Splenomegaly is a clinical condition that can be caused by various underlying conditions. While it is commonly associated with diseases such as liver cirrhosis, it can also be a sign of systemic inflammatory response syndrome (SIRS) and multiple organ failure syndrome (MOFS). In this study, we aimed to evaluate the relationship between splenic volume and the risk of readmission for heart failure among patients with acute decompensated heart failure.

Methods

Summary

The spleen is associated with inflammation, and the size of the spleen is affected by hemodynamic congestion and sympathetic stimulation. However, the association between splenic size and prognosis in patients with heart failure remains unknown. Between January 2015 and March 2017, we analyzed 125 patients with acute decompensated heart failure who were assessed by computed tomography (CT) on the day of admission. The spleen was measured by 3-dimensional CT and then the patients were assigned to groups according to their median splenic volume indexes (SpVi; splenic volume/body surface area). We then compared their baseline characteristics and rates of readmission for heart failure after one year. The median SpVi was 63.7 (interquartile range: 44.7-95.3) cm³/m². Age did not significantly differ between the groups. Patients with a high SpVi had more significantly enlarged left atria and left ventricles. Multiple regression analysis identified significant positive correlations between SpVi and posterior wall thickness as well as left ventricular mass index. Kaplan-Meier analysis revealed lower event-free rates in the patients with a high, than a low SpVi (P = 0.041, log-rank test). After adjustment for potential confounding factors, SpVi was independently associated with readmission for heart failure (Hazard ratio, 2.25; 95% confidence interval, 1.01-5.02; P = 0.047). In conclusion, increased splenic volume is independently associated with readmission for heart failure among patients with acute decompensated heart failure.
Figure 1. Study flow chart. We assigned 125 patients with acute decompensated heart failure to groups based on splenic volume index. ADHF indicates acute decompensated heart failure; and CT, computed tomography.
Characteristics of the patients: We assessed data from 125 patients. The reason for performing CT scan upon admission was as follows: examination of the lung fields \((n = 84)\), searching for focus of infection/inflammation \((n = 21)\), searching for the cause of chest pain \((n = 7)\), ruling out acute pulmonary embolism \((n = 4)\), examination of elevated liver enzymes \((n = 4)\), searching for the cause of anemia \((n = 2)\), searching for malignant tumors \((n = 2)\), and other reasons \((n = 1)\).

The median splenic volume determined using 3D-CT volumetry was 103 (IQR, 68-147; range, 20-449) cm\(^3\) and the mean splenic volume was 123 ± 80 cm\(^3\). The median SpVi was 63.7 (IQR, 44.7-95.3; range, 13.6-231.1) cm\(^3\)/m\(^2\). Figure 3 shows the distribution of splenic volume and SpVi. Patients were assigned to groups according to whether they had a low or a high SpVi (< 63.7 cm\(^3\)/m\(^2\), \(n = 62\) and ≥ 63.7 cm\(^3\)/m\(^2\), \(n = 63\), respectively). Table I shows the demographic and clinical parameters of the patients. Age did not significantly differ between the 2 groups. The group with a high SpVi had more males and prior history of cardiac surgery than the low SpVi group. Laboratory data showed that values for potassium and B-type natriuretic peptide were lower for the group with a high, than a low SpVi. Complete blood counts including monocytes did not significantly differ between the groups. Echocardiographic parameters associated increased left atrial diameter, PWT, LVEDD and LVMI with a high SpVi, although left ventricular ejection fraction did not significantly differ between the groups. Medication with loop diuretics and mineralocorticoid receptor antagonists was more prevalent among the group with a high SpVi.

Comparison of calculated and CT-generated splenic volumes: The median splenic volumes calculated using the Prassopoulos and prolate ellipsoid formulae were 133 (IQR, 97-175) and 162 (IQR, 103-239) cm\(^3\), respectively. Both of these values closely correlated with the splenic

Results

Characteristics of the patients: We assessed data from

New York Heart Association classification, systolic blood pressure, creatinine, hemoglobin, and B-type natriuretic peptide were entered into a multivariate analysis because these variables can be associated with the risk of clinical events in patients with heart failure. Values with \(P < 0.05\) were considered statistically significant. All data were analyzed using JMP ver. 13.1.0 (SAS Institute, Cary, NC, USA).
### Table 1. Baseline Clinical Characteristics

| Clinical demographics | Small splenic volume index | Large splenic volume index | P value |
|------------------------|-----------------------------|----------------------------|---------|
| Age, years             | 76 (73–83)                  | 77 (68–82)                 | 0.36    |
| Male, n (%)            | 30 (48)                     | 43 (68)                    | 0.024   |
| Height, cm             | 157.5 ± 8.4                 | 161.0 ± 10.8               | 0.049   |
| Body weight, kg        | 54.9 (47.4–64.2)            | 61.6 (52.9–73.4)           | 0.003   |
| Body mass index, kg/m² | 22.0 (19.6–24.9)            | 24.7 (21.2–27.3)           | 0.023   |
| Hypertension, n (%)    | 50 (81)                     | 55 (87)                    | 0.31    |
| Dyslipidemia, n (%)    | 37 (60)                     | 39 (62)                    | 0.80    |
| Diabetes mellitus, n (%) | 24 (39)                 | 21 (33)                    | 0.53    |
| Smoking: never/past/current, n | 34/23/5       | 27/30/5                    | 0.42    |
| Prior history of heart failure, n (%) | 33 (53)             | 42 (68)                    | 0.098   |
| Coronary revascularization, n (%) | 13 (21)             | 25 (40)                    | 0.019   |
| Prior cardiac surgery, n (%) | 10 (16)              | 21 (34)                    | 0.023   |
| Systolic blood pressure, mmHg | 132 ± 26                 | 136 ± 31                   | 0.48    |
| Diastolic blood pressure, mmHg | 79 ± 16                   | 80 ± 20                    | 0.81    |
| Heart rate, beats/minute | 88 (73–104)            | 84 (70–100)                | 0.25    |
| NYHA classification II/III/IV, n | 2/25/35               | 2/24/37                    | 0.97    |
| Atrial fibrillation, n (%) | 27 (44)                   | 33 (52)                    | 0.32    |

### Laboratory data

| Parameter | Small splenic volume index | Large splenic volume index | P value |
|-----------|-----------------------------|----------------------------|---------|
| Albumin, g/dL | 3.5 (3.2–3.8)          | 3.6 (3.2–4.0)              | 0.12    |
| Estimated GFR, mL/minute/1.73 m² | 43 (30–57)        | 44 (31–57)                 | 0.91    |
| Total bilirubin, mg/dL | 0.7 (0.5–1.1)      | 0.8 (0.5–1.2)              | 0.57    |
| Aspartate aminotransferase, U/L | 34 (26–51)       | 24 (20–33)                 | < 0.001 |
| Alanine aminotransferase, U/L | 24 (17–44)       | 16 (13–27)                 | 0.005   |
| LDH, U/L | 267 (215–336)               | 255 (208–316)              | 0.41    |
| Gamma-glutamyl transferase, U/L | 48 (24–84)       | 46 (30–85)                 | 0.66    |
| Alkaline phosphatase, U/L | 278 (219–344)     | 251 (196–340)              | 0.35    |
| Sodium, mEq/L | 140 (137–142)       | 141 (139–143)              | 0.034   |
| Potassium, mEq/L | 4.4 (3.9–4.9)    | 4.1 (3.5–4.4)              | 0.008   |
| Chloride, mEq/L | 104 (101–107)      | 104 (100–107)              | 0.95    |
| Iron, μg/dL | 41 (28–66)             | 45 (26–83)                 | 0.58    |
| C-reactive protein, mg/dL | 0.65 (0.17–3.17)  | 0.51 (0.15–1.88)           | 0.52    |
| White blood cells, 10³/μL | 8.25 (5.91–10.36) | 6.37 (5.58–8.97)           | 0.066   |
| Monocytes, μL/L | 407 (295–571)      | 392 (308–508)              | 0.49    |
| Red blood cells, 10¹²/μL | 3.81 ± 0.69        | 3.80 ± 0.78                | 0.88    |
| Hemoglobin, g/dL | 11.9 ± 2.3           | 11.5 ± 2.2                 | 0.34    |
| Platelet count, 10⁹/μL | 190 (134–256)     | 168 (134–219)              | 0.31    |
| B-type natriuretic peptide, pg/mL | 623 (366–1372) | 453 (262–715)              | 0.015   |

### Echocardiographic parameters

| Parameter | Small splenic volume index | Large splenic volume index | P value |
|-----------|-----------------------------|----------------------------|---------|
| Left atrial diameter, mm | 46.8 ± 8.1           | 52.4 ± 9.2                 | < 0.001 |
| IVST, mm | 9.6 ± 2.2                    | 10.1 ± 2.0                 | 0.20    |
| PWT, mm | 9 (8–11)                     | 10 (9–11)                  | 0.027   |
| LVEDD, mm | 51 (44–56)                 | 56 (51–61)                 | < 0.001 |
| LVESD, mm | 39.3 ± 10.8                 | 44.4 ± 11.4                | 0.013   |
| LVMI, g/m² | 105 (89–128)               | 130 (111–165)              | < 0.001 |
| LVEF, % | 48.5 ± 15.0                  | 45.8 ± 15.8                | 0.34    |
| IVC at expiration, cm | 1.8 ± 0.5             | 2.0 ± 0.6                  | 0.018   |
| TR-PG, mmHg | 33 (24–45)                | 35 (25–47)                 | 0.36    |
| E/A | 1.33 (0.76–2.10)            | 1.15 (0.76–2.51)           | 0.71    |
| E/e’ | 12.5 (10.8–16.2)            | 12.6 (8.7–17.8)            | 0.76    |

### Medication at admission

| Parameter | Small splenic volume index | Large splenic volume index | P value |
|-----------|-----------------------------|----------------------------|---------|
| ACE-I, n (%) | 3 (5)                      | 7 (11)                     | 0.19    |
| ARB, n (%) | 23 (37)                     | 29 (46)                    | 0.31    |
| β-blockers, n (%) | 30 (48)                 | 38 (60)                    | 0.18    |
| Loop diuretics, n (%) | 30 (48)                  | 48 (76)                    | 0.001   |
| MRA, n (%) | 11 (17)                     | 27 (43)                    | 0.002   |
| Tolvaptan, n (%) | 3 (5)                     | 9 (14)                     | 0.073   |

ACE-I indicates angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; E, early diastolic filling velocity; e’, early diastolic mitral annular velocity; IVC, inferior vena cava; IVST, interventricular septum thickness; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; MRA, mineralocorticoid receptor antagonists; PWT, posterior wall thickness; and TR-PG, tricuspid regurgitation pressure gradient.
Figure 4. Kaplan-Meier analysis of readmission for heart failure. High splenic volume index is associated with low event-free rates ($P = 0.041$, log-rank test).

Table II. Correlation and Multivariate Regression Analysis Between Splenic Volume Index and Patients’ Characteristics

|                  | SpVi, Correlation | SpVi, Multivariate Model 1 | SpVi, Multivariate Model 2 |
|------------------|-------------------|----------------------------|----------------------------|
|                  | Correlation       | $P$ value                  | $\beta$ | $t$ value | $P$ value | $\beta$ | $t$ value | $P$ value |
| Age              | -0.23             | 0.020                      | -0.060 | -0.52     | 0.61      | -0.15   | -1.36     | 0.18      |
| Height           | 0.15              | 0.15                       |        |           |           |         |           |           |
| Body weight      | 0.24              | 0.020                      |        |           |           |         |           |           |
| Systolic blood pressure | 0.028       | 0.79                       |        |           |           |         |           |           |
| Diastolic blood pressure | 0.017       | 0.87                       |        |           |           |         |           |           |
| Heart rate       | -0.015            | 0.88                       |        |           |           |         |           |           |
| Albumin          | -0.10             | 0.34                       |        |           |           |         |           |           |
| Total bilirubin  | -0.018            | 0.86                       |        |           |           |         |           |           |
| Aspartic aminotransferase | -0.16      | 0.12                       |        |           |           |         |           |           |
| Alanine aminotransferase | -0.21     | 0.040                      | -0.13  | -1.31     | 0.19      | -0.13   | -1.22     | 0.22      |
| LDH              | -0.14             | 0.17                       |        |           |           |         |           |           |
| Creatinine       | 0.048             | 0.65                       |        |           |           |         |           |           |
| Sodium           | 0.14              | 0.16                       |        |           |           |         |           |           |
| Potassium        | -0.31             | 0.002                      | -0.20  | -2.01     | 0.048     | -0.24   | -2.27     | 0.027     |
| Iron             | -0.028            | 0.81                       |        |           |           |         |           |           |
| C-reactive protein | -0.12            | 0.24                       |        |           |           |         |           |           |
| White blood cells | -0.16             | 0.12                       |        |           |           |         |           |           |
| Monocytes        | 0.089             | 0.39                       |        |           |           |         |           |           |
| Hemoglobin       | -0.13             | 0.21                       |        |           |           |         |           |           |
| Platelet count   | -0.110            | 0.29                       |        |           |           |         |           |           |
| B-type natriuretic peptide | -0.17       | 0.10                       |        |           |           |         |           |           |
| Left atrial diameter | 0.32             | 0.002                      | 0.24   | 2.48      | 0.015     | 0.22    | 2.08      | 0.041     |
| IVST             | 0.16              | 0.12                       |        |           |           |         |           |           |
| PWT              | 0.25              | 0.017                      | 0.23   | 2.22      | 0.029     |         |           |           |
| LVEDD            | 0.28              | 0.010                      | 0.11   | 0.95      | 0.35      |         |           |           |
| LVESD            | 0.12              | 0.24                       |        |           |           |         |           |           |
| LVEF             | 0.011             | 0.92                       |        |           |           |         |           |           |
| LVMI             | 0.32              | 0.005                      |        |           |           |         |           |           |
| TR-PG            | 0.050             | 0.64                       |        |           |           |         |           |           |
| IVC              | 0.15              | 0.16                       |        |           |           |         |           |           |
| E/A              | -0.12             | 0.45                       |        |           |           |         |           |           |
| E/e'             | 0.013             | 0.91                       |        |           |           |         |           |           |

A indicates atrial filling velocity; E, early diastolic filling velocity; e’, early diastolic mitral annular velocity; IVC, inferior vena cava; IVST, interventricular septum thickness; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; PWT, posterior wall thickness; and TR-PG, tricuspid regurgitation pressure gradient.

Univariate and multivariate analysis of correlations with SpVi: Table II shows the results of the correlation and multivariate analyses. Body weight and body mass index significantly and positively correlated with SpVi, although we adjusted splenic volume for BSA. White blood cells, hemoglobin, platelets and C-reactive protein values did not correlate with SpVi. The echocardiographic parameters of the diameters of the left atrium, PWT, LVEDD, and LVMI positively correlated with SpVi. Multiple regression analyses adjusted for variables with $P < 0.10$ in univariate analyses independently and significantly associated left atrial diameter, PWT and LVMI with SpVi. Endpoint: Forty-five patients were readmitted for heart failure within one year of follow-up. The primary endpoint was reached more frequently in the group with a high, than a low SpVi (44% versus 27%, $P = 0.047$). Kaplan-Meier analysis revealed a significantly lower volume determined by 3D-CT (Prassopoulos and prolate ellipsoid formulae: $r = 0.89$ and $r = 0.91$, respectively, $P < 0.001$ for both).

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event-free rate for the group with a high SpVi (Hazard ratio, 1.85; 95% confidence interval, 1.02–3.46, \( P = 0.041 \)) (Figure 4). Cox proportional hazards analyses after adjusting for potential cofounding factors selected SpVi as an independent prognostic factor for readmission due to heart failure (Table III).

**Discussion**

This study investigated associations between splenic volume measured by CT volumetry and cardiac functions or prognosis in patients with acute decompensated heart failure. We found that SpVi is independently associated with cardiac hypertrophy and that a large spleen is associated with readmission due to heart failure. Splenic volume has been assessed using various means including ultrasonography, magnetic resonance imaging and CT. Among these, all 3D-CT scans closely correlated with manual segmentation for splenic volume and the measurement requires approximately one minute.\(^{17,18}\) We determined splenic volume using 3D-CT volumetry within 3 minutes and the results closely correlated with the splenic volume estimated using standard formulae.

Kaneko, et al. described normal splenic volumes determined from CT images of 150\(^{19}\) and 238\(^{20}\) healthy Japanese donors for liver transplantation as 112 ± 40 (range, 32–209) and 123 ± 45 (range, 37–285) cm\(^3\), respectively. They found that splenic volume correlated negatively with age and positively with body mass or BSA.\(^{20}\) The mean splenic volume in the present study was 123 ± 80 (range, 20–449) cm\(^3\), which was similar to previous findings. However, the distribution differed and some of our patients had larger than normal spleens although they were older and had a smaller BSA than those previously described.\(^{19}\) This could account for differences in baseline characteristics such as comorbidities between the studies.

The size of the spleen in patients with acute heart failure is influenced by various factors, including activation of the sympathetic nervous system,\(^{21,22}\) hyperperfusion,\(^{20,21}\) and portal hypertension due to right heart failure.\(^{21}\) A study showed that spleen size assessed by ultrasound was larger in patients with heart failure than normal subjects.\(^{20}\) The same study revealed that spleen size was associated with right atrial pressure or right ventricular end-diastolic pressure. In the current study, the high SpVi group had a larger inferior vena cava and received diuretics more frequently than the low SpVi group. Moreover, the high SpVi group had a slightly higher prevalence of a history of heart failure. These findings suggested volume overload was associated with increased splenic volume. However, BNP was lower in the high SpVi group in our study. We believe this was because the high SpVi group had more men, higher body mass index and prevalence of a history of open-heart surgery. It is well known that being male,\(^{23}\) obesity,\(^{24,25}\) and a prior history of open-heart surgery\(^{26}\) are associated with low BNP. We speculate that increased splenic volume reflects venous congestion due to right heart failure, which might result in readmission for heart failure.

The subcapsular red pulp of the spleen stores monocytes\(^{27}\) that modulate inflammatory processes by producing inflammatory cytokines or chemokines,\(^{27}\) and thus might contribute to systemic inflammation in patients with heart failure.\(^{28,29}\) One clinical study has shown positive correlations between diastolic dysfunction and cardiac inflammation as well as fibrosis in patients with heart failure and preserved ejection fraction.\(^{28}\) Others have shown that monocytes play a role in cardiac remodeling after myocardial infarction.\(^{30,31}\) Inflammatory mediators including cytokines or chemokines released from monocytes and monocytes themselves cause inflammation and ventricular dilatation or the development of heart failure.\(^{30,31}\) Thus, the spleen appears to be closely associated with cardiac remodeling or diastolic function. The present study did not find a correlation between the numbers of monocytes upon admission and splenic volume. This was because the cells that initially respond to inflammation during the hyperacute phase are neutrophils, not monocytes.\(^{32}\) Cardiac remodeling can be caused by cardiac stress or injury such as volume overload and ischemia,\(^{33}\) resulting in worse clinical outcomes in patients with heart failure.\(^{30}\) In the current study, increased splenic volume was associated with greater prevalence of heart failure, coronary revascularization, and open-heart surgery. Furthermore, left atrial diameter, PWT, LVEDD, LVESD, and LVMI were significantly higher in high SpVi, and multiple regression analyses showed left atrial diameter, PWT, and LVMI were significantly associated with SpVi. These results may suggest that increased splenic volume reflects cardiac damage and progression of cardiac remodeling, leading to poor prognosis in patients with heart failure. In summary, increased splenic volume may reflect systemic congestion or progression of cardiac remodeling in acute heart failure; therefore, patients with an increased spleen size may need strict decongestion therapy, more renin-angiotensin-aldosterone system inhibitors, or careful follow-up. We think clinicians should take notice of the size of spleen in patients with heart failure.

This study has several limitations including those imposed by the retrospective design with respect to selection bias and the small cohort of patients. Some patients might have had systemic disorders that affected spleen size. We did not fully exclude patients with cancer or liver/spleen diseases. Thus, the possibility that extracardiac diseases

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**Table III. Cox Proportional Hazard Model of Heart Failure Readmission**

| Splenic volume index as categorical variable | Hazard ratio | 95% CI | \( P \) value |
|-----------------------------------------------|-------------|-------|--------------|
| Non-adjusted model                            | 1.85        | 1.02–3.46 | 0.041        |
| Adjusted model*                               | 2.25        | 1.01–5.02 | 0.047        |

*Adjusted for age, sex, a history of heart failure, prior coronary revascularization, a history of cardiac surgery, atrial fibrillation, NYHA classification, systolic blood pressure, creatinine, hemoglobin and log B-type natriuretic peptide.
influenced the prognosis cannot be ruled out. We did not evaluate sympathetic nerve system activation (such as 123I-metaiodobenzylguanidine or plasma norepinephrine) which can affect the size of the spleen. Because there is scant evidence about the association between splenic volume and heart failure, the current study is an exploratory study. Therefore, it was necessary to test the relationships between many variables and splenic volumes, which may lead to multiplicity. In addition, the relationships between echocardiographic parameters and splenic volumes were not strong in the current study; thus, there may be unknown factors which are more intimately associated with splenic volumes. Finally, we did not examine the size of the spleen in the “chronic phase”. Further studies are needed to evaluate the associations of the spleen with hemodynamics or prognosis in patients with heart failure.

Conclusion

Some patients with acute decompensated heart failure had larger than normal splenic volumes at the time of admission. Increased splenic volume might be associated with cardiac remodeling and it could serve as a prognostic factor for patients with acute decompensated heart failure.

Disclosure

Conflicts of interest: None declared.

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