Simple algorithm to narrow down the candidates to receive echocardiography in patients with chronic liver disease for suspected pulmonary hypertension

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Because patients who develop PoPH have a poor prognosis after diagnosis,12 early diagnosis and intervention have become a challenge in recent years. Generally, patients who have

Introduction

In recent years, the treatment of chronic hepatitis has made progress and, especially, hepatitis B and C have been well controlled by drug therapy. On the other hand, in the case of hepatitis C, for example, it is known that portal hypertension does not improve in cases of cirrhosis and portal hypertension, even if hepatitis C virus is eradicated.1–3 Progression of liver fibrosis and development of portal hypertension leads to various complications, such as ascites, hepatic encephalopathy, and gastroesophageal varices. Various examinations and treatments for these complications have been studied4,5 and the importance of complication control has been recognized. Rare but important complications are pulmonary circulatory abnormalities with poor prognosis such as hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH); HPS occurs in 5–30% of cirrhotic patients6 and PoPH in 1–2%.7,8
advanced pulmonary arterial hypertension complain of shortness of breath, irrespective of the etiology. However, the early stages of PoPH are not always symptomatic. What is unique in the differential diagnosis of PoPH is that the shortness of breath could also be caused by various common conditions related to chronic liver disease, such as anemia, hepatic pleural effusion, and ascites. Therefore, PoPH, a rare complication, is often overlooked in clinical practice. To promote early diagnosis, a simple and readily available method that triggers suspicion of PoPH is needed.

The definitive diagnosis of PoPH is usually made by measurement of mean pulmonary arterial pressure, pulmonary artery wedge pressure, and pulmonary vascular resistance by right heart catheterization. Alternatively, pulmonary arterial hypertension could be estimated noninvasively from the tricuspid regurgitant pressure gradient (TRPG), measured by echocardiography. In clinical practice, it is not realistic to perform invasive right heart catheterization, or even echocardiography, in all patients with chronic liver disease, limiting the wide range of screening.

From this background, we investigated a method that could be used in daily clinical practice to identify patients with possible PoPH. Using a high TRPG value as a surrogate endpoint, we established a simple algorithm to identify chronic liver disease patients with a high TRPG value, leading to the narrowing down of the candidates to receive echocardiography for suspected PoPH.

Methods

Patients. This was a prospective observational study involving 152 consecutive patients with chronic liver disease who gave consent to participate in this study at Musashino Red Cross Hospital between April 2019 and October 2020. The diagnosis of chronic liver disease was made by either liver biopsy or by imaging studies. Blood tests including brain natriuretic peptide (BNP) were measured and echocardiography was performed. The results of the endoscopy, computed tomography (CT), and magnetic resonance imaging that were performed as part of routine clinical practice were used as clinical information. Patients who have been diagnosed with obvious pulmonary or cardiac disease, those who had history of pulmonary or cardiac disease, and those with chronic kidney disease were excluded. The study was conducted in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the ethics committee of our institute.

Echocardiography. Transthoracic echocardiography and tissue Doppler echocardiography were performed with ACUSON SC2000 (Siemens Healthcare, Tokyo, Japan) and LISENDO 880 (FUJIFILM, Tokyo, Japan). TRPG is an index calculated with the Bernoulli equation from TRV (tricuspid regurgitation velocity) values, and its formula is as follows: TRPG (mmHg) = 4 × (TRV (m/sec)²). TRPG value correlates with the right ventricular systolic pressure and to the estimated pulmonary artery systolic pressure in the absence of obvious outflow tract stenosis. In practice, it is known from previous reports that a mean PAP of 25 mmHg is comparable to a TRPG of 36 mmHg. The European Society of Cardiology guidelines use TRV values in the practice of pulmonary hypertension, and TRPG ≥33.6 mmHg corresponds to TRV ≥2.9 m/s for possible intermediate pulmonary hypertension. Since this study was designed to narrow down the candidate of patients who might have PoPH, the cutoff value of TRPG was set at 30 mmHg for the surrogate endpoint of possible pulmonary artery hypertension.

Statistical analysis. Patient characteristics between those with TRPG ≤30 mmHg and > 30 mmHg were compared using the Mann–Whitney U test or Fisher’s exact test. A receiver operating characteristic curve analysis and the Youden index were used to determine an optimal threshold of serum markers for TRPG >30 mmHg. Factors with P < 0.05 on univariate analysis were selected for multivariable backward stepwise regression analysis. For the analysis of the correlation coefficient, Pearson’s correlation coefficient was used for data with normal distribution and Spearman’s correlation coefficient was used for data that did not have a normal distribution. Values of P < 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics. Clinical features are shown in Table 1. In this study, ascites was defined as CT-confirmed or preexisting and controlled with diuretics, hepatic encephalopathy as symptomatic or on medication, esophageal varices as F2 or worse, and portal vein thrombosis/tumor thrombosis as being present in the first branch, bilateral branches, or the main trunk of the portal vein. The percentages of patients with esophageal varices, ascites, or hepatic encephalopathy were 29.6%, 42.8%, and 31.6%, respectively. Patients with known cardiac disease at baseline were excluded from the study. However, cardiac disease was noted in several cases by performing echocardiography after

Table 1  Baseline characteristics

| Variable                                         | Patients, n = 152 |
|--------------------------------------------------|-------------------|
| Gender (male/female)                             | 79/73             |
| Age (years)                                      | 77                |
| Etiology (alcohol/HBV/HCV/AIH or PBC/NASH/others) | 33/13/57/15/21/13 |
| Esophageal varices                               | 45 (29.6%)        |
| Ascites                                          | 65 (42.8%)        |
| Hepatic encephalopathy                           | 48 (31.6%)        |
| Portal vein thrombosis/tumor thrombosis          | 15 (9.9%)         |
| Total bilirubin (mg/dL)                          | 0.9 (0.2–15.6)    |
| Serum albumin (g/dL)                            | 3.2 (1.6–4.8)     |
| Prothrombin time (%)                             | 78 (14–120)       |
| Platelet (×10^3/μL)                              | 11.8 (2.8–41.5)   |
| BNP (pg/mL)                                      | 82.9 (5–8996)     |
| Child–Pugh class (A/B/C)                         | 71/51/30          |
| Shortness of breath                              | 22 (14.5%)        |

AIH, autoimmune hepatitis; BNP, brain natriuretic peptide; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis.
entry to the study such as six cases of left heart failure, six cases of atrial fibrillation, one case of valvular disease, and one case of coronary artery disease.

Shortness of breath was present in 14.5% of the patients. Shortness of breath was declared by the patient or indicated by the healthcare worker with reference to the Medical Research

Table 2  Baseline characteristics of patients with TRPG ≤30 mmHg and >30 mmHg

| Variable                                      | TRPG ≤30 mmHg | TRPG >30 mmHg | P value |
|-----------------------------------------------|---------------|---------------|---------|
| Gender (male/female)                          | 66/58         | 13/15         | 0.56    |
| Age (years)                                   | 75            | 81            | 0.001   |
| Etiology (alcohol/HBV/HCV/AIH or PBC/NASH/others) | 29/12/10/14/11 | 4/1/5/6/3    | 0.30    |
| Esophageal varices                            | 38 (30.6%)    | 7 (25.0%)     | 0.65    |
| Ascites                                       | 49 (39.5%)    | 16 (57.1%)    | 0.10    |
| Hepatic encephalopathy                        | 39 (31.5%)    | 9 (32.1%)     | 1.00    |
| Portal vein thrombosis/tumor thrombosis       | 13 (10.5%)    | 2 (7.1%)      | 0.74    |
| Total bilirubin (mg/dL)                       | 0.9 (0.2–15.6)| 0.8 (0.3–3.4)| 0.45    |
| Serum albumin (g/dL)                          | 3.3 (1.7–4.8) | 2.9 (1.6–4.5)| 0.005   |
| Prothrombin activity (%)                      | 81 (27–120)   | 71 (14–120)   | 0.007   |
| Platelet (<10^5/μL)                           | 12.1 (2.9–41.5)| 11.4 (2.8–31.9)| 0.69 |
| BNP (pg/mL)                                   | 74.9 (5–8995.7)| 206.2 (54.2–1693.5)| <0.01 |
| Child–Pugh class (A/B/C)                      | 61/41/22      | 10/10/8       | 0.32    |
| Shortness of breath                           | 11 (8.9%)     | 11 (39.3%)    | <0.001  |

AIH, autoimmune hepatitis; BNP, brain natriuretic peptide; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; TRPG, tricuspid regurgitant pressure gradient.

Figure 1  Tricuspid regurgitant pressure gradient (TRPG) values in terms of background. Box plots of TRPG in terms of cirrhosis status (a), the presence of ascites, hepatic encephalopathy or esophageal varices (b), and the presence of shortness of breath (c). TRPG levels did not differ in terms of cirrhosis status, the presence of ascites, hepatic encephalopathy, or esophageal varices, while the TRPG was significantly high in patients with shortness of breath. TRPG, tricuspid regurgitant pressure gradient.
In this screening, Grade 2 (feeling short of breath when walking briskly on level ground or going up a gentle slope) or higher was defined as having shortness of breath. Regarding the relationship between ascites and anemia and shortness of breath, we thought that patients with ascites or low hemoglobin might have shortness of breath, but in fact, only 52% of the patients with shortness of breath had ascites, and the median hemoglobin was 11.2 g/dL in both group with and without shortness of breath with no significant difference.

**Characteristics of patients with high TRPG.** There were 28 (18%) cases with TRPG >30 mmHg. The baseline characteristics of the patients with TRPG ≤30 mmHg and >30 mmHg were compared (Table 2). In the univariate analysis, patients with TRPG >30 mmHg were older, had lower serum albumin levels and prothrombin activity, higher serum BNP levels, and a higher incidence of shortness of breath. Median of serum BNP level was significantly high in cirrhotic patients compared with non-cirrhotic patients (89.0 vs 60.2 pg/mL, *P = 0.03*). For shortness of breath, there was also a significant difference (18.5% vs 3%, *P = 0.03*).

| Variable            | HR   | 95% CI      | *P* value |
|---------------------|------|-------------|-----------|
| Shortness of breath | 7.43 | 2.35–23.50  | <0.001    |
| BNP >122 pg/mL      | 4.55 | 1.6–12.90   | 0.004     |
| Alb ≤3.2 g/dL       | 4.35 | 12.45–15.17 | 0.02      |

Variable: PT >78%, Alb >3.2 g/dL, BNP >122 pg/mL. Age >77 years, shortness of breath.

Alb, albumin; BNP, brain natriuretic peptide; PT, prothrombin time; TRPG, tricuspid regurgitant pressure gradient.

However, for TRPG, there was no significant difference (22 vs 22 mmHg, *P = 0.85*). Therefore, the presence of cirrhosis was associated with increased frequency of high serum BNP and shortness of breath, but not high TRPG. On the other hand, Child–Pugh class and symptoms such as ascites, hepatic encephalopathy, and esophageal varices were not associated with high TRPG levels (Fig. 1). By receiver operating curve analysis using the Youden index, the best cutoff values of age, serum albumin, prothrombin activity, and BNP for TRPG >30 mmHg were 77 years old, 3.2 g/dL, 78%, and 122 pg/mL, respectively. Using these variables in multivariate analysis, the presence of shortness of breath (OR: 7.43, 95% CI: 2.35–23.50, *P < 0.001*), serum BNP >122 pg/mL (OR: 4.55, 95% CI: 1.6–12.90, *P = 0.004*), and serum albumin ≤3.2 g/dL (OR: 4.35, 95% CI: 12.45–15.17, *P = 0.02*) were independent factors predictive of TRPG >30 mmHg (Table 3).

**Correlation between TRPG and serum BNP or albumin.** TRPG and serum BNP and albumin levels were plotted, and their correlation was examined (Fig. 2). Serum BNP levels showed a positive correlation with TRPG (*R = 0.409, *P < 0.001*), while albumin levels showed a marginal but significant negative correlation (*R = -0.157, *P = 0.031*). Using a cutoff value of serum BNP 122 pg/mL, determined by the Youden index, the sensitivity and specificity to identify patients with TRPG >30 mmHg were 71.4% and 71.0%, respectively. On the other hand, when another cutoff value of BNP >50 pg/mL was used, the sensitivity became 100% (Table 4). For serum albumin, we were not able to establish a cutoff that could enhance the sensitivity.

**Subgroup analysis.** Since the presence of ascites may be linked to the presence of shortness of breath or elevated BNP, we performed an analysis in a subgroup of 87 patients who did not have ascites. Even in this subgroup of patients, Alb ≤3.2 (g/dL) (OR: 6.17, *P = 0.005*), BNP > 122 pg/mL (OR: 6.17,
Shortness of breath (OR: 6.70, \(P = 0.009\)) and shortness of breath (OR: 6.70, \(P = 0.009\)) were predictive factors for TRPG >30 mmHg, respectively significant.

**Classification tree algorithm to stratify the probability of TRPG >30 mmHg.** We aimed to develop an algorithm to narrow down patients with TRPG high using statistically significant factors, referred to as classification and regression tree (CART) and validated. A combination of three independent factors predictive of TRPG >30 mmHg in multivariate analysis was used to build a classification tree. In this algorithm, shortness of breath was used as the first predictor of TRPG >30 mmHg, followed by serum BNP, and serum albumin (Fig. 3). The algorithm consisted of eight groups with variable probability of TRPG >30 mmHg, ranging from a group of high probability (positive predictive value [PPV] of 83%), three groups of intermediate probability (PPV of 25%, 29%, and 34%), and four groups of low probability (PPV of 0%) (Table 4). The group with the highest PPV comprised patients with shortness of breath and serum BNP >122 pg/mL. Twelve of the 152 patients (8%) fell into this group. The PPV of TRPG >30 mmHg was as high as 83%. Three groups with intermediate PPV were patients with shortness of breath and serum BNP

| Variables                | Number of patients | Sensitivity | Specificity | PPV  | NPV  |
|--------------------------|--------------------|-------------|-------------|------|------|
| Shortness of breath      | 23                 | 42.9%       | 91.1%       | 52.2%| 87.6%|
| BNP >122 pg/mL           | 55                 | 71.4%       | 71.0%       | 35.7%| 91.7%|
| BNP >50 pg/mL            | 105                | 100%        | 62.1%       | 29.7%| 100% |
| Albumin <3.2 g/dL        | 28                 | 28.2%       | 91.9%       | 78.6%| 52.4%|

**Algorithm**

- **High**
  - 12 patients (8%)
    - Shortness of breath and serum BNP >122 pg/mL
      - Sensitivity: 35.8%
      - Specificity: 98.4%
      - PPV: 83.3%
      - NPV: 87.1%

- **High or intermediate**
  - 72 patients (47%)
    - Sensitivity: 100%
    - Specificity: 62.1%
    - PPV: 38.9%
    - NPV: 100%

- **Intermediate**
  - 50 patients (33%)
    - Sensitivity: 71.4%
    - Specificity: 71.0%
    - PPV: 35.7%
    - NPV: 91.7%

- **Low**
  - 18 patients (12%)
    - Sensitivity: 28.2%
    - Specificity: 91.9%
    - PPV: 29.7%
    - NPV: 78.6%

**Table 4** Accuracy to predict TRPG >30 mmHg by single variable and by algorithm

- **Variables**
  - Number of patients
  - Sensitivity
  - Specificity
  - PPV
  - NPV

- **Shortness of breath**
  - 23 patients (15%)
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    - NPV: 87.6%

- **BNP >122 pg/mL**
  - 55 patients (36%)
    - Sensitivity: 71.4%
    - Specificity: 71.0%
    - PPV: 35.7%
    - NPV: 91.7%

- **BNP >50 pg/mL**
  - 105 patients (69%)
    - Sensitivity: 100%
    - Specificity: 62.1%
    - PPV: 29.7%
    - NPV: 78.6%

- **Albumin <3.2 g/dL**
  - 28 patients (18%)
    - Sensitivity: 28.2%
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    - NPV: 52.4%

**Accuracy to predict TRPG >30 mmHg by single variable and by algorithm**

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    - NPV: 78.6%
Because the prognosis is poor, even in patients without shortness of breath, serum BNP >122 pg/mL, and serum albumin ≤3.2 g/dL (n = 29), and patients without shortness of breath, serum BNP 50–122 pg/mL, and serum albumin ≤3.2 g/dL (n = 24). A total of 60 patients (39%) fell into these groups. Finally, three groups of low probability were patients with shortness of breath but serum BNP <50 pg/mL (n = 4), patients without shortness of breath, and serum BNP <50 pg/mL (n = 43), patients without shortness of breath, serum BNP >122 pg/mL, and serum albumin >3.2 g/dL (n = 14), and patients without shortness of breath, serum BNP 50–122 pg/mL, and serum albumin >3.2 g/dL (n = 19). A total of 80 patients (53%) fell into these groups. Because the PPV of TRPG >30 mmHg was 0%, echocardiography was likely to be unnecessary.

Discussion

Early diagnosis of PoPH is extremely important because PoPH found at an advanced stage has a poor prognosis, even after therapeutic intervention. Because the prognosis is poor, even in Child–Pugh class A and B patients without symptoms of decompensation, we have to suspect PoPH, irrespective of the status of liver function. The initial symptom of PoPH is mild shortness of breath, a nonspecific symptom. For the diagnosis, invasive right heart catheterization or, alternatively, echocardiography should be performed. Actually, the previously published meta-analysis reported that in the diagnosis of PoPH, echocardiography is useful for screening but requires catheterization for diagnosis. For patients with high TRPG where pulmonary hypertension is suspected on echocardiography, RHC should be considered. However, in real-world clinical practice, it is not realistic to perform invasive right heart catheterization or even echocardiography in all patients with chronic liver disease, limiting the wide range of screening. Echocardiography should be performed in patients with cirrhosis before liver transplantation. On the other hand, the age of patients with cirrhosis in Japan is older compared with the Western countries, and therefore there are few opportunities to be the candidates for liver transplantation in these patients. Even in these cases, diagnosis of PoPH and adequate management may lead to prolonged survival. The purpose of this study is to build an algorithm to efficiently pick up cases in which echocardiography should be performed for the screening of PoPH among patients with chronic liver disease irrespective of the indication of liver transplantation. For patients with high TRPG where pulmonary hypertension is suspected on echocardiography, RHC should be considered.

In previous reports, macrophage migration inhibitory and bone morphogenetic protein 9 are excellent sensitive and specific biomarkers for PoPH. These novel biomarkers will be useful for future. These markers were not measured in the present study since the aim of this study was to enclose cases of suspected pulmonary hypertension based on existing biomarkers and symptoms used in daily practice. However, these novel biomarkers will be the subject for our future study. Therefore, we focused on readily available variables and established a simple algorithm using the presence of shortness of breath and serum BNP and albumin levels that could identify patients with high and low probabilities of PoPH. As far as we could find, there are only a few reports on the usefulness of BNP measurement in the diagnosis of PoPH, and this is the first report to focus on the combination of a symptom and serum BNP and albumin. According to our algorithm, we were able to narrow down the candidates to receive echocardiography by 53%. This algorithm is very simple and, thus, suitable for screening many patients in routine clinical practice, and there were no differences in factors predicting high TRPG levels depending on the presence or absence of ascites.

Because the aim of this study was to promote the wide range of screening for PoPH, TRPG >30 mmHg by echocardiography was set as the surrogate endpoint of possible pulmonary artery hypertension, which is comparable to mean PAP of 20 mmHg, based on a previous report that a mean PAP of 25 mmHg is comparable to a TRPG of 36 mmHg. Multivariate analysis showed that BNP >122 pg/mL was a significant predictive factor of high TRPG, independent of the symptom and serum albumin. Using this cutoff value, the sensitivity to identify patients with TRPG >30 mmHg was 71.4%. On the other hand, another cutoff value of 50 pg/mL was selected to emphasize sensitivity and reduce oversight. Using this cutoff value, the specificity decreased but the sensitivity became 100%; thus, all patients with BNP ≤50 pg/mL had low TRPG levels, making this cutoff valuable to identify patients with no risk of PoPH.

On the other hand, 69% of the patients in this study had a BNP >50 pg/mL, indicating that there are still too many cases that require echocardiography if serum BNP >50 pg/mL is used as a single criterion. Therefore, we focused on the combination of three independent predictors. Using the CART method, patients were stratified into eight groups. Of note, the serum albumin level with a cutoff value of 3.2 g/dL could identify patients with no risk of PoPH, among those who did not have shortness of breath and serum BNP >50 pg/mL. Finally, PPV for TRPG >30 mmHg was 0% in 80 of the 152 patients (53%). The PPV was 0% in patients with serum BNP <50 pg/mL, irrespective of shortness of breath. Among patients without shortness of breath and serum BNP 50–122 pg/mL, the PPV was 0% if serum albumin was >3.2 g/dL. Because screening for PoPH by echocardiography may not be necessary in these patients, this algorithm has reduced the number of patients needing echocardiography by 53%.

This algorithm also identified patients with high and intermediate probabilities of PoPH. In patients with shortness of breath, echocardiography is strongly recommended when the BNP is >122 pg/mL, because the PPV for TRPG >30 mmHg was as high as 83%. Twelve of the 152 patients (8%) fell into this group, and 2 were diagnosed by right heart catheterization as definite PoPH, which 3 did not undergo right heart catheterization but were highly suspected of PoPH, according to the clinical diagnosis of a cardiologist specialist. The remaining 60 patients (39%) fell into the intermediate probability groups.

In this study, we found TRPG >30 mmHg in 18% of patients, and among them, we were able to diagnose PoPH in two cases (1.3%) and five cases (3.3%) including suspected cases, which were not different from previous reports. We recognize that high TRPG value does not directly indicate the presence of PoPH, but could be hallmark of patients who need to proceed to RHC.

It should be noted that clinical diagnosis of non-cirrhosis in routine practice may overlook some cases of early cirrhosis with mild portal hypertension. Actually, previous study indicated that about 15.4% of patients diagnosed as pulmonary hypertension did not have clinically evident cirrhosis. Also, in the present study, there were no significant differences in TRPG
between patients with and without cirrhosis, both being 22 mmHg. This may suggest that some cases of cirrhosis are not diagnosed in the clinical setting. Taking into account this point, we did not exclude non-cirrhotic patients at entry and discussed how to pick up pulmonary hypertension in routine practice in chronic liver disease.

From a previous report, AIH and female are risk factors for PoPH.26 In the present study, the number of cases with a final diagnosis of PoPH was small, and it was not possible to examine the risk factors for PoPH including background liver disease or gender. However, TRPG tended to be significantly higher in female compared with male (21.0 vs 24.2 pg/mL, P = 0.03). Further study of risk factors for PoPH may be necessary with larger number of patients.

This study has several limitations. First, it was conducted at a single institution. Second, the patients selected for this study may have been subject to selection bias and may differ in nature from the population with chronic liver disease encountered in daily practice. Thus, the PPV may vary if applied to different cohorts of patients. Third, the validity of using TRPG 30 as a cutoff value. There are many patients with TRPG >30 mmHg but who did not undergo right cardiac catheterization. There are several reasons for this, including exacerbation of the liver disease or comorbidities and refusal to undergo an invasive test, mostly elderly patients. Since our study was designed to narrow down the candidate of patients who might have PoPH, the cutoff value of TRPG was set at 30 mmHg. However, there are no specific criteria of TRPG established for the diagnosis of PoPH, and there are no reports on the correlations between the data of right heart catheterization and TRPG by echocardiography in PoPH patients. Whether the general criteria for PAH apply to the hyperdynamic state of liver disease is a subject for future study, and further studies are necessary to confirm the validity of our findings. The utilization of other echocardiographic measurements such as size of right atrium, right ventricle, and pulmonary artery, or right ventricle dysfunction and the eccentricity index may lead to improved estimate of probability of PoPH, but these measurements were not collected and reviewed in the present study. We recognize that further study is necessary. Forth, while shortness of breath and serum BNP are useful in picking up a wide range of possible cases of PoPH, we recognize that the low specificity is an issue. Therefore, a group of patients with high probability of elevated TRPG should undergo a thorough examination to make a definitive diagnosis.

In conclusion, we developed a simple algorithm using the presence of shortness of breath and serum BNP and albumin levels that could identify patients with high and low probabilities of PoPH among those with chronic liver disease, leading to the narrowing down of the candidates to receive echocardiography. Because PoPH can occur in any patient, irrespective of liver function, and has a poor prognosis if untreated, we hope that our algorithm contributes to the wide range of screening leading to the early diagnosis.

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