicate studies and were excluded. Following the title and abstract review of 738 studies, 42 full-text articles were reviewed against the eligibility criteria. A total of nine studies were included in this systematic review; the reasons for excluding the full-text articles are provided in Fig. 1. One study by Kummen et al. [10] was excluded as the same dataset was used by Mayerhofer et al. [11], which has been included in this study.

The nine included studies comprised 827 participants (317 HF patients and 510 HCs). All studies included were



Fig, 1. PRISMA Flow Diagram for Study Selection

observational studies and were conducted in China (four studies) [8, 12-14], Japan (two studies) [15, 16], Germany (one study) [17], Norway (one study) [11], and Australia (one study) [6]. Most HF patients had NYHA class II to IV. From the nine studies, four (Luedde et al. [17], Cui et al. [12], Katsimichas et al. [7], Mayerhofer et al. [11]) recruited only HF patients with reduced ejection fraction (HFrEF), two (Beale et al. [6] and Huang et al. [13]) recruited only HF patients with preserved ejection fraction (HFpEF), two (Kamo et al. [4] and Sun et al.[8]) recruited a mixture of HFrEF and HFpEF patients and one remaining (Wang et al. [14]) did not specify the subtype of chronic HF. Most studies reported that the recruited patients did not take antibiotics and/or probiotics within a specified duration; however, three studies [8, 15, 17] had missing information on the antibiotic status of HCs, while one study [14] had missing information on the antibiotic status of both HF patients and HCs (Table I, Supplementary files - Tables II and III). Dietary information known to affect the gut microbiota composition was not provided in four studies [4, 8, 13, 14].

Summary of Study Methodology

Of the assessed studies, all but two studies used the 16S rRNA sequencing methods. However, studies amplified different regions of the 16S rRNA, such as V1-V2, V3-V4, and V4-V5. Only Wang et al. [14] used the 16S rDNA approach to amplify the V3/V4 region, and Cui et al.[12] utilised metagenomic sequencing. The pipeline used was variable (from less to more frequently used): Usearch, SOAPdenovo2, and QIIME. Meanwhile, the database used for taxonomy classification included the RDP classifier, Greengenes, and SILVA (Supplementary file, Table II).

Quality Assessment

The overall quality of the included studies was generally moderate to high, with the lowest score of 5 and the highest score of 8 (Table I, Supplementary file - Table IV). Five studies were of moderate quality (NOS score of 4-6), while the remaining four were of high quality (NOS score of 7-9). Of the high-quality studies, three were adjusted for age, gender, and BMI, while the remaining was unadjusted. In contrast, only one moderate-quality study performed an adjusted analysis.

Gut Microbiota Richness and Diversity (Alpha Diversity) in HF patients compared with HCs

A total of eight studies performed the alpha diversity analysis to compare the gut microbiota diversity and/or richness of patients with HF and HCs. Two studies reported only microbial diversity, one reported only microbial richness, and the remaining reported both outcomes (Table II). Different alpha diversity outcomes were used throughout the included studies, such as Chao1 index, Shannon index, Simpson index, observed OTUs, and Phylogenetic Diversity (PD)-whole-tree index. Among HFrEF patients, the microbial richness was reported to be similar in one study [16] and decreased in another study [11]; meanwhile, the microbial diversity was reported to be similar to HCs in two (67%) studies [11, 16] compared to one (33%) study [17] which reported a decreased microbial diversity. As for HFpEF patients, two studies [6, 13] demonstrated reduced microbial richness but with similar microbial diversity. In unspecified and combined HFrEF and HFpEF patients, the microbial richness and diversity were reported to be similar in one study [15] and reduced the other.

Table I. Characteristics of the included studies

First author	Country	Study Period	Case / Control	N	Age	Male (%)	HT (%)	DM (%)	NYHAN (%)	Abx Status	Sequencing method	NOS
Kamo (2017)	Japan	Apr 14 – Mar 16	HF-Y (0% HFrEF)	12	47±3	11 (92)	1 (8)	4 (33)	I: 0 (0) II: 3 (25) III: 7 (58) IV: 2 (17)	R	16S rRNA (V1-V2)	6
			HF-O (40% HFrEF)	10	74±3#	7 (70)	6 (60)	3 (30)	I: 0 (0) II: 6 (60) III: 4 (40) IV: 0 (0)	R		
			HC	12	41±2#	9 (75)	0 (0)	0 (0)	N/A	NR		
Luedde (2017)	Germany	NR	HFrEF	20	65±3	11 (55)	14 (70)	7 (35)	I: 1 (5) II: 4 (20) III: 6 (30) IV: 9 (45)	R	16S rRNA (V1-V2)	8
			HC	20	65±3	11 (55)	8 (40)	3 (15)	N/A	NR		
Cui (2018)	China	NR	HFrEF	53	58±13	44 (83)	30 (57)#	15 (28)#	I: 0 (0) II: 3 (6) III: 27 (51) IV: 23 (43)	R	Metagenomic Sequencing	6
			HC	41	54±6	32 (78)	0 (0)#	2 (5)#	N/A	R		
Katsimichas (2018)	Japan	Oct 15 - Apr 17	HFrEF	28	51±10#	21 (75)	NR	NR	III-IV: 17 (61)	R	16S rRNA (V1-V2)	7
			HC	19	36±6#	16 (84)	NR	NR	N/A	R		
Mayerhofer (2020)	Norway	Jul 14 - Dec 16	HFrEF	84	59 (39–74)#	34 (40)	25 (30)#	18 (21)#	I: 0 (0) II: 41 (49) III: 38 (45) IV: 5 (6)	R	16S rRNA (V3-V4)	8
			HC	266	46 (30-61)#	107 (40)	11 (4)#	2 (1)#	N/A	R		
Beale (2021)	Australia	Aug 17 - Jan 20	HFpEF	26	68±8#	6 (23)#	18 (69)#	4 (15)#	II-III: 26 (100)	R	16S rRNA (V4-V5)	8
			Metro-politan HC	39	58±8#	22 (56)#	15 (38)#	0 (0)#	N/A	R		
			Regional HC	28	61±6#	9 (32)	5 (18)#	0 (0)#	N/A	R		
Huang (2021)	China	Aug 20 - Oct 21	HFpEF	30	71±9	19 (63)	25 (83)	NR	I: 0 (0) II: 6 (20)II I: 18 (60) IV: 6 (20)	R	16S rRNA (V4-V5)	6
			HC	30	67±7	17 (57)	N/A	N/A	N/A	R		
Wang (2021)	China	NR	CHF (unspecified)	25	65±3	14 (56)	NR	NR	I: 2 (8) II: 5 (20) III: 7 (28) IV: 11 (44)	NR	16S rDNA (V3/V4)	5
			HC	25	65±3	13 (52)	NR	NR	N/A	NR		
Sun (2022)	China	Apr 20 – Aug 20	CHF (3% HFpEF)	29	61±12	24 (83)#	14 (48)	10 (34)	I: 0 (0) II: 0 (0) III: 10 (34) IV: 19 (66)	R	16S rRNA (V3-V4)	6
			HC	30	60±10	10 (33)#	11 (37)	5 (17)	N/A	NR		

#: Significant difference; abx: antibiotic; CHF: chronic heart failure; DM: diabetes mellitus; HC: healthy control; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HF-O: old heart failure patients; HF-Y: young heart failure patients; HT: hypertension; N: number of subjects; N/A: not applicable; NOS: Newcastle-Ottawa Scale score; NR: not reported; NYHA: New York Heart Association Classification of Heart Failure; R: reported.

Gut Microbiota Composition (Beta Diversity) in HF patients compared with HCs

Of the nine studies, only Wang et al. [14] did not report the beta diversity analysis in HF patients against HCs. The beta diversity, which explored the similarity of gut microbiota composition between the comparison groups, was assessed using the weighted and unweighted Unifrac and Bray-Curtis dissimilarity and was visualized with the Principal Coordinate Analysis (PCoA). All the studies (100%) that reported the beta diversity outcomes demonstrated a significantly different gut microbiota composition between patients with HF and HCs across all spectrums of HF, either HFrEF or HFpEF (Table II).

Table II. Summary of the gut microbiota alpha and beta diversity results in HF patients compared to HCs

Studies	Alpha Diversity		Beta Diversity
	Microbial Richness	Microbial Diversity	
HFrEF			
Luedde (2017)	NR	↓	Significantly different gut microbiota composition between groups
Cui (2018)	NR	NR	Significantly different gut microbiota composition between groups
Katsimichas (2018)	(=)	(=)	Significantly different gut microbiota composition between groups
Mayerhofer (2020)	↓	(=)	Significantly different gut microbiota composition between groups
HFpEF			
Beale (2021)	↓	NR	Significantly different gut microbiota composition between groups
Huang (2021)	↓	(=)	Significantly different gut microbiota composition between groups
HFrEF + HFpEF			
Kamo (2017)	(=)	(=)	Significantly different gut microbiota composition between groups
Sun (2022)	↓	↓	Significantly different gut microbiota composition between groups
Unspecified CHF			
Wang (2021)	NR	↓	NR

(=) no change/similar; ↓ decreased; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HC: healthy controls; NR: not reported.

Change in Relative Abundance of Gut Microbiota Taxonomy in HF patients compared with HCs

The summary of changes in the relative abundance of gut microbiota taxonomy in HF patients compared to HCs reported by each study is summarized in Table III. To summarize, a total of five phyla, four families, 52 genera, and eight species were reported in the included studies regardless of the HF subtypes (Supplementary file, Table 5). At the phylum level, the relative abundance of Firmicutes was reported in two studies to be lower in HF patients than HCs. Meanwhile, studies have reported increased *Actinobacteria*, *Proteobacteria*, and *Synergistetes* in HF patients. At the family level, only one study reported decreased *Coriobacteriaceae*, *Erysipelotrichaceae*, *Lachnospiraceae*, and *Ruminococcaceae* in patients with HF compared to HCs. As for the genus level, there was a greater abundance of *Enterococcus*, *Escherichia*, *Klebsiella*, *Lactobacillus*, *Streptococcus*, and *Veillonella*, while a decreased abundance of *Blautia*, *Eubacterium*, *Faecalibacterium*, and *Lachnospiraceae FCS020* in HF patients. When involving HFrEF patients only, studies consistently reported an increased abundance of *Streptococcus* and *Veillonella* and decreased abundance of *Blautia* and *Faecalibacterium* compared to HCs. Lastly, at the species level, each bacterium was only reported by one study and showed an increase in Ruminococcus gnavus, *Streptococcus* sp., and *Veillonella sp*. and a decrease in *Dorea longicatena*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Oscillibacter sp*., and *Sutterella wadsworthensis*.

DISCUSSION

Summary of Main Results

This systematic review summarized the growing body of evidence exploring the role of gut microbiota composition in HF patients. Our review showed that the gut microbiota profiles of HF patients were altered, as evident by the diminished gut microbiota richness, similar or reduced microbial diversity, and the significant differences in the inter-individual gut microbiota composition compared to HCs. At the phylum level, depletion of Firmicutes and a greater abundance of *Actinobacteria*, *Proteobacteria*, and *Synergistetes* in HF patients were observed. As for the family level, the number of *Coriobacteriaceae*, *Erysipelotrichaceae*, *Lachnospiraceae*, and *Ruminococcaceae* plummeted in HF patients. At the genus level, an increased abundance of *Enterococcus*, *Escherichia*, *Klebsiella*, *Lactobacillus*, *Streptococcus*, and *Veillonella* were reported in HF patients; meanwhile, *Blautia*, *Eubacterium*, *Faecalibacterium*, and *Lachnospiraceae FCS020* were depleted. In terms of species, *Eubacterium rectale*, *Dorea longicatena*, and *Faecalibacterium prausnitzii* were less abundant in HF patients.

Interaction between Gut Microbiota and Heart Failure

Host microbiota interactions with inflammatory and metabolic pathways have been associated with the pathogenesis of numerous immune-mediated diseases, including HF [7]. Hypothetically, the low cardiac output in HF patients can lead to intestinal hypoperfusion and ischemia, and the destruction of the intestinal barrier integrity, which ultimately promote bacterial translocation and endotoxin circulation in the blood and subsequently stimulate high inflammatory states [3]. Additionally, the damaged intestinal barrier alters the microbiome composition characterized by proliferation of pathogenic microorganisms (especially anaerobic types) and the reduced number of beneficial gut bacteria [18, 19]. Overgrowth of pathogenic bacteria such as *Escherichia* can lead to harmful substance and metabolite production, such as lipopolysaccharide (LPS), Trimethylamine N-oxide (TMAO), and indoxyl sulfate (IS), which could worsen HF conditions [19, 20]. Indoxyl sulfate, a protein-bound uremic solute generated from dietary tryptophan, is known for its deleterious effects on the cardiovascular system, impairing left ventricular diastolic function and inducing inflammation and endothelial dysfunction. Therefore, gut dysbiosis worsens several risk factors for HF, such as atherosclerosis, hypertension, diabetes, obesity, and kidney disorders [21].

Table III. Increased/Decreased/No Change in the Relative Abundance of the Gut Microbiota Taxonomy in HF patients compared to HCs

First author	Phylum	Genus	Species
HFrEF			
Luedde (2017)		↑*Escherichia-Shigella* ↓*Blautia, Collinsella, Faecalibacterium, Uncl. Erysipelotrichaceae, Uncl. Ruminococcaceae*	
Cui (2018)		↑*Ruminococcus, Acinetobacter, Veillonella, Lactobacillus, Streptococcus* ↓*Alistipes, Faecalibacterium, Oscillibacter, Bilophila*	↑*R. gnavus, Streptococcus sp., Veillonella sp.* ↓*F. prausnitzii, Oscillibacter sp., S. wadsworthensis*
Katsimichas (2018)		↑*Streptococcus, Veillonella* ↓*SMB53*	
Mayerhofer (2020)	↑*Bacteroidetes* ↓*Firmicutes*	↑*Prevotella, Hungatella, Succiniclasticum* ↓*Anaerostipes, Blautia, Coprococcus, Fusicatenibacter, Lachnospiraceae FCS020, Lachnospiraceae NC2004, Lachnospiraceae ND3007, Pseudobutyrivibrio, Eubacterium hallii group, Faecalibacterium, Bifidobacterium*	
HFpEF			
Beale (2021)		↑ *Akkermansia, Sutterella, Ammoniphilus, Megasphaera, Acholeplasma, Bacteroides, Erwinia, Streptococcus* ↓*Caldicellulosiruptor, Ruminococcus, Mitsuokella, L7A_E11*	
Huang (2021)	↑*Synergistetes*	↑*Enterococcus, Lactobacillus* ↓*Butyricicoccus, Sutterella, Lachnospira, Ruminiclostridium*	
HFrEF + HFpEF			
Kamo (2017)	=*Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria*	↑*Streptococcus, Lactobacillus* =*Ruminococcus, Faecalibacterium, Blautia, Anaerostipes, Bacteroides, Prevotella, Parabacteroides, Bifidobacterium, Collinsella, Escherichia, Klebsiella* ↓*Clostridium, Dorea, Eubacterium*	↓*E. rectale, D. longicatena*
Sun (2022)	↑*Proteobacteria, Actinobacteria* ↓*Bacteroidetes, Firmicutes*	↑*Escherichia-Shigella, Enterococcus, Klebsiella* ↓*Faecalibacterium, Ruminococcaceae UCG-004, Ruminococcaceae UCG-002, Lachnospiraceae FCS020 group, Dialister*	
Unspecified CHF			
Wang (2021)		↑*Ruminococcus gnavus group, Escherichia-Shigella, Ruminococcaceae UCG 005, Ruminococcaceae UCG 002, Lactobacillus, Atopobium, Romboutsia, Streptococcus, Haemophilus, Klebsiella*	

↑: increased abundance; =: no change in abundance; ↓: decreased abundance; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HC: healthy control

Alpha and Beta Diversity Changes in Heart Failure compared to Healthy Controls

The association between HF and gut dysbiosis was shown in this study by the alpha and beta diversity changes in the HF population compared with HCs. Firmicutes are known to dominate the healthy gut microbiota composition and can modify the environment through the ecological adaptation process [22]. However, Firmicutes were reported to be depleted in HF patients [8, 11]. On the contrary, there was a higher abundance of *Proteobacteria*, gram-negative pathogenic bacteria, in patients with HF compared to HCs [8]. Lipopolysaccharides (LPS), the outermost membrane of *Proteobacteria*, could trigger the production of proinflammatory cytokines once they enter the blood circulation. These cytokines will then induce apoptosis, hypertrophy, and cardiomyocyte fibrosis, hence worsening the development of HF [8]. This pathophysiology mechanism could explain the higher circulating LPS observed in decompensated HF patients [23].

Role of Diminished Short-chain Fatty Acid (SCFA)-producing Bacteria in Heart Failure

Lipopolysaccharides-induced endothelial activation is influenced by short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. Short-chain fatty acids reduce the release of proinflammatory cytokines, such as interleukin-6 (IL-6) and IL-8, and inhibit the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [24]. These two endothelial adhesion receptors are evidence of the leukocyte transmigration process over the endothelium, and when presented in immoderate amounts could indicate an early sign of atherosclerosis [25]. Physiologically, SCFAs are known to improve blood pressure and myocardial repair, reduce inflammation, strengthen the gut barrier through regulation of the neuro-immunoendocrine system, and maintain normal heart contractile function and electrical stability [6, 26]. Reduced SCFAs and the presence of underlying comorbidities, such as hypertension, participate in HF progression and exacerbation. HFpEF pathophysiology

suggests that the systemic inflammatory state is inflicted through comorbidities, which cause various pathological changes such as fibrosis, myocardial hypertrophy, depletion of nitric oxide availability, coronary microvascular inflammation, and diastolic dysfunction [27].

The family of *Ruminococcaceae* and *Lachnospiraceae*, the genus *Faecalibacterium*, and prominent SCFA producer species, such as *Dorea longicatena* and *Eubacterium rectale*, were found to be depleted in HF patients. *Ruminococcaceae* and the family of *Lachnospiraceae* aids in the fermentation process of fiber, resistant starch, and plant polysaccharides to produce SCFAs. Kummen et al. [10] demonstrated that *Lachnospiraceae* number was conversely related to soluble CD25, a marker for T cell activation and inflammation. Thus, diminished *Lachnospiraceae* in HF patients could be associated with a high inflammatory condition in such patients [10]. Likewise, *Faecalibacterium prausnitzii*, a notable anti-inflammatory commensal bacterium, is associated with worsening inflammation and poor prognosis in HF patients as they age [12, 15].

Interstudy Variability in Gut Microbiota Changes

Interestingly, we noted inconsistencies in the reporting of the following genera between studies: (1) Ruminococcus was reported to be increased in one HFrEF study while decreased in one HFpEF study, (2) *Ruminococcaceae* UCG-002 was reported to be increased in a study with unspecified HF patients while decreased in another study that include both HFrEF and HFpEF patients, and (3) Sutterrella was reported to be increased in one HFpEF study and decreased in another HFpEF study. A possible explanation may involve the variable taxonomy classification references used by each study. Classification of sequences depends mainly on the training set that incorporates sequence representative for known microbial taxa. However, existing taxonomy classification programs tend to classify sequences to specific microbial taxa despite being a novel taxonomic group without any representative sequence available in the kit. These inaccuracies lead to "overclassification" which should be considered when conducting microbiome studies [28].

Implications

The association between gut microbiome dysbiosis and HF unfolds the potential of dietary, medical, and supplementation (prebiotics or probiotics) interventions to restore healthy gut composition [3]. A healthy gut microbiome will facilitate the synthesis of specific vitamins, fermentation of indigestible dietary substances, and production of SCFAs, which aim to regulate metabolism, inflammation, and hormone secretion [29].

Limitations

We acknowledge that this study had several limitations. Firstly, only nine studies were eligible for inclusion in this systematic review accounting for six different countries, with the majority (four studies) conducted in China. Different environments and lifestyles contribute to the heterogeneity of human gut microbiota; hence, resulting in difficulty comparing the composition of the microbiota between studies. Secondly, variations in sample collection and handling techniques and sequencing methods between studies could ultimately impact the reported results. Thirdly, some studies failed to adjust for important confounding factors, including age, gender, presence of comorbidities (hypertension and diabetes, among others), dietary habits, lifestyle, and ethnicity, with some studies missing the reporting of antibiotics/probiotics status and dietary information [30]. Variations in gut microbiota and their metabolites are highly influenced by intrinsic and extrinsic factors, highlighting that differences in age, ethnicity, certain comorbidities, HF severity, cultural customs, and personal habits may affect one's daily dietary intake, including the use of gut-altering medications [31]. Subtle, short-term dietary changes unreported in self-reported questionnaires and underlying medical comorbidities or medication intake may be reflected in the gut microbiome, which could favor certain cardiovascular conditions [32]. Further studies should identify factors that significantly affect gut microbiome diversity and aim to control for those confounders. Fourthly, only limited evidence was available for each subtype of HF (HFrEF and HFpEF), making pooling of data difficult, especially with different outcomes across studies. In this study, we combined the results from HFrEF and HFpEF groups and performed subgroup analysis where data was sufficient. However, we noted that gut microbiota has been demonstrated to differ between HF subtypes. HFrEF is known to also result in hypoperfusion of visceral organs, including the gut [33]. This gut hypoperfusion and ischemia leads to microbiome alteration via increased intestinal permeability and proliferation of pathogenic microbes, subsequently causing translocation of harmful substances and metabolites into the bloodstream and hence promoting chronic inflammation [34]. On the contrary, HFpEF is primarily driven by multifactorial endothelial dysfunction, which does not correlate with intestinal hypoxemia (unless splanchnic congestion caused by right-sided HF is present [35]. Therefore, dysbiosis is hypothesized to be more evident in HFrEF than HFpEF subtypes [36]. Further studies should focus on analysis based on HF subtypes to allow a better understanding of the association between the gut microbiome and HF pathophysiology and progression. Lastly, this systematic review cannot conclude a temporal relationship between gut dysbiosis and HF. Longitudinal studies reporting gut microbiota profiles in pre-HF and post-HF patients are needed to support temporality.

CONCLUSIONS

Our systematic review demonstrated a diminished gut microbiota richness and microbial diversity in HF patients compared to HCs, and significant differences in the composition of gut microbiota between the two groups. Overall, a decrease in Firmicutes, a dominant phylum observed in the healthy gut microbiota, was notable in HF patients compared to HCs. Furthermore, there was a depletion in SCFA-producing gut bacteria in HF patients, which may ultimately contribute to changes in immune modulation and neuro-enteroendocrine hormone imbalance; therefore, affecting the progression or worsening of HF. Nevertheless, we acknowledged that differences in lifestyle, including dietary changes in varying

settings, especially in different subtypes of HF (HFpEF and HFrEF), can also reflect gut microbiota alterations.

Conflicts of interest: None to declare.

Authors' contribution: D.M.S., B.B.S. and M.S. conceived the study. D.M.S., S.A., P.A.W. and A.D.W. collected the data. D.M.S., H.Z.A., H.S.M., B.B.S. and M.S. analyzed the data and interpreted the results. D.M.S., S.A., P.A.W. and A.D.W. drafted the manuscript. D.M.S., P.A.W., H.Z.A., H.S.M., B.B.S. and M.S. critically revised the paper. All the authors read and approved the final version of the paper.

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