A systematic review of the gut microbiota profile in patients with heart failure

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INTRODUCTION

- Traditional cardiovascular risk factors are already well-established; however, the human gut microbiota has been increasingly suggested to be associated with the occurrence of heart failure (HF)
- The **"gut-heart axis"** describes the **inter-connection between dysbiosis of the gut microbiome** and the **occurrence of cardiovascular diseases**, including HF
- Previous studies suggested **notable differences in gut microbiota composition** of HF patients compared to the average population

Aim: To summarize available knowledge on gut microbiota composition in HF and define the baseline gut microbiota characteristics observed in HF patients

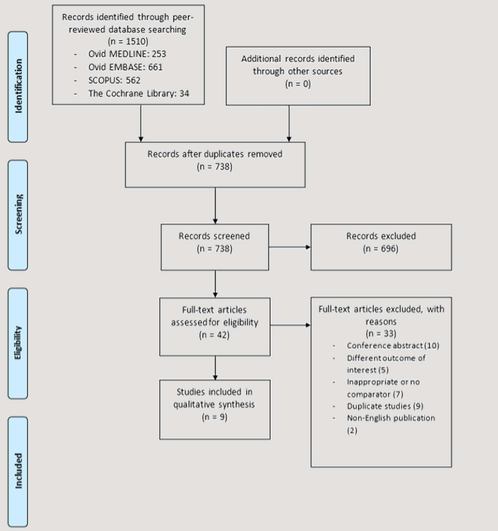

Figure 1. PRISMA Flow Diagram for Study Selection

Table 1. Characteristics of the Included Studies

First author	Country	Study Period	Case / Control	N	Age	Male (%)	HT (%)	DM (%)	NYHA N (%)	Abx Status	Sequencing method	NOS
Kamo (2017)	Japan	Apr 14 – Mar 16	HF-Y (EF≥ 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
			Metropolitan 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) III: 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		

Notes
= 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

METHODS

- Peer-reviewed papers were searched using the following keywords and MeSH terms: "gut microbiota", "heart failure"
- Human studies that compared **the gut microbiota profile** in adult **HF patients to healthy controls (HCs)** were included
- Interventional studies investigating the effects of gut modulating substances were **excluded**
- The Newscastle-Ottawa Scale (NOS) was used to assess the quality of included studies

RESULTS

- A total of **9 studies** were included in this systematic review. comprising of 827 participants (317 HF patients & 510 HCs)
- All studies were observational and conducted in China, Japan, Germany, Norway, and Australia
- The alpha diversity analysis compared the gut microbiota diversity and/or richness of patients with HF and HCs
  - Among **HFrEF patients:** microbial richness and diversity were **similar with HCs or decreased**
  - Among **HFpEF patients**: **decreased microbial richness** with **similar microbial diversity**
- All the studies (n=8) reported a **significantly different gut microbiota composition (beta diversity)** between the HF patients and HCs **across all spectrums of HF**, either HFrEF or HFpEF
- There were **changes in the relative abundance of gut microbiota taxonomy** in HF patients compared to HCs

Table 2. Summary of the Gut Microbiota Alpha and Beta Diversity Results in HF patients compared to HCs

Studies	Alpha Diversity: Microbial Richness	Alpha Diversity: Microbial Diversity	Beta 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
Unspecfied CHF			
Wang (2021)	NR	↓	NR

Notes
=: 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

DISCUSSION

- We demonstrated the association between HF and gut dysbiosis from the **alpha and beta diversity changes** in the HF population compared with HCs
- **Firmicutes**, a phylum dominant in the healthy gut microbiota, were found to be **consistently depleted in HF patients**
- **Notable reductions in the number of SCFA-fermenting bacteria** also **decreases the amount of "beneficial SCFAs"** produced
  - More SCFAs shown to **improve blood pressure** & **myocardial repair**, **reduce inflammation**, **regulate the neuro-immunoendocrine system**, **strengthen the gut barrier, modulate immune function**, & **maintain normal heart contractile function** & **electrical stability**
- Meanwhile, a **higher abundance of Proteobacteria** was found, which may be responsible for worsening the development of HF due to **pro-inflammatory cytokines produced**
- The association between gut microbiome dysbiosis and HF **unfolds the potential of dietary, medical, and supplementation (prebiotics/ probiotics)** interventions in restoring healthy gut composition
- However, this study had several limitations such as environmental and lifestyle modification which play a role in the heterogeneity of the human gut microbiota

CONCLUSION

- **Diminished gut microbiota richness** and **microbial diversity** in HF patients compared to HCs
- Significant **differences in gut microbiota composition** between the 2 groups
- **Decrease in Firmicutes,** a dominant phylum observed in the healthy gut microbiota, was notable in HF patients compared to HCs.
- **Depletion in SCFA-producing gut bacteria** in HF patients, which may ultimately contribute to changes in immune modulation and neuro-enteroendocrine hormone imbalance; therefore affect the worsening of HF.

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