Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Small Intestinal Bacterial Overgrowth With Heart Failure and Its Prediction for Short-Term Outcomes

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BACKGROUND: Small intestinal bacterial overgrowth (SIBO) is a common pathological condition of intestinal microbiota. The prevalence of SIBO and its prognostic value in patients with heart failure (HF) are unknown.

METHODS AND RESULTS: A total of 287 patients tested for SIBO using lactulose hydrogen-methane breath test were evaluated. At least 1 of the following criteria fulfilled was SIBO positive: patients with fasting hydrogen level ≥20 parts per million (ppm) or a ≥20 ppm rise in hydrogen by 90 minutes were diagnosed with SIBO (H_2) positive; and patients with methane levels ≥10 ppm at any test point were diagnosed with SIBO (CH_4) positive. The association between SIBO and the composite of cardiovascular death and HF rehospitalization was investigated. In 287 consecutive patients with HF, 128 (45%) were positive for SIBO. Our result showed SIBO increased the risk of HF rehospitalization in patients with HF with reduced ejection fraction (P<0.001), and the risk of cardiovascular death in patients with HF with preserved EF (P=0.011). SIBO was an independent risk factor of primary end point in patients with HF (hazard ratio [HR], 2.13; 95% CI; 1.26–3.58; P=0.005). In addition, SIBO (CH_4) showed a prognostic value on adverse outcomes (HR, 2.35; 95% CI, 1.38–4.02; P<0.001), whereas the association between SIBO (H_2) and outcomes was not statistically significant.

CONCLUSIONS: There was high prevalence of SIBO in patients with HF, and SIBO was independently associated with poor outcomes. Proactive treatment for SIBO may provide extra benefit for patients with HF.

Key Words: gut microbiota ■ heart failure ■ outcome ■ small intestinal bacterial overgrowth

Heart failure (HF) is the end stage of most heart diseases with insufficient cardiac output and redistribution of peripheral circulation. Gastrointestinal tissue hypoperfusion, intestinal mucosal ischemia, intestinal wall edema, and high permeability are common consequence in patients with HF.[1,2] Increasing evidence has showed that the altered intestinal function induces the bacterial translocation, microbes, and endotoxins entering into circulation, which triggers the systemic inflammatory and immune responses,[3] especially in patients with HF with malnutrition and late-stage cachexia.[4] Recently, the analysis of metagenomics and 16S rRNA gene sequence in excreta samples has revealed that patients with HF present more dysfunctional gut flora than healthy people.[5,6]

Small intestinal bacterial overgrowth (SIBO) is identified as one kind of bacterial translocation of anaerobic bacteria from colon to jejunum and duodenum[7] and presents changes in composition and quantity of intestinal microflora. A growing body of evidence has suggested that SIBO is highly prevalent both in patients with digestive diseases and

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015292.

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For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Small intestinal bacterial overgrowth (SIBO) was highly prevalent and independently associated with poor outcomes in patients with heart failure (HF).
- The prognostic significance of SIBO in different types of HF seemed to differ; SIBO increased the risk of HF rehospitalization in patients with HF with reduced ejection fraction, as well as the risk of cardiovascular death in patients with preserved ejection fraction.

What Are the Clinical Implications?

- Given the high prevalence and prognostic correlation of SIBO in patients with HF, proactive treatment for patients with HF and SIBO may improve the prognosis and quality of life.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
NYHA	New York Heart Association
SIBO	small intestinal bacterial overgrowth

nondigestive diseases.[7] The abnormal anatomy, motility, pH, and immunity in the gastrointestinal tract contribute to the development of SIBO.[8] In some cases, a vicious circle arises: an underlying disease is complicated by SIBO and then SIBO directly (as a morphological impact) or vicariously (by malabsorption or nutrient deficiency) causes further deterioration of the underlying disease.[7] In patients with HF, there is a possible hypothesis that the destruction of intestinal microvilli and microcirculation and the impairment of immune defense of the gastrointestinal tract result in intestinal microbiota imbalance, the bacteria translocation, and eventually SIBO. Mollar et al recently found exhaled concentration of hydrogen in breath test was associated with higher risk of adverse clinical events in 102 patients with HF.[9] Nevertheless, the association between SIBO and HF warrants further study; it is especially important to study the role of SIBO in HF subtypes. Therefore, the aim of this study is to investigate the prevalence of SIBO and its prognostic value for adverse outcomes in hospitalized patients with different types of HF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Patients with HF who were hospitalized from July 2017 to May 2019 were prospectively enrolled. The inclusion criteria were (1) HF symptoms (exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea) and signs (pulmonary rales, edema of lower extremity, cardiac souffle, or engorgement of the neck veins); (2) the level of NT-proBNP (N-terminal pro-B-type natriuretic peptide) >125 pg/mL; (3) left ventricular ejection fraction <40% in HF with reduced ejection fraction (HFrEF); (4) left ventricular ejection fraction ≥40% in HF with preserved ejection fraction (HFpEF), and patients with HFpEF who also have evidence of abnormal cardiac structure, such as left ventricular hypertrophy, left atrial enlargement or diastolic dysfunction. The exclusion criteria were (1) use of any antibiotics or probiotics within a month; (2) use of promotility drugs and laxatives within a week; and (3) patients with acute coronary syndrome, severe acute decompensated HF (failing to finish the sample collection), digestive diseases (irritable bowel syndrome, liver cirrhosis, inflammatory bowel disease, chronic pancreatitis and gastrointestinal tumors), severe systemic disease, or history of abdominal surgery. The protocol in this study conforms to Declaration of Helsinki and its later amendments and was approved by the local ethics committee of Zhongshan Hospital, Fudan University. All participants gave the informed consent.

Lactulose Hydrogen-Methane Breath Test

Hydrogen-methane breath test was used as a noninvasive test for SIBO. All subjects fasted for 8 to 12 hours. Fermentable foods, such as dairy products, soy products, and fiber-rich foods, were avoided on the day before the test. Smoking and physical activity were prohibited, and the oral cavity was kept clean on the day of test. After preparation, the subjects held their breath for at least 10 seconds and then blew into the collection bag, avoiding ventilation throughout the process. Then, 10 g lactulose was taken orally and the gas collection step was repeated every 30 minutes. The test lasted for 90 minutes, and 4 gas bags were collected. After collecting exhaled gas, the concentration of hydrogen and methane was measured via Nano Coulomb Breath Analyzer (Sunvou Biotechnology Co., Ltd, Wuxi, Jiangsu, China).

Diagnostic Criteria of SIBO

Patients meeting the following positive criteria for hydrogen/methane breath test were considered positive for SIBO.[10,11] Hydrogen test positive: (1) fasting hydrogen level ≥20 parts per million (ppm); or (2) a ≥20 ppm rise in hydrogen by 90 minutes. Methane test positive: methane levels ≥10 ppm at any test point.

Demographic, Clinical, Biochemical, and Echocardiographic Parameters

Demographic data and clinical variables including age, sex, body mass index, smoking history, comorbidities, New York Heart Association (NYHA) classification, heart rate, blood pressure, and discharge medication, were collected. Biochemical variables included total bilirubin, conjugated bilirubin (CB), hs-CRP (high-sensitivity C-reactive protein), creatinine, uric acid, estimated glomerular filtration rate, cTnT (cardiac troponin T), and NT-proBNP. Echocardiography was performed according to the recommendations of the Chinese Society of Echocardiography.[12] Left atrial diameter (LAD), left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septal thickness, pulmonary systolic pressure (PASP), and left ventricular ejection fraction were recorded. Left ventricular ejection fraction is estimated by Simpson biplane method. In patients with atrial fibrillation, at least 10 beats were recorded and averaged.

Follow-Up and Outcomes

All patients continued with standardized treatment for HF after discharge and were followed up. Information about the outcomes was obtained from outpatient system and telephone contact with the patients or their proxies. The primary end point was a composite of cardiovascular death and HF rehospitalization. Clinical end points were verified by investigators blinded to patient's clinical characteristics and to the results of the hydrogen-methane breath test. The follow-up time was calculated from discharge to cardiovascular death, first readmission, or termination of the study.

Statistical Analysis

Continuous variables are expressed as mean±SD or median and interquartile range, and categorical variables are expressed in terms of frequency and percentage. In the intergroup analysis, *t* test is for continuous data fitted normal distribution; Mann-Whitney test is for continuous data fitted abnormal distribution; chi-square test or Fisher's exact test is for categorical data. Kaplan–Meier survival curves estimation were performed for testing prognostic value of SIBO. Cox proportional hazard model was used to analyze the relationship between the outcomes and variables. Variables were selected based on their relevance and clinical importance to SIBO and adverse outcome. Collinearity among variables was checked and found to have no significance. Variables with $P<0.05$ in univariate Cox regression model were entered into a multivariate Cox regression model, which included SIBO, body mass index, NYHA III-IV class, use of β blocker and aldosterone antagonist, and the level of CB, NT-proBNP, LAD, and PASP. The association between outcomes and variables were presented as hazard ratio (HR) and 95% CI. $P<0.05$ was considered statistically significant. All statistical process was analyzed by SPSS 25.0.

RESULTS

Prevalence of SIBO in Patients With HF

Among the 370 patients with HF who were initially recruited into the study, 9 patients failed to complete the sample collection because of severe acute decompensated HF, 3 patients received antibiotics treatment, 35 patients falling short of inclusion criteria were excluded, and 36 patients were lost to follow-up. Eventually, 287 consecutive patients were selected in this study (Figure 1). Random censoring was applied to patients without primary end point at the last follow-up date. The subjects who died of noncardiovascular death (N=2, cancer death) or remained alive at the last follow-up date (N=205) were considered censored; 207 patients among 287 subjects were censored.

Of the 287 patients with HF, 128 (45%) were positive for SIBO; 78 (41%) were positive for SIBO in 189 patients with HFrEF, and 50 (51%) were positive for SIBO in 98 patients with HFpEF ($P=0.115$) (Figure 2A). The prevalence of H_2+ and CH_4+ was 83 (29%) and 71 (25%), respectively. The prevalence of H_2+ and CH_4+ was 25% and 23% in HFrEF and 37% and 28% in HFpEF (Figure 2B).

Baseline Characteristics Comparison in Patients With or Without SIBO

In the whole cohort with HF (Table 1), compared with patients who were SIBO negative patients, patients who were SIBO positive showed higher rates of NYHA III–IV (61% versus 46%, $P=0.015$), atrial fibrillation (36% versus 24%, $P=0.026$), peripheral edema (45% versus 26%, $P=0.001$), the use of spironolactone (76% versus 64%, $P=0.034$), and intravenous diuretics (46% versus 35%, $P=0.048$), and lower use of β blockers

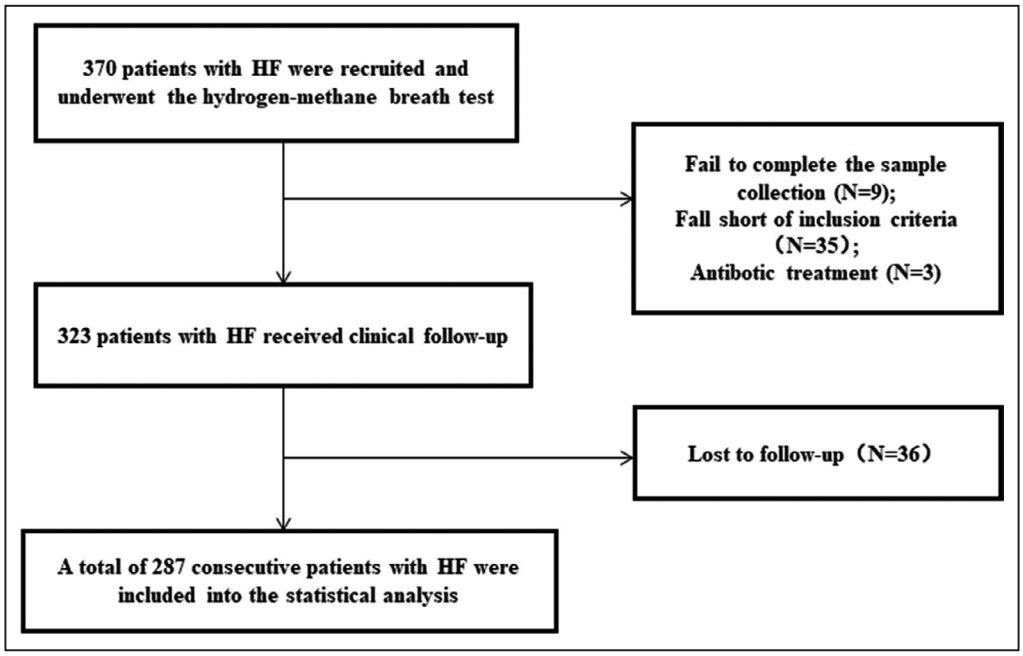

Figure 1. Flow chart.
HF indicates heart failure.

(81% versus 91%, *P*=0.023). Additionally, patients with SIBO presented increased LAD (50.1±8.3 mm versus 48.2±7.3 mm, *P*=0.043) and PASP (41.9±12.3 mm Hg versus 38.0±9.5 mm Hg, *P*=0.004) compared with patients without SIBO.

In patients with HFrEF, patients who were SIBO positive showed a higher proportion of edema of lower extremity (27 [24%] versus 35 [45%], *P*=0.003) compared with patients who were SIBO negative. Furthermore, higher frequency of intravenous diuretics treatment (41 [37%] versus 44 [56%], *P*=0.008) and lower frequency of β blocker treatment (104 [94%] versus 65 [83%], *P*=0.023) presented in the group who were SIBO positive. Finally, the level of CB (9.5±8.7 versus 6.6±4.8, *P*=0.008), NT-proBNP (3159 [1366–6481] versus 1772 [980–4417], *P*=0.018), and PASP (43.7±12.8 versus 38.8±10.4, *P*=0.004) increased in patients who were SIBO positive. However, in patients with HFpEF, the increased LAD (49.7±9.1 versus 45.7±5.5, *P*=0.010) was the only variable with significant difference between patients with or without SIBO (Table S1).

Association Between SIBO and Outcomes in HFrEF and HFpEF

After a median follow-up of 8 (4–12) months, 80 patients reached the primary end point (25 [15%] in SIBO– versus 55 [43%] in SIBO+, *P*<0.001), of whom 15 patients died and 68 patients were rehospitalized because of

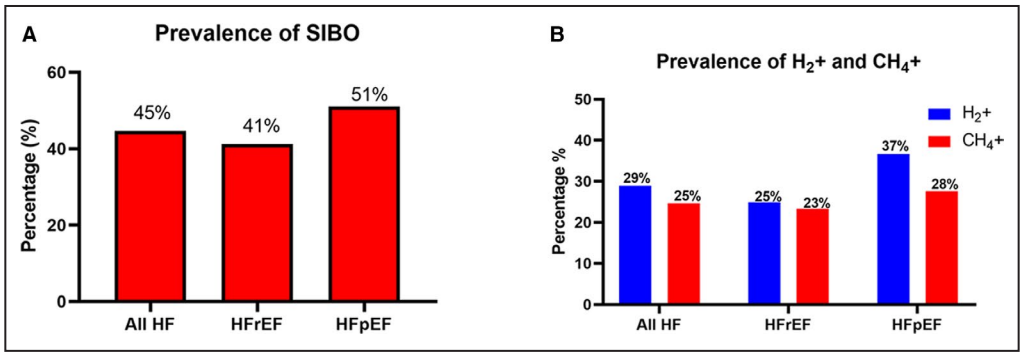

Figure 2. The prevalence of SIBO in patients with HF.
A, The prevalence of SIBO in all patients with HF; (**B**) The prevalence of SIBO (H_2) and SIBO (CH_4) in patients with HF. HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and SIBO, small intestinal bacterial overgrowth.

Table 1. Baseline Characteristics of Patients With or Without SIBO

Variables	SIBO– (N=159)	SIBO+ (N=128)	*P* Value
Age, y	56.5±14.1	58.3±15.0	0.240
Male, n (%)	125 (79)	93 (73)	0.213
Body mass index, kg/m^2	25.2±4.2	24.2±4.3	0.059
Smoking, n (%)	60 (38)	50 (39)	0.818
Systolic blood pressure, mm Hg	118.6±25.2	117.0±24.0	0.586
Diastolic blood pressure, mm Hg	76.7±15.9	73.6±14.1	0.077
Heart rate, bpm	80.1±17.8	77.6±14.2	0.215
New York Heart Association classification, n (%)			0.015*
I–II	85 (54)	50 (39)	
III–IV	74 (46)	78 (61)	
Coronary artery disease, n (%)	22 (14)	23 (18)	0.339
Hypertension, n (%)	66 (42)	54 (42)	0.908
Atrial fibrillation, n (%)	38 (24)	46 (36)	0.026*
Diabetes mellitus, n (%)	32 (20)	27 (21)	0.840
Renal insufficiency, n (%)	21 (13)	13 (10)	0.427
Edema of lower extremity, n (%)	41 (26)	57 (45)	0.001*
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/ angiotensin receptor-neprilysin inhibitors, n (%)	130 (82)	108 (84)	0.559
β blocker, n (%)	143 (90)	103 (81)	0.023*
Oral diuretics, n (%)	124 (78)	110 (86)	0.084
Aldosterone antagonist, n (%)	102 (64)	97 (76)	0.034
Digoxin, n (%)	26 (14)	32 (25)	0.070
Intravenous diuretics, n (%)	55 (35)	59 (46)	0.048*
High-sensitivity C-reactive protein, mg/dL	2.2 (0.8–10.3)	2.6 (1.1–9.8)	0.483
Total bilirubin, μmol/L	16.5±10.1	18.9±12.3	0.079
Conjugated bilirubin, μmol/L	6.3±5.1	8.3±7.8	0.013*
Creatinine, μmol/L	97.3±39.4	102.1±45.8	0.339
Uric acid, μmol/L	450.4±154.7	468.8±149.0	0.312
Estimated glomerular filtration rate, mL/min per 1.73 m^2	77.5±21.7	73.6±24.7	0.163
Cardiac troponin T, ng/mL	0.027 (0.014–0.050)	0.024 (0.013–0.044)	0.366
N-terminal pro-B-type natriuretic peptide, pg/mL	1555 (820–3460)	2336 (937–4637)	0.060
Left atrial diameter, mm	48.2±7.3	50.1±8.3	0.043*
Left ventricular end diastolic diameter, mm	62.4±10.9	61.6±10.5	0.554
Left ventricular end systolic diameter, mm	50.4±12.5	49.7±12.7	0.650
Interventricular septal thickness, mm	10.1±2.3	10.4±3.5	0.402
Pulmonary artery systolic pressure, mm Hg	38.0±9.5	41.9±12.3	0.004*
Left ventricular ejection fraction, %	38.9±13.3	39.7±13.7	0.628

Values are expressed as mean±SD, frequency (percentage), or median (interquartile range). SIBO indicates small intestinal bacterial overgrowth.
**P* value <0.05 are significant for the difference between SIBO- and SIBO+.

worsening HF. The primary end point occurred in 62 patients with HFrEF (22 [20%] in SIBO– versus 40 [51%] in SIBO+, *P*<0.001) and 18 patients with HFpEF (3 [6%] in SIBO– versus 15 [30%] in SIBO+, *P*=0.003). In patients with HFrEF, there were 8 cardiovascular deaths (4 [4%] in SIBO– versus 4 [5%] in SIBO+, *P*=0.719) and 56 HF rehospitalizations (20 [18%] in SIBO– versus 36 [46%] in SIBO+, *P*<0.001). However, in patients with HFpEF, there were 7 cardiovascular deaths (7 [14%] only in SIBO+, *P*=0.013), and 23 HF rehospitalizations (3 [6%] in SIBO– versus 9 [18%] in SIBO+, *P*=0.122) (Table 2).

Patients who were SIBO positive with HFrEF showed a 2.77-fold increased risk of HF rehospitalization (HR, 2.77; 95% CI, 1.62–4.74; *P*<0.001) and no difference in cardiovascular death (HR, 1.66; 95% CI, 0.40–6.94; *P*=0.467) (Figure 3A and 3B). Interestingly, patients who were SIBO positive with HFpEF increased the risk of cardiovascular death (HR, 7.34; 95% CI, 1.58–34.13; *P*=0.011) rather than

Table 2. Outcomes of Patients With HF

Outcomes	SIBO−	SIBO+	*P* Value
All HF, n (%)	159 (55)	128 (45)	
Primary end point, n (%)	25 (15)	55 (43)	<0.001
Cardiovascular death, n (%)	4 (3)	11 (9)	0.031
HF rehospitalization, n (%)	23 (15)	45 (35)	<0.001
HF with reduced ejection fraction, n (%)	111 (59)	78 (41)	
Primary end point, n (%)	22 (20)	40 (51)	<0.001
Cardiovascular death, n (%)	4 (4)	4 (5)	0.719
HF rehospitalization, n (%)	20 (18)	36 (46)	<0.001
HF with preserved ejection fraction, n (%)	48 (49)	50 (51)	
Primary end point, n (%)	3 (6)	15 (30)	0.003
Cardiovascular death, n (%)	0 (0)	7 (14)	0.013
HF rehospitalization, n (%)	3 (6)	9 (18)	0.122

The outcomes of patients with HF after a median follow-up of 8 (4–12) months. HF indicates heart failure; and SIBO, small intestinal bacterial overgrowth.

HF rehospitalization (HR, 3.03; 95% CI, 0.98–9.38; *P*=0.077) (Figure 3C and 3D).

SIBO, SIBO (H_2), and SIBO (CH_4) in HF

SIBO was associated with the risk of primary end point in univariate Cox regression (HR, 2.91; 95% CI, 1.81–4.68; *P*<0.001). After the adjustment of body mass index, NYHA III-IV class, use of β blocker and aldosterone antagonist, and the level of CB, NT-proBNP, LAD, and PASP, SIBO was independently correlated to primary end point in all patients with HF (HR, 2.13; 95% CI, 1.26–3.58; *P*=0.005) (Table 3).

SIBO (H_2) contributed to the higher risk of primary end point (HR, 1.55; 95% CI, 0.96–2.50; *P*=0.052) (Figure 4A), but the association was not statistically significant. SIBO (CH_4) showed a significant prognostic value on primary end point (HR, 2.35; 95% CI, 1.38–4.02; *P*<0.001) (Figure 4B), and the association still presented after adjustment (HR, 2.19; 95% CI, 1.39–3.48; *P*=0.001). Patients with SIBO (H_2 and CH_4) had similar outcomes to SIBO (H_2) or SIBO (CH_4) and showed the higher risk of primary end point than patients without SIBO (Figure 4C).

DISCUSSION

This study demonstrated patients with HF had a high prevalence of SIBO, and the presence of SIBO was associated with the poor outcomes of cardiovascular death and HF rehospitalization.

Increasing evidence has showed that HF is accompanied by intestinal dysfunction.[4,13,14] The disruption of intestinal barrier contributes the progress of HF in return through promoting the systemic inflammatory state that is caused by the translocation of endotoxins, microbial components, and derived metabolites.[15,16] Gut microbiota imbalance may be a considerable driving factor in this process. A growing body of evidence has established the correlation between HF and gut microbiota.

Under physiological conditions, the small intestine is relatively sterile compared with the colon colonized by multitudes of microbes. SIBO is characterized by the increased number and the change in composition of bacteria in the small intestine. SIBO manifests with a variety of gastrointestinal symptoms, including constipation, diarrhea, bloating, abdominal pain, nausea, emesis, or no obvious symptom. The gold standard for diagnosing SIBO is the microbiological quantities ≥10^5 colony forming units per milliliter in the intestinal fluid. But the hydrogen-methane breath test is more commonly used because of its convenience and noninvasion,[17,18] working on the assumption that the only source of H_2 production in the body is from fermentation of carbohydrates by gut microbiota.[19] In addition, about 15% to 30% of people are colonized with methanobrevibacter, which can reduce CO_2 to CH_4 by using H_2 as electron donor.[20] H_2 and CH_4 enter the circulation and lung via the small intestine villi and then are exhaled. The excessive exhaled gases indirectly reflect the small intestinal microbiota dysbiosis-SIBO.

SIBO has also been shown to be closely associated with many parenteral diseases, such as deep vein thrombosis,[21] Parkinson's disease,[22] diabetes mellitus,[23] atherosclerosis,[24] and coronary artery disease.[25] Patients with HF often have pathophysiological changes in the gastrointestinal tract, but the association between SIBO and the outcomes of HF is still unknown. The clinical manifestations of SIBO are nonspecific and similar to the gastrointestinal congestion due to right HF, so the presence of SIBO is usually overlooked. In our study, patients with HFrEF and SIBO had a higher proportion of NYHA III–IV class, edema of lower extremity, and higher frequency of intravenous diuretics treatment in admission, which may suggest this subgroup of patients with HF had worse volume load. The morphological or functional intestinal abnormalities may already exist in these patients, whether they have some obvious symptom about gastrointestinal disturbance or not. Left atrial enlargement is the important cardiac structure change for HFpEF; a significantly enlarged LAD of patients who are SIBO positivein HFpEF may indicate a severe left atrial remodeling. Therefore, identification for patients who are SIBO positive may be helpful to assessment of HF progress.

Although the pathophysiological relationship between SIBO and HF remains unclear, chronic inflammation may be one of the mechanisms. Although we have not observed a significant difference of hs-CRP

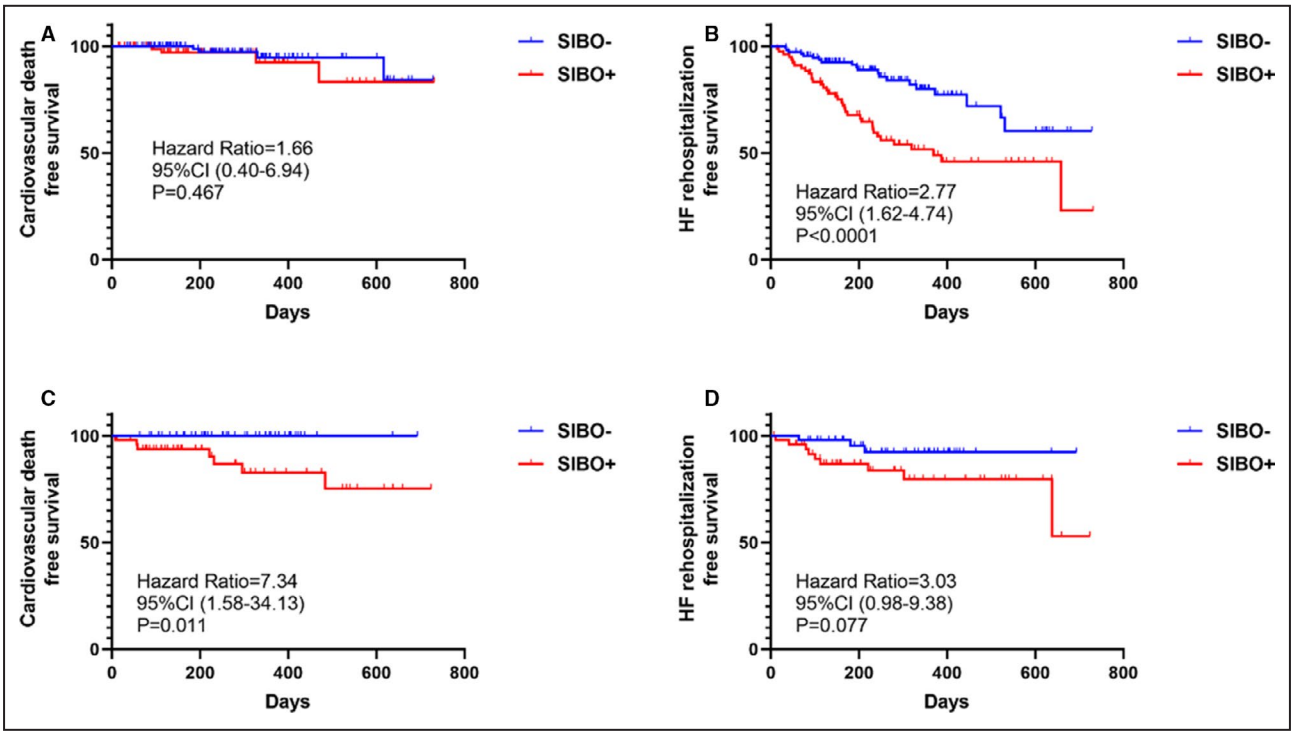

Figure 3. Adverse outcome (cardiovascular death or HF rehospitalization) free survival for patients with SIBO in different types of HF.

A, Kaplan–Meier survival curve for cardiovascular death in HFrEF; (**B**) Kaplan–Meier survival curve for HF rehospitalization in HFrEF; (**C**) Kaplan–Meier survival curve for cardiovascular death in HFpEF; (**D**) Kaplan–Meier survival curve for HF rehospitalization in HFpEF. HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and SIBO, small intestinal bacterial overgrowth.

between patients who are SIBO positive and SIBO negative, the previous study showed the concentration of hydrogen in a breath test was related to inflammatory markers (interleukin-1β, interleukin-10, and tumor necrosis factor-α).[9] Increase in sympathetic activity and withdrawal of vagal activity are the main mechanisms of HF.[26] Robinson-Papp et al found that patients who are SIBO positive with vagal dysfunction had elevated

Table 3. Variables in the Cox Proportional Hazards Model Associated With Primary End Point

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y; Δ=10 y)	0.98 (0.85–1.12)	0.733		
Sex (male)	1.92 (0.55–1.54)	0.753		
Body mass index, kg/m^2	0.93 (0.88–0.99)	0.019	0.95 (0.90–1.00)	0.067
New York Heart Association III–IV	2.78 (1.68–4.62)	<0.001	1.12 (0.61–2.07)	0.715
Edema of lower extremity	2.33 (1.50–3.61)	<0.001	0.75 (0.43–1.30)	0.306
Intravenous diuretics	3.34 (2.10–5.30)	<0.001	1.13 (0.61–2.09)	0.692
β blocker	0.42 (0.25–0.71)	0.001	0.64 (0.36–1.12)	0.118
Aldosterone antagonist	2.10 (1.20–3.69)	0.010	1.11 (0.60–2.03)	0.745
Conjugated bilirubin, μmol/L	1.08 (1.05–1.10)	<0.001	1.05 (1.02–1.08)	0.001
N-terminal pro-B-type natriuretic peptide (per log unit)	3.68 (2.43–5.55)	<0.001	2.69 (1.54–4.71)	0.001
Left atrial diameter, mm	1.05 (1.03–1.08)	<0.001	1.03 (0.99–1.06)	0.105
Pulmonary artery systolic pressure, mm Hg	1.04 (1.02–1.06)	<0.001	1.00 (0.98–1.02)	0.836
SIBO+	2.91 (1.81–4.68)	<0.001	2.13 (1.26–3.58)	0.005

The correlation between SIBO and primary end point was analyzed by stepwise Cox proportional hazards model. HR indicates hazard ratio; and SIBO, small intestinal bacterial overgrowth.

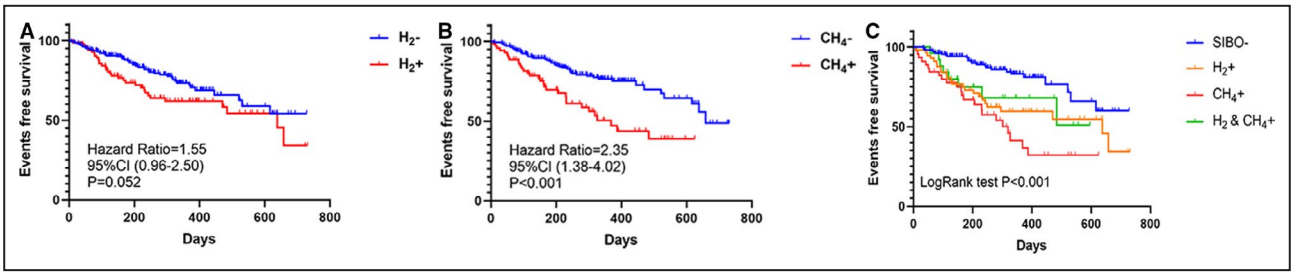

Figure 4. The primary end point event free survival for SIBO (H_2) and SIBO (CH_4) in patients with HF.
A, Kaplan–Meier survival curve for primary end point in SIBO (H_2); (**B**) Kaplan–Meier survival curve for primary end point in SIBO (CH_4); (**C**) Kaplan–Meier survival curve for primary end point in SIBO (H_2 and CH_4). HF indicates heart failure; and SIBO, small intestinal bacterial overgrowth.

levels of interleukin-6, interferon-α, and interleukin-2.[27] Niebauer et al confirmed that raised concentrations of endotoxin and cytokines are found in patients with chronic HF during peripheral edematous exacerbation, whereas intensified diuretic treatment can reduce endotoxin concentrations.[28] Based on these evidences, we hypothesize that during HF, bacterial translocation resulting from the disruption of intestinal barrier causes SIBO; and then SIBO leads to endotoxins, microbial components, and metabolites entering the intestinal mesenteric artery, which activates systemic inflammatory and immunological responses, eventually causing the hypertrophy, apoptosis, and fibrosis of cardiomyocyte.

According to our data, SIBO was associated with a 2.13-fold increased risk of primary end point in patients with HF, which means SIBO may be an unheeded comorbidity needing intervention. Somewhat differently, SIBO was correlated to HF rehospitalization in HFrEF but associated with cardiovascular death in HFpEF. Although there were no multivariate results of outcomes in different types of HF subgroups because of the small sample size, our data still gave us some revelation that SIBO may contribute to HF progression through a pathophysiologic mechanism. Baseline data confirm that patients with SIBO have peripheral edema, CB and NT-proBNP increased volume load, and other manifestations of volume overload, and the volume overload resulting from fluid retention is the main reason for rehospitalization of patients with HF, which may explain why SIBO in patients with HFrEF increased the risk of rehospitalization. SIBO was associated with the risk of cardiovascular death in patients with HFpEF, indicating that SIBO may be involved in the etiological mechanism of HFpEF. Patients with SIBO with HFpEF have a larger LAD, which means a more severe atrial remodeling. The underlying mechanism may include the cardiomyocyte and endothelial inflammation caused by the endotoxin and trimetlylamine oxide released by SIBO. The systemic inflammatory state induced by comorbidities are considered as main pathological mechanisms of HFpEF, and it seems that SIBO is a proinflammatory comorbidity according to our hypothesis. Investigating the clinical significance of SIBO may contribute a deeper understanding of HFpEF. Moreover, the previous study showed SIBO (H_2) was correlated to death/all-cause hospitalization, rather than SIBO (CH_4)[9]; whereas our study was inclined to support the predictive effect of SIBO (CH_4). The different prevalence of H_2+ and CH_4+ (H_2+/CH_4+ in our study=29%/25%, H_2+/CH_4+ in previous study=38%/47%) may be the plausible reason. Discrepant composition of gut microbiota derived from different races and diet structure between China and the West are more likely to be the underlying mechanism.

Although a growing body of evidence has showed that interventions in gut microbiota improves cardiac function in patients with HF and animal model,[29–31] there is no published evidence showed the beneficial effect of treatment for gut microbiota in poor prognosis of HF. Our data indicate treatment of SIBO may provide extra benefit for the prognosis of this subgroup of patients with HF. Currently, treatment for SIBO is available and well documented compared with strategies being studied. The previous studies showed rifaximin improved the symptoms of SIBO, and the negative transformation rate of lactulose hydrogen-methane breath test was about 84%.[32,33] For the patients who failed monotherapy with rifaximin, the combination with antibiotics that are not absorbed by the gut (eg, metronidazole, neomycin) is an alternative strategy.[34] Further studies are needed to elucidate the prognostic improvement effect of treatment for SIBO in HF.

Limitations

The current trial has several limitations. First, we reported small-sample data, from a single center. Because of lacking the onset time of HF or SIBO, it is hard to identify the exact causal link, so we postulate the association between SIBO and HF is reciprocal.

Second, hydrogen-methane breath test is not the gold standard for SIBO diagnosis but has an acceptable accuracy. Third, age- and sex-matched controls were not involved in our study, the prevalence of them is necessary to understanding the correlation between HF and SIBO. Fourth, we must interpret the results prudently because of the limitation from the exclusion of patients with HF with digestive disease and the bias from losing 36 eligible patients to follow-up. Fifth, the inclusion criteria requiring NT-proBNP level >125 pg/mL could have led to the exclusion of a significant number of patients with HFpEF as HFpEF can be associated with fairly normal NT-proBNP levels. At last, although positive results are obtained after a median follow-up of 8 months, a longer follow-up time will be needed to evaluate the effect of SIBO on the outcomes of HF.

CONCLUSIONS

In summary, patients with HF have a high prevalence of SIBO, and SIBO was independently associated with poor outcomes. SIBO increased the risk of HF rehospitalization in patients with HFrEF, as well as the risk of cardiovascular death in patients with HFpEF. Our result showed that SIBO (CH_4) may have a better prognostic value than SIBO (H_2). Proactive treatment for patients with HF and SIBO may improve the prognosis and quality of life.

ARTICLE INFORMATION

Received November 13, 2019; accepted February 1, 2021.

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Acknowledgments

We gratefully acknowledge all the people who participated in this study for their efforts in the conduction of the study.

Sources of Funding

None.

Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients with or without SIBO in HFrEF and HFpEF.

Variables	HFrEF			HFpEF		
	SIBO- (N=111)	SIBO+ (N=78)	*P* value	SIBO- (N=48)	SIBO+ (N=50)	*P* value
Age, years	53.2±13.7	53.7±14.2	0.813	64.0±12.2	53.7±14.2	0.561
Male, n (%)	90 (81)	56 (72)	0.134	35 (73)	37 (74)	0.903
BMI, kg/m^2	25.6±4.4	24.2±4.6	**0.033**	24.1±3.5	24.2±4.0	0.889
Smoking, n (%)	41 (37)	31 (40)	0.696	19 (40)	19 (38)	0.872
SBP, mmhg	116.1±22.7	111.1±19.7	0.115	124.5±29.9	126.2±27.2	0.763
DBP, mmhg	77.0±15.6	72.1±14.6	0.031	76.2±16.6	75.8±13.3	0.903
Heart rate, bpm	82.0±16.7	78.8±15.5	0.195	75.6±19.7	75.7±11.7	0.962
NYHA classification, n (%)			**0.027**			0.149
I-II	55 (49)	26 (33)		30 (62)	24 (48)	
III-IV	56 (51)	52 (67)		18 (38)	26 (52)	
Coronary artery disease, n (%)	14 (13)	15 (19)	0.214	8 (17)	8 (16)	0.929
Hypertension, n (%)	44 (40)	32 (41)	0.848	22 (46)	22 (44)	0.855
Atrial fibrillation, n (%)	21 (19)	20 (26)	0.270	17 (35)	26 (52)	0.098
Diabetes, n (%)	23 (21)	19 (24)	0.554	9 (19)	8 (16)	0.719
Renal insufficiency, n (%)	18 (16)	6 (8)	0.083	3 (6)	7 (14)	0.318
Edema of lower extremity, n (%)	27 (24)	35 (45)	**0.003**	14 (29)	22 (44)	0.128
ACEI/ARB/ARNI, n (%)	96 (87)	67 (87)	0.908	34 (71)	41 (82)	0.192
β-blocker, n (%)	104 (94)	65 (83)	**0.023**	39(81)	38(76)	0.527
Oral diuretics, n (%)	94 (85)	73 (94)	0.060	30(63)	37 (74)	0.221
Aldosterone antagonist, n (%)	81 (73)	66 (85)	0.058	21 (13)	44 (62)	0.070
Digoxin, n (%)	21 (19)	23 (30)	0.091	5 (10)	9 (18)	0.389
Intravenous diuretics, n (%)	41 (37)	44 (56)	**0.008**	14 (29)	15 (30)	0.928
hs-CRP, mg/dL	2.6 (0.8-10.6)	3.2 (1.1-11.8)	0.534	1.5 (0.5-5.9)	1.6 (0.8-7.6)	0.529
TB, umol/L	17.1±10.0	20.3±12.8	0.054	15.2±10.2	16.7±11.2	0.503
CB, umol/L	6.6±4.8	9.5±8.7	**0.008**	5.7±5.7	6.5±5.6	0.520
Creatinine, umol/L	100.8±41.7	101.6±37.8	0.898	89.3±32.6	103.1±56.6	0.142
Uric acid, umol/L	470.2±167.9	507.1±141.4	0.114	405.3±107.9	408.9±141.8	0.632
eGFR, mL/min/1.73m^2	77.4±22.4	75.1±24.4	0.515	77.7±20.2	71.3±25.2	0.170
cTnT, ng/mL	0.030 (0.017-0.049)	0.030 (0.016-0.047)	0.925	0.020 (0.010-0.062)	0.018 (0.010-0.039)	0.445
NT-proBNP, pg/mL	1772 (980-4417)	3159 (1366-6481)	**0.018**	984 (668-2128)	1224 (505-3100)	0.631
LAD, mm	49.2±7.8	50.3±7.9	0.364	45.7±5.5	49.7±9.1	**0.010**
LVEDD, mm	66.5±8.8	66.5±9.2	0.998	52.9±9.1	54.0±7.7	0.495
LVESD, mm	56.0±9.2	56.6±9.8	0.662	37.5±9.4	39.0±8.6	0.413
IVST, mm	9.5±1.5	9.5±2.2	0.979	11.5±3.3	11.8±4.7	0.713
PASP, mmhg	38.8±10.4	43.7±12.8	**0.004**	36.2±6.8	38.9±10.8	0.139
LVEF, %	31.8±6.8	30.9±6.6	0.328	55.3±9.7	53.5±9.8	0.349

Values are expressed as mean ± standard deviation, frequency (percent), or median (interquartile range). BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association ; ACEI, angiotensin-converting enzyme inhibitors ; ARB, angiotensin-II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular

filtration rate; TB, total bilirubin; CB, conjugated bilirubin; hs-CRP, highsensitivity C-reactive protein; cTnT, cardiac troponin T; NT-proBNP, N terminal pro brain natriuretic peptide, LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; IVST, interventricular septal thickness; PASP, pulmonary artery systolic pressure; LVEF, left ventricular ejection fraction; SIBO, small intestinal bacterial overgrowth .