Heart and Vessels (2018) 33:740–751
https://doi.org/10.1007/s00380-018-1117-5

ORIGINAL ARTICLE

Portal congestion and intestinal edema in hospitalized patients with heart failure

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Received: 20 August 2017 / Accepted: 5 January 2018 / Published online: 11 January 2018

Abstract
An interaction between the intestine and cardiovascular disease has been suggested. We thought to clarify the association between intestinal conditions and clinical outcomes in patients with heart failure (HF). Hemodynamic parameters in intestinal vessels [superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and portal vein (PV)] and average colon wall thickness (aCWT) from the ascending colon to sigmoid colon were evaluated in 224 hospitalized HF patients. Echocardiographic parameters and composite event rates (all-cause mortality, readmission for HF deterioration, major ventricular arrhythmias) were also examined. Higher PV congestion index (CI) and aCWT were observed in patients with New York Heart Association (NYHA) class III/IV. Higher PVCI [hazard ratio (HR) per + 1 standard deviation (SD) 1.50, $p < 0.01$] and aCWT (HR per + 1 SD 1.45, $p < 0.01$) were independently associated with higher composite event rates during the follow-up of 122 ± 68 days. None of SMA/IMA hemodynamic parameters were associated with NYHA class or composite event rates. Higher right ventricular end-diastolic dimension (38 ± 7 vs 34 ± 9 mm, $p < 0.01$) and lower tricuspid annual plane systolic excursion (15 ± 5 vs 19 ± 5 mm, $p < 0.001$) were observed in patients with higher PVCI (> 0.031 cm s) and aCWT (> 2.8 mm) relative to those in others. In conclusion, increased portal congestion and intestinal edema were associated with severe HF symptoms and poor outcomes in hospitalized HF patients, in addition to being associated with impaired right-sided cardiac function.

Keywords Heart failure · Congestion · Right ventricular function · Intestinal dysbiosis

Introduction

Heart failure (HF) progression involves multiple organ failure, such as of the lung [1], kidney [2], and liver [3], leading to worse quality of life and prognosis. These organ injuries are predominantly caused by systemic sodium and water retention [4]. Recently, the importance of elevation in right-sided pressures, which result in the characteristic signs of organ congestion, has been reported [5–7].

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Current studies on multiple organ contributions to HF progression have observed systemic chronic inflammation. A strong link has been reported between elevated right-sided pressures and systemic inflammation leading to cardiac cachexia [8], accompanied with neurohumoral imbalance [9], inflammatory-cytokine overexpression [9], and malabsorption in the small intestine [10].

The colon wall serves as a barrier against numerous intestinal bacteria, directly leading to systemic inflammation [11]. Hemodynamic disorders caused by cardiac dysfunction could lead to intestinal edema and colonic barrier disruption, which potentially leads to the entry of lipopolysaccharide or endotoxin produced by Gram-negative bacteria into the host's circulatory system. Increased colon wall thickness as a manifestation of intestinal edema and increased bacterial populations adherent to colonic mucosa has been demonstrated in patients with chronic HF [12].

We postulate that intestinal-immunological disturbances in right-sided HF are associated with disease progression in

patients with HF. However, there is no solid data to clarify the association between intestinal change and clinical outcome in HF setting. The aim of this investigation was to clarify whether there is any association among hemodynamic/morphological changes in the intestine, cardiac function, and outcomes in patients with HF.

Materials and methods

Study population

This was a single-center, prospective, observational study in Japanese patients with HF and was approved by the ethics committee of Kitasato University Hospital. Consecutive patients who were admitted to Kitasato University Hospital for acute decompensated HF from February 1, 2015 through August 31, 2016 were screened. The exclusion criteria included age < 20 years, patients who did not wish to participate, acute coronary syndrome within the last 3 months, and patients with active gastrointestinal disease, including gastrointestinal cancer, any cause of enteritis/colitis, inflammatory bowel disease, food hypersensitivity, and ileus. The diagnosis of HF was based on the Framingham classification. All patients received optimal HF treatments during the hospitalization according to the current HF guidelines [13, 14].

Clinical measurements

Clinical parameters, such as demographics, medications, physical examination, blood sampling parameters, and echocardiography, were obtained under stable conditions as close to discharge within 2 days before or after abdominal ultrasonography for intestinal parameters. Transthoracic echocardiographic studies were performed in standard fashion according to the current guidelines [15, 16] by one experienced ultrasonographer and reviewed by another ultrasonographer unaware of abdominal ultrasonographic parameters. Abdominal ultrasonography was also performed to assess blood flow parameters and intestinal wall thickness by one experienced ultrasonographer and reviewed by another ultrasonographer independent of the patient's clinical information. Intestinal blood flow parameters, including the cross-sectional area (CSA), maximum velocity, blood flow volume, pulsatility index (PI) [= (maximum velocity − minimum velocity)/mean velocity] [17, 18], and congestion index [CI, only at the portal vein (PV)] (= CSA/mean velocity) [19, 20], were obtained at the superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and PV. Intestinal wall thickness was evaluated at the ascending, transverse, descending, and sigmoid colon as previously reported [21]. Average colon wall thickness (aCWT) was calculated according to the following formula: aCWT = (ascending + transverse + descending + sigmoid colon wall thickness)/4. Representative images to evaluate blood flow parameters and intestinal wall thickness are presented in Fig. 1. The presence or absence of ascites was also evaluated.

Outcome

Primary endpoints were determined prior to population enrollment, and approved by the ethics committee in our institute. Patients were observed for evaluation of composite events, including the first events among all-cause mortality, unplanned readmission for HF worsening, or major ventricular arrhythmias (including ventricular fibrillation and sustained ventricular tachycardia defined as ≥ 30 s consecutive premature complexes at a mean rate > 120 beats/min). Patient outcomes were evaluated until December 17, 2016 or the date of composite events. Physicians were unaware of the abdominal ultrasonographic parameters in their patients.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. For comparison between groups, Student's *t* test or the Wilcoxon rank sum test was used for continuous variables; the Chi-square test or Fisher's exact test was used for categorical variables. To explore the strength of correlation, Spearman's correlation coefficient was calculated. The Kaplan–Meier method was used to draw the stratified composite event-free rates; the log-rank test was used to compare between groups. Optimal cutoff values for PVCI and aCWT were determined on the basis of the maximal *p* value of the log-rank test. To elucidate the relationships between clinical parameters and binary variables, such as the New York Heart Association (NYHA) class (I/II or III/IV) and to identify predictive factors, a logistic regression model was used, and the odds ratio and corresponding 95% confidence interval were calculated. To identify predictive (associated) factors for the composite event rates, a Cox proportional hazard model was used, and the hazard ratio (HR) and the 95% confidence interval were calculated. The *p* value for interaction was calculated between subgroups. The factors with $p < 0.05$ in univariate regression analyses were identified as candidate predictive factors for NYHA class or composite event rates; predictive factors were identified in the multivariate analysis by backward stepwise selection ($p < 0.05$). A *p* value < 0.05 was considered as indicating statistical significance. All statistical analyses were performed using JMP 10.0 software (SAS Institute, Cary, NC, USA).

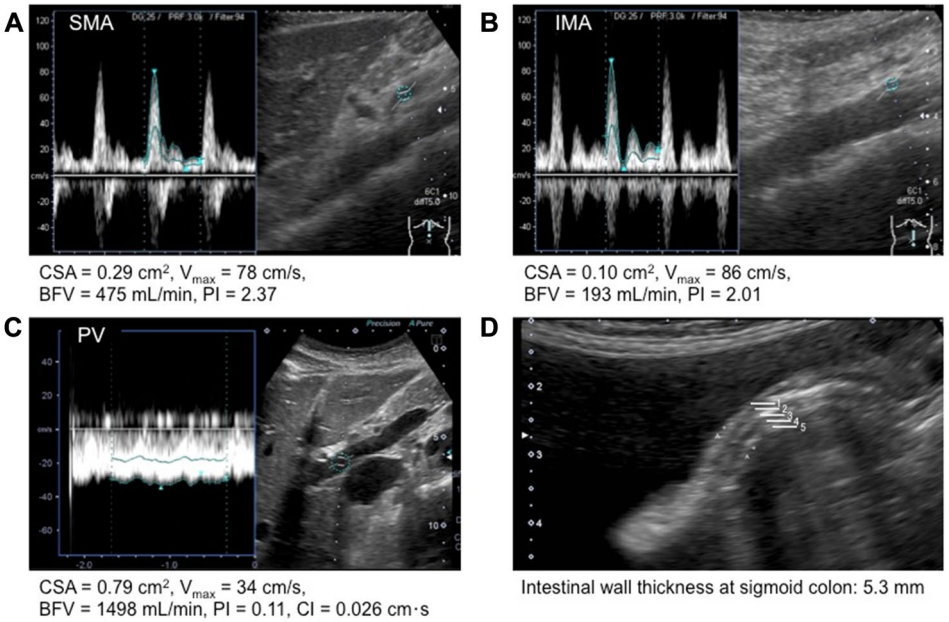

Fig. 1 Representative images to evaluate blood flow parameters and intestinal wall thickness. Blood flow parameters were obtained in SMA (**a**), IMA (**b**), and PV (**c**). PI and CI were calculated using the following formula: PI = (V_{max} − minimum velocity)/mean velocity; CI = CSA/mean velocity. As shown in a patient with ascites and thickened sigmoid colon wall (**d**), a gastrointestinal wall has five layers. Layer 1 (high echoic): adventitia (or serosa with subserosal fat); layer 2 (low echoic): muscularis propria; layer 3 (high echoic): submucosa; layer 4 (low echoic): deep mucosa; and layer 5 (high echoic): interface echo and superficial mucosa. We measured the distance between outermost of the layer 1 and innermost of the layer 5 at each colonic wall (**d**). *SMA* superior mesenteric artery, *IMA* inferior mesenteric artery, *PV* portal vein, *CSA* cross sectional area, V_{max} maximum velocity, *BFV* blood flow volume, *PI* pulsatility index, *CI* congestion index

Results

Study patients

This study comprised 224 hospitalized patients after acute decompensated HF who met the inclusion criteria during the study period for screening. The follow-up period was 122 ± 68 days to measure the midterm outcome; there were 57 patients (25.4%) with composite events (cardiac death in 18 who all died because of worsened HF, noncardiac death in 1, unplanned readmission for worsened HF in 33, or major ventricular arrhythmias in 5). The patients' demographics, medications, and clinical conditions at enrollment stratified by the NYHA class, and the presence or absence of composite events are presented in Table 1.

Intestinal parameters

Intestinal parameters stratified by the NYHA class (depending on NYHA class I/II or III/IV) and the presence or absence of composite events are summarized in Table 2. Among the hemodynamic condition variables, PVPI and PVCI were higher in the patients with NYHA class III/IV and with composite events. For morphological conditions, all intestinal wall thicknesses (from the ascending colon to sigmoid colon) and aCWT were thicker in the patients with NYHA class III/IV and with composite events. To clarify the association between hemodynamic/morphological conditions in the intestine and clinical outcomes in hospitalized HF patients, we selected PVCI and aCWT as representative variables in abdominal ultrasonography.

Association with HF symptom and midterm outcome

Univariate and multivariate analyses for association with NYHA class III/IV or for prediction of composite events are presented in Table 3. Higher PVCI and aCWT were independently associated with NYHA class III/IV and higher composite event rates.

Midterm outcome among groups stratified by intestinal parameters

Composite event-free rates stratified by optimal cutoff values of PVCI and aCWT are presented in Fig. 2. The cutoff value for PVCI was 0.031 cm s, and that for aCWT was 2.8 mm. Patients with PVCI > 0.031 cm s [high-PVCI group, n = 94 (42%): unadjusted HR 2.22, 95% confidence interval 1.31–3.78; p = 0.003] and aCWT > 2.8 mm

Table 1 Patient characteristics at enrollment

Variables	All ($n = 224$)	NYHA group		p value	Composite events group		p value	PVCI and aCWT group		p value
		NYHA I/II ($n = 106$)	NYHA III/IV ($n = 118$)		Composite events (−) ($n = 167$)	Composite events (+) ($n = 57$)		Low-PVCI or low-aCWT ($n = 182$)	High-PVCI and high-aCWT ($n = 42$)	
Demographic data										
Age (years)	68 ± 14	65 ± 13	70 ± 13	0.002	67 ± 13	71 ± 14	0.003	68 ± 13	67 ± 15	0.7
Gender, males, *n* (%)	130 (58)	66 (62)	54 (54)	0.2	96 (57)	34 (60)	0.8	101 (55)	29 (69)	0.1
Ischemic etiology, *n* (%)	78 (35)	39 (37)	39 (33)	0.5	62 (37)	16 (28)	0.2	65 (36)	13 (31)	0.5
Hypertension, *n* (%)	123 (55)	62 (58)	61 (52)	0.3	96 (57)	27 (47)	0.2	100 (55)	23 (55)	0.9
Dyslipidemia, *n* (%)	95 (42)	46 (43)	49 (42)	0.7	71 (43)	24 (42)	0.9	81 (45)	14 (33)	0.1
Diabetes, *n* (%)	92 (41)	40 (38)	52 (44)	0.3	66 (40)	26 (46)	0.4	73 (40)	19 (45)	0.5
Medication										
Beta-blockers, *n* (%)	179 (80)	89 (84)	90 (76)	0.1	134 (80)	45 (79)	0.8	146 (80)	33 (79)	0.8
ACEi or ARB, *n* (%)	199 (89)	93 (88)	106 (90)	0.6	146 (87)	53 (93)	0.3	162 (89)	37 (88)	0.8
Aldosterone antagonists, *n* (%)	120 (54)	55 (52)	65 (55)	0.6	88 (53)	32 (56)	0.7	95 (52)	25 (60)	0.3
Loop diuretics, *n* (%)	178 (79)	69 (65)	109 (92)	< 0.0001	124 (74)	54 (95)	0.0005	139 (76)	39 (93)	0.01
Clinical condition										
NYHA III/IV, *n* (%)	118 (53)	–	–	–	69 (41)	49 (86)	< 0.0001	80 (44)	38 (90)	< 0.0001
Systolic blood pressure (mmHg)	110 ± 19	110 ± 16	109 ± 21	0.3	111 ± 19	104 ± 18	0.009	110 ± 19	109 ± 21	0.6
Heart rate (beats/min)	72 ± 12	71 ± 11	74 ± 13	0.09	72 ± 13	72 ± 11	0.8	71 ± 11	77 ± 15	0.02
Atrial fibrillation, *n* (%)	50 (22)	18 (17)	32 (27)	0.07	35 (21)	15 (26)	0.4	34 (19)	16 (38)	0.006
Estimated GFR ≤ 60 mL/min/1.73 m^2, *n* (%)	170 (76)	68 (64)	102 (86)	0.0001	118 (71)	52 (91)	0.001	134 (74)	36 (86)	0.09
BNP (pg/mL)	623 ± 782	352 ± 312	866 ± 975	< 0.0001	532 ± 661	891 ± 1021	0.0005	551 ± 656	933 ± 1142	0.004
LVEF ≤ 40%, *n* (%)	118 (53)	44 (42)	74 (63)	0.002	79 (47)	39 (68)	0.008	91 (50)	27 (64)	0.1
Moderate to severe MR, *n* (%)	77 (34)	29 (27)	48 (41)	0.04	50 (30)	27 (47)	0.02	60 (33)	17 (40)	0.3
Moderate to severe TR, *n* (%)	68 (30)	18 (17)	50 (42)	< 0.0001	40 (24)	28 (49)	0.0007	54 (30)	14 (33)	0.7

Values are presented as mean ± standard deviation, or number of patients (%). The continuous variable PVCI was divided into groups of values ≤ 0.031 (low-PVCI) and > 0.031 cm s (high-PVCI), and aCWT was divided into ≤ 2.8 (low-aCWT) and > 2.8 mm (high-aCWT)

NYHA New York Heart Association class, *PVCI* portal vein congestion index, *aCWT* average colon wall thickness, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blockers, *GFR* glomerular filtration rate, *BNP* B-type natriuretic peptide, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *TR* tricuspid regurgitation

Table 2 Intestinal hemodynamic and morphologic parameters divided by New York Heart Association class or incident composite events

Variables	All ($n = 224$)	NYHA group			Composite events group		
		NYHA I/II ($n = 106$)	NYHA III/IV ($n = 118$)	p value	Composite events (−) ($n = 167$)	Composite events (+) ($n = 57$)	p value
Blood flow parameters							
SMA							
CSA (cm^2)	0.28 ± 0.11	0.27 ± 0.10	0.29 ± 0.11	0.1	0.28 ± 0.11	0.28 ± 0.10	0.9
V_{max} (cm/s)	174 ± 67	178 ± 70	170 ± 64	0.3	175 ± 68	168 ± 65	0.5
BFV (mL/min)	949 ± 503	947 ± 495	951 ± 512	0.8	960 ± 517	912 ± 453	0.5
PI	2.62 ± 0.89	2.62 ± 0.92	2.62 ± 0.87	0.9	2.64 ± 0.93	2.55 ± 0.77	0.5
IMA							
CSA (cm^2)	0.11 ± 0.08	0.11 ± 0.10	0.10 ± 0.06	0.5	0.11 ± 0.09	0.10 ± 0.04	0.6
V_{max} (cm/s)	122 ± 62	120 ± 65	125 ± 59	0.5	118 ± 59	136 ± 71	0.1
BFV (mL/min)	228 ± 205	226 ± 233	218 ± 168	0.9	225 ± 203	237 ± 214	0.7
PI	3.34 ± 1.35	3.30 ± 1.26	3.38 ± 1.44	0.9	3.25 ± 1.32	3.65 ± 1.42	0.1
PV							
CSA (cm^2)	0.65 ± 0.26	0.60 ± 0.23	0.70 ± 0.28	0.002	0.64 ± 0.26	0.69 ± 0.28	0.2
V_{max} (cm/s)	33 ± 13	34 ± 15	32 ± 11	0.5	34 ± 14	30 ± 11	0.05
BFV (mL/min)	1018 ± 460	1021 ± 503	1014 ± 419	0.5	1029 ± 437	983 ± 525	0.5
PI	0.34 ± 0.28	0.26 ± 0.20	0.41 ± 0.31	< 0.0001	0.31 ± 0.24	0.43 ± 0.35	0.03
CI (cm s)	0.034 ± 0.024	0.029 ± 0.015	0.038 ± 0.028	0.003	0.031 ± 0.018	0.041 ± 0.035	0.009
Colon wall thickness							
Ascending colon (mm)	2.7 ± 1.0	2.3 ± 0.8	3.0 ± 1.1	< 0.0001	2.6 ± 0.9	2.9 ± 1.2	0.008
Transverse colon (mm)	2.5 ± 0.8	2.3 ± 0.7	2.8 ± 0.9	< 0.0001	2.4 ± 0.8	2.9 ± 0.9	0.0008
Descending colon (mm)	2.6 ± 0.9	2.3 ± 0.7	2.9 ± 0.9	< 0.0001	2.5 ± 0.8	2.9 ± 1.0	0.001
Sigmoid colon (mm)	2.8 ± 1.0	2.5 ± 0.7	3.0 ± 1.1	0.0004	2.7 ± 0.9	3.0 ± 1.1	0.04
aCWT (mm)	2.6 ± 0.8	2.3 ± 0.6	2.9 ± 0.8	< 0.0001	2.5 ± 0.7	2.9 ± 0.9	0.0009

Values are presented as mean ± standard deviation

NYHA New York Heart Association class, *SMA* superior mesenteric artery, *IMA* inferior mesenteric artery, PV = portal vein, *CSA* cross sectional area, V_{max} maximum velocity, *BFV* blood flow volume, *PI* pulsatile index, *CI* congestion index, *aCWT* average colon wall thickness

[high-aCWT group, $n = 84$ (38%): unadjusted HR 2.55, 95% confidence interval 1.51–4.33; $p = 0.0005$] had lower composite event rates than those of patients without [low-PVCI group, $n = 130$ (58%) and low-aCWT group, $n = 140$ (62%), respectively]. Patients with both PVCI > 0.031 cm s and aCWT > 2.8 mm (high-PVCI and high-aCWT group, $n = 42$) had lower composite event-free rates than those with lower values (low-PVCI or low-aCWT group, $n = 182$; unadjusted HR 4.21, 95% confidence interval 2.38–7.24; $p < 0.0001$).

Similar results were shown for the all-cause mortality overall survival (high-PVCI group vs low-PVCI group, unadjusted HR 2.28, 95% confidence interval 0.92–5.89, $p = 0.07$; high-aCWT group vs low-aCWT group, unadjusted HR 3.33, 95% confidence interval 1.34–8.96, $p = 0.009$) or for event-free rates focused on unplanned readmission for HF worsening (high-PVCI group vs low-PVCI group, unadjusted HR 2.08, 95% confidence interval 1.17–3.70, $p = 0.01$; high-aCWT group vs low-aCWT group, unadjusted HR 2.67, 95% confidence interval 1.51–4.77, $p = 0.0008$).

Among clinical subgroups, unadjusted HR for composite events of the (high-PVCI and high-aCWT) group compared with that of the (low-PVCI or low-aCWT) group is presented in Fig. 3. The (high-PVCI and high-aCWT) group had significant higher risks in all subgroups, including age, gender, etiology, laboratory parameters, ventricular function, and valvular insufficiency. In the younger subgroup, a higher risk of the (high-PVCI and high-aCWT) group was much more than that in the elder subgroup.

Table 3 Univariate and multivariate analyses for association with New York Heart Association class III/IV or for prediction of composite events

Variables	For association with NYHA III/IV				For prediction of composite events			
	Unadjusted OR (95% confidence interval)	*p* value	Adjusted OR (95% confidence interval)	*p* value	Unadjusted HR (95% confidence interval)	*p* value	Adjusted HR (95% confidence interval)	*p* value
PVCI, per + 1 SD	1.70 (1.20–2.52)	0.001	1.53 (1.004–2.45)	0.04	1.55 (1.24–1.87)	0.0004	1.50 (1.15–1.87)	0.003
aCWT, per + 1 SD	2.52 (1.82–3.59)	< 0.0001	3.21 (2.15–5.01)	< 0.0001	1.61 (1.26–2.05)	0.0002	1.45 (1.14–1.84)	0.002
Age, per + 1 SD	1.44 (1.09–1.90)	0.007	1.20 (0.83–1.75)	0.3	1.48 (1.08–2.06)	0.01	1.41 (1.04–1.94)	0.02
Loop diuretics	6.49 (3.07–15.0)	< 0.0001			5.38 (1.98–22.1)	0.0002		
Systolic blood pressure, per + 1SD	0.93 (0.71–1.21)	0.5			0.70 (0.52–0.94)	0.01		
Heart rate, per + 1SD	1.30 (1.00–1.73)	0.04			0.98 (0.74–1.27)	0.9		
Estimated GFR ≤ 60 mL/min/1.73 m^2	3.56 (1.87–7.04)	< 0.0001	2.33 (1.03–5.46)	0.04	3.81 (1.67–10.9)	0.0006		
BNP, per + 1 SD	4.18 (2.45–7.68)	< 0.0001	3.32 (1.76–6.86)	< 0.0001	1.49 (1.22–1.75)	0.0003	1.18 (0.89–1.50)	0.2
LVEF ≤ 40%	2.36 (1.39–4.07)	0.001			2.22 (1.28–3.98)	0.003	1.93 (1.04–3.70)	0.03
Moderate to severe MR	1.82 (1.04–3.22)	0.03			1.95 (1.15–3.29)	0.01		
Moderate to severe TR	3.59 (1.95–6.85)	< 0.0001	4.09 (1.89–9.28)	0.0003	2.28 (1.35–3.85)	0.002	2.22 (1.28–3.88)	0.004

OR was evaluated by logistic regression analysis for association with NYHA III/IV, and HR was evaluated by Cox-proportion hazard analysis for prediction of composite events. Covariates into multivariate analyses were selected using a backward stepwise method

NYHA New York Heart Association class, *OR* odds ratio, *HR* hazard ratio, *PVCI* portal vein congestion index, *SD* standard deviation, *aCWT* average colon wall thickness, *GFR* glomerular filtration rate, *BNP* B-type natriuretic peptide, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *TR* tricuspid regurgitation

Association between hemodynamic and morphological parameters in the intestine

There was no significant difference in the hemodynamic parameters of SMA/IMA between the high-aCWT group and the low-aCWT group (all $p \geq 0.05$). Conversely, PVCSA (0.71 ± 0.20 vs 0.61 ± 0.28 cm^2, $p < 0.0001$) and PVCI (0.039 ± 0.030 vs 0.030 ± 0.017 cm s, $p = 0.004$) were higher in the high-aCWT group than those in the low-aCWT group. As continuous variables, PVCSA (correlation coefficient 0.265, $p < 0.0001$) and PVCI (correlation coefficient 0.166, $p = 0.01$) had weakly positive correlations with aCWT, whereas other intestinal parameters had no significant correlations with aCWT (all $p \geq 0.05$).

Patients with ascites [$n = 34$ (15%)] had higher PVCI values than those of patients without [$n = 190$ (85%)] (0.045 ± 0.042 vs 0.032 ± 0.018 cm s, $p = 0.002$), whereas there was no significant difference in aCWT between the patients with ascites and those without (2.8 ± 0.9 vs 2.6 ± 0.7 mm, $p = 0.1$).

Association with laboratory parameters

Blood sampling laboratory parameters for association with PVCI or aCWT are presented in Table 4. B-type natriuretic peptide (BNP) and total bilirubin were higher in the high-PVCI group than those in the low-PVCI group. Conversely, high-sensitive C-reactive protein (hs-CRP) was higher; serum albumin was lower in the high-aCWT group than those in the low-aCWT group.

Association with echocardiographic parameters

Echocardiographic parameters for association with PVCI or aCWT are presented in Table 4. The high-PVCI group had higher left ventricular end-diastolic dimension (LVEDD), lower left ventricular ejection fraction (LVEF), lower tricuspid annual plane systolic excursion (TAPSE), higher ratio of mitral *E*/average *E*′, and higher inferior vena cava (IVC) dimension than those of the low-PVCI group. Conversely, the high-aCWT group had higher right ventricular end-diastolic

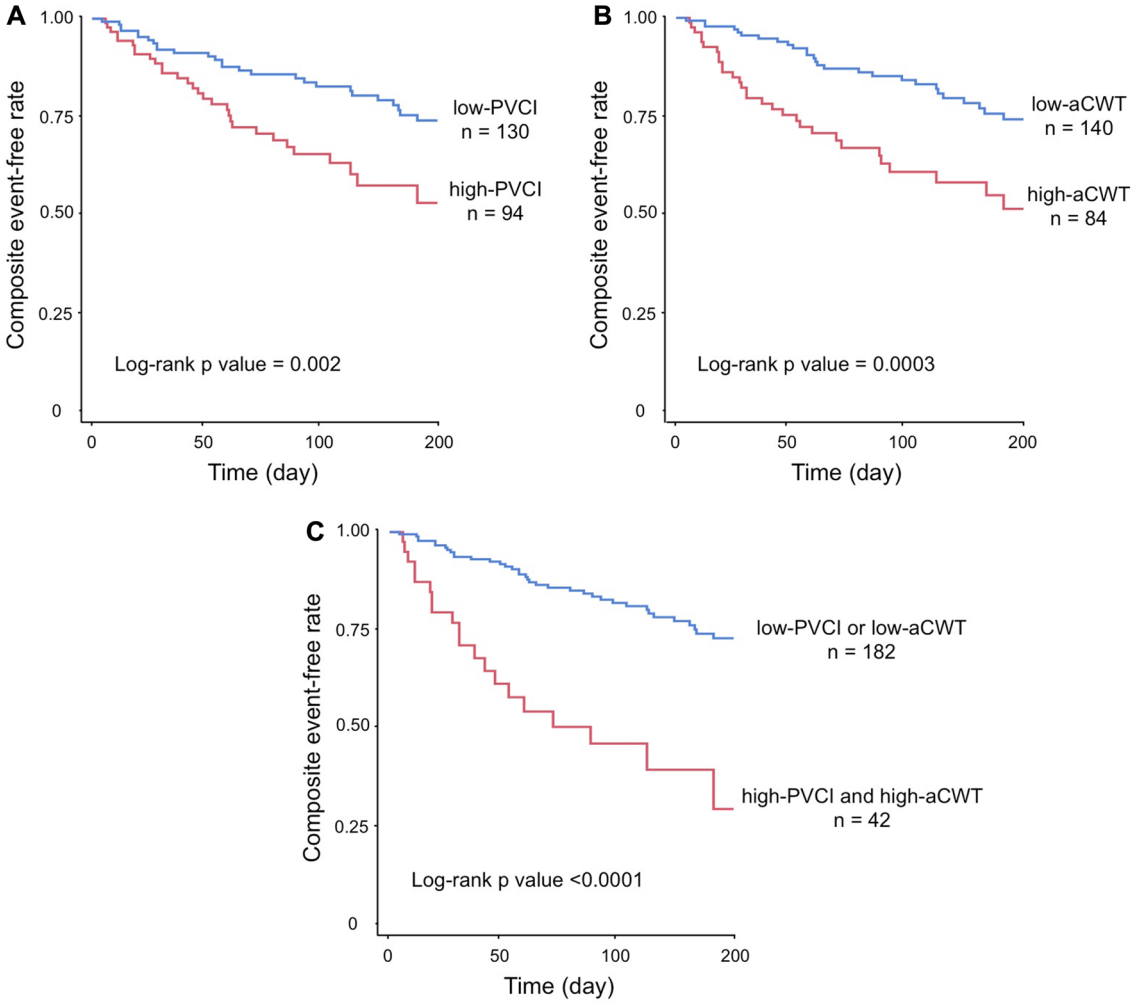

Fig. 2 Composite event-free rates stratified by the cutoff values of PVCI (**a**), aCWT (**b**), and their combination (**c**). The continuous variable PVCI was divided into groups of values ≤ 0.031 (low-PVCI) and > 0.031 cm s (high-PVCI), and aCWT was divided into ≤ 2.8 (low-aCWT) and > 2.8 mm (high-aCWT). *PVCI* portal vein congestion index, *aCWT* average colon wall thickness

dimension (RVEDD) and lower TAPSE than those of the low-aCWT group.

The LV and RV function were compared between subgroups by combined PVCI and aCWT stratification (Fig. 4), and their characteristics at enrollment are presented in Table 1. There was no significant difference in the LV systolic performances (LVEDD and LVEF) between the (high-PVCI and high-aCWT) group and the (low-PVCI or low-aCWT) group. Conversely, the (high-PVCI and high-aCWT) group had lower RV systolic performances (higher RVEDD and lower TAPSE) than those of the (low-PVCI or low-aCWT) group.

Discussion

Major findings

There were two major findings of this study: portal congestion, depicted by high PVCI, and intestinal edema, depicted by high aCWT, were independently associated with severe HF symptoms and poor midterm outcomes in hospitalized HF patients; portal congestion and intestinal edema were associated with advanced RV dysfunction.

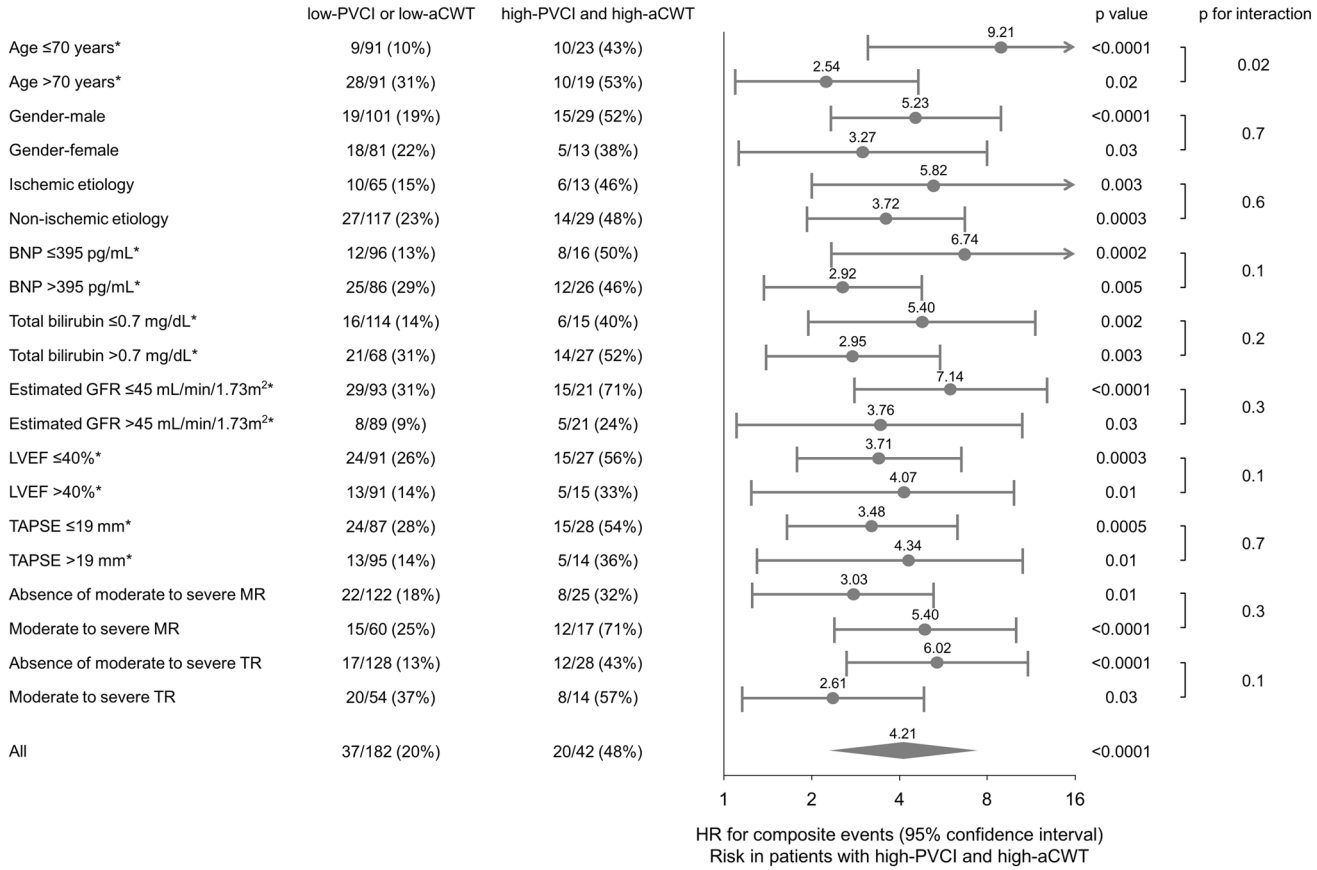

Fig. 3 Unadjusted HR for composite events of the high-PVCI and high-aCWT group among clinical subgroups. The continuous variable PVCI was divided into groups of values ≤ 0.031 (low-PVCI) and > 0.031 cm s (high-PVCI), and aCWT was divided into ≤ 2.8 (low-aCWT) and > 2.8 mm (high-aCWT). *PVCI* portal vein congestion index, *aCWT* average colon wall thickness, *BNP* B-type natriuretic peptide, *GFR* glomerular filtration rate, *LVEF* left ventricular ejection fraction, *TAPSE* tricuspid annual plane systolic excursion, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *HR* hazard ratio. Asterisk, continuous variables were divided depending on the median of each variable

Portal congestion in HF

The hemodynamic relationship between PV flow parameters and right-sided pressures in patients with HF has been reported [20, 22, 23]. Our results showed that higher PVCI was associated with higher BNP and total bilirubin among laboratory parameters. It was also associated with lower LV performance, lower TAPSE, and higher IVC dimension among echocardiographic parameters. Patients with ascites had higher PVCI than patients without ascites. These results showed that higher PVCI was associated with advanced LV and concomitant RV dysfunction with increased right atrial pressure. Elevated right-sided pressure anatomically causes portal and intestinal congestion subsequent to liver congestion. Higher PVCI may be indicated by higher portal congestion following elevation in right-sided pressure. Elevated right-sided pressure also leads to concomitant renal congestion, which is related to kidney injury in patients with acute and chronic HF [2, 6]. However, we found no significant association between PVCI and estimated glomerular filtration rate.

Our results further revealed that higher PVCI was associated with higher composite event rate, which was consistent with a previous finding that elevated right-sided pressure was associated with poorer HF outcomes [24]. Decongestion in acute HF is important in clinical settings involving HF treatment [4]. Approximately half of hospitalized patients with HF are resistant to decongestive treatments [25]; residual signs and symptoms are independent determinants of poorer prognosis in chronic HF [26]. An optimal strategy for decongestion may help reduce the occurrence of adverse events in acute decompensated patients with HF with higher PVCI.

Intestinal edema in HF

Increased CWT as a morphological manifestation of intestinal edema has been shown in a recent report [27].

Table 4 Association with portal vein congestion index and average colon wall thickness among laboratory/echocardiographic parameters

Variables	PVCI group				aCWT group			
	Low-PVCI ($n = 130$)	High-PVCI ($n = 94$)	p value	Unadjusted OR, per + 1 SD (95% confidence interval)	Low-aCWT ($n = 140$)	High-aCWT ($n = 84$)	p value	Unadjusted OR, per + 1 SD (95% confidence interval)
Laboratory parameters								
BNP (pg/mL)	528 ± 713	754 ± 854	0.0005	1.36 (1.02–1.90)*	579 ± 697	696 ± 904	0.4	1.15 (0.88–1.53)
hs-CRP (mg/dL)	0.60 ± 0.92	0.93 ± 1.60	0.1	1.31 (0.99–1.80)	0.52 ± 0.82	1.13 ± 1.71	0.0006	1.74 (1.26–2.54)‡
Albumin (g/dL)	3.5 ± 0.6	3.3 ± 0.5	0.1	0.82 (0.62–1.08)	3.5 ± 0.5	3.3 ± 0.6	0.02	0.74 (0.55–0.97)*
Total bilirubin (mg/dL)	0.74 ± 0.50	0.87 ± 0.49	0.01	1.29 (1.01–1.71)*	0.79 ± 0.52	0.81 ± 0.47	0.4	1.02 (0.77–1.33)
Estimated GFR (mL/min/1.73 m^2)	46 ± 20	44 ± 20	0.5	0.92 (0.70–1.21)	45 ± 21	46 ± 20	0.8	1.02 (0.77–1.35)
Echocardiographic parameters								
LVEDD (mm)	55 ± 11	59 ± 15	0.01	1.37 (1.05–1.82)*	57 ± 13	56 ± 13	0.6	0.93 (0.70–1.22)
LVEF (%)	43 ± 17	35 ± 17	0.0004	0.61 (0.46–0.81)‡	39 ± 17	42 ± 18	0.1	1.21 (0.92–1.59)
RVEDD (mm)	34 ± 8	36 ± 9	0.06	1.28 (0.98–1.68)	33 ± 9	37 ± 8	0.001	1.40 (1.07–1.86)*
TAPSE (mm)	19 ± 5	17 ± 5	0.002	0.67 (0.51–0.88)†	19 ± 5	17 ± 5	0.004	0.70 (0.53–0.92)*
SV (mL)	49 ± 20	47 ± 29	0.1	0.91 (0.68–1.19)	50 ± 26	47 ± 19	0.5	0.87 (0.63–1.15)
E/E′	17 ± 8	21 ± 12	0.002	1.55 (1.16–2.12)†	18 ± 9	19 ± 11	0.7	1.07 (0.81–1.40)
IVC dimension (mm)	16 ± 5	19 ± 6	0.001	1.65 (1.25–2.23)‡	17 ± 6	18 ± 6	0.1	1.19 (0.91–1.56)
MR-EROA (cm^2)	0.20 ± 0.24	0.22 ± 0.30	0.5	1.10 (0.84–1.45)	0.19 ± 0.24	0.22 ± 0.30	0.5	1.10 (0.84–1.44)
TR-EROA (cm^2)	0.32 ± 0.63	0.45 ± 1.38	0.1	1.14 (0.86–1.65)	0.30 ± 0.55	0.50 ± 1.49	0.3	1.26 (0.93–1.92)
LVEDD (mm)	55 ± 11	59 ± 15	0.01	1.37 (1.05–1.82)*	57 ± 13	56 ± 13	0.6	0.93 (0.70–1.22)

The continuous variable PVCI was divided into groups of values ≤ 0.031 (low-PVCI) and > 0.031 cm·s (high-PVCI), and aCWT was divided into ≤ 2.8 (low-aCWT) and > 2.8 mm (high-aCWT)

PVCI portal vein congestion index, *OR* odds ratio, *SD* standard deviation, *aCWT* average colon wall thickness, *BNP* B-type natriuretic peptide, *hs-CRP* high sensitive C-type reactive protein, *GFR* glomerular filtration rate, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *RVEDD* right ventricular end-diastolic dimension, *TAPSE* tricuspid annual plane systolic excursion, *SV* stroke volume, *E/E′* ratio of mitral *E*/average *E*′, *IVC* inferior vena cava, *MR* mitral regurgitation, *EROA* effective regurgitant orifice area, *TR* tricuspid regurgitation

*$p < 0.05$ by logistic regression analysis

†$p < 0.01$ by logistic regression analysis

‡$p < 0.001$ by logistic regression analysis

The effect of increased CWT on prognosis of patients with acute decompensated HF was demonstrated in our previous retrospective study using computed tomographic imaging [28]. Although intestinal edema may be a pathophysiology through hypoperfusion or systemic congestion in lower cardiac performance, the relationship between hemodynamic parameters of SMA/IMA/PV and morphological changes in the colonic wall remain unclear. A higher aCWT was associated with a higher PVCSA and PVCI, whereas it had no association with parameters in SMA/IMA. Our results suggested that intestinal edema is partially caused by intestinal congestion accompanied by portal congestion. Our results further showed higher composite event rates in patients with higher aCWT. Intestinal edema is associated with malabsorption [10] and dyschezia [29], and then causes cardiac cachexia [30], drug resistance for HF treatments [31], and advanced gastro-intestinal symptoms, which has led to poorer quality of life and outcomes in patients with HF. Our results showed that higher aCWT was associated with higher hs-CRP and lower serum albumin among laboratory parameters. Higher aCWT was also associated with dilated RVEDD and lower TAPSE among echocardiographic parameters. These findings are consistent with the results of a recent report on the associations among cachexia, right heart dysfunction, and intestinal edema

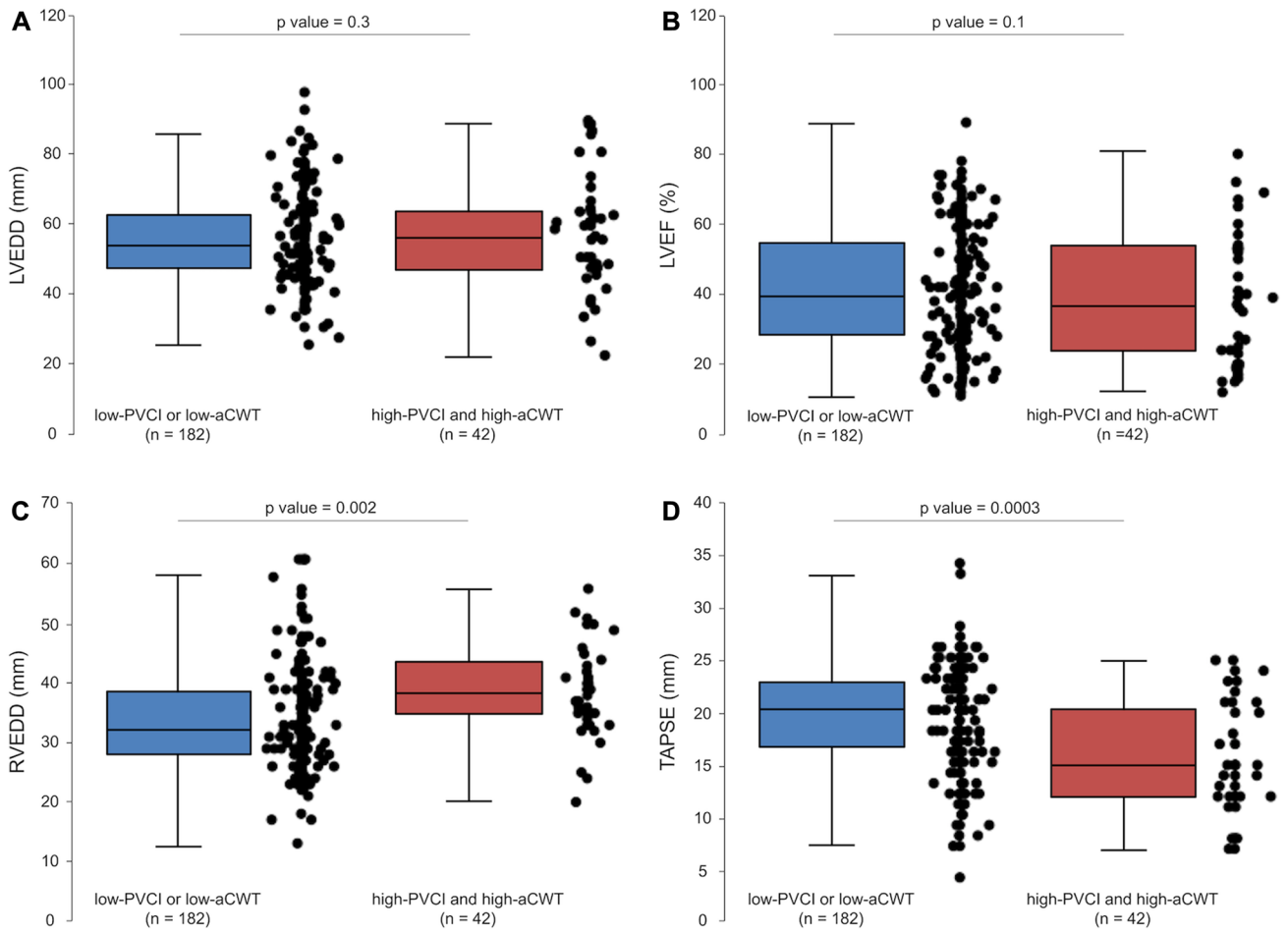

Fig. 4 Comparison of left and right ventricular function between groups by combined stratification using PVCI and aCWT. The continuous variable PVCI was divided into groups of values ≤ 0.031 (low-PVCI) and > 0.031 cm s (high-PVCI), and aCWT was divided into ≤ 2.8 (low-aCWT) and > 2.8 mm (high-aCWT). These combinations were used to stratify the left and right ventricular functions [LVEDD (**a**), LVEF (**b**), RVEDD (**c**), and TAPSE (**d**)]. *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *RVEDD* right ventricular end-diastolic dimension, *TAPSE* tricuspid annual plane systolic excursion, *PVCI* portal vein congestion index, *aCWT* average colon wall thickness

[8]. Intestinal edema may be related to numerous factors, including increased hydrostatic pressure due to hemodynamic load under HF condition and increased vascular osmotic pressure due to systemic chronic inflammation.

Intestine, host immune, and right-sided HF

The colon wall acts as a barrier against intestinal bacteria that has the potential for immunogenic activation when bacteria enter the host systemic circulation. Hemodynamic disturbances may disrupt mucosal intestinal bacteria and the in-host immune system in patients with HF [32]. Recently, higher metabolite levels generated by intestinal microbiota were predictive of higher incidence and poorer prognosis of cardiovascular disease [33] and higher mortality risks in patients with HF [34, 35]. There has been an increasing focus on the potential mechanisms underlying the contribution of intestinal microbiota and other intestinal functions on HF progression. Systemic inflammation via bacterial dysbiosis in gut flora [11] would accelerate the vicious cycle that leads to poor HF prognosis. Cardiac cachexia [36] and LV/RV remodeling [37–39] effect prognosis via systemic inflammation. Portal congestion and intestinal edema may create this vicious cycle that leads to poor prognosis via activation of systemic inflammation induced by bacterial dysbiosis in gut flora, through interactions among the intestine, in-host immune system, and right-sided HF. We found that patients with higher PVCI and aCWT had a strong association with poorer clinical outcomes in every subgroup. It implies that intestinal disrupted conditions may have a complementary role in poor clinical outcomes independent of patients' demographics, concomitant other organ failures, or

LV/RV function. However, the question of whether an intestine–heart interaction in patients with HF could be a novel therapeutic target or is simply the result of hemodynamic changes remains unclear. Further investigation is needed to answer this question.

Limitations

This study had some limitations. Because the study involved a small number of patients at a single center, the possibility of some selection bias could not be excluded. Further investigations to validate our results are needed. Although we strictly excluded cases with active gastrointestinal diseases that would affect CWT, the possibility of some interminglement could not be excluded. We enrolled patients with acute decompensated HF. Clinical parameters were obtained under stable conditions as close to discharge, but the HF conditions in the current cohort were not uniform. Thus, our results cannot be applied to all patients with chronic HF. Although we evaluated right-sided cardiac function in only RVEDD, TAPSE, and IVC dimension, more detailed right-sided cardiac parameters should be evaluated in future investigation to evaluate relationships between abdominal condition and right-sided HF. Despite these limitations, our findings suggest associations among hemodynamic/morphological conditions in the intestine, in-host immune activation, cardiac remodeling, and prognosis in patients with acute decompensated HF.

Conclusions

Increased portal congestion and intestinal edema were found to be associated with severe HF symptoms and poor outcomes in hospitalized HF patients, in addition to being associated with higher inflammatory laboratory markers and advanced right-sided cardiac dysfunction. Our findings suggest links among the intestine, in-host immune system, and right-sided HF.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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