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Elevated non-invasive liver fibrosis markers and risk of liver carcinoma in adult patients after repair of tetralogy of Fallot☆

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ABSTRACT

Background: Congestive hepatopathy and hepatocellular carcinoma is a serious complication after Fontan procedure. Liver fibrosis due to hepatic congestion could occur also in adult patients after repair of tetralogy of Fallot (rTOF). However, the incidence and severity remain unclear.
Methods: A total of 111 patients with adult congenital heart disease between 2009 and 2016 were enrolled. Liver fibrosis markers and hemodynamic parameters assessed by cardiac magnetic resonance imaging and catheterization were analyzed in 50 rTOF patients having significant pulmonary regurgitation and/or stenosis, 50 Fontan patients and 11 controls.
Results: Liver fibrosis markers in patients with rTOF were significantly higher than controls, and tended to be lower than Fontan patients (median, hyaluronic acid: 25.8 *vs.* 15.9 *vs.* 40.8, type IV collagen: 129 *vs.* 113 *vs.* 166, ng/mL, $p < 0.05$, respectively). Patients with rTOF showed abnormal hyaluronic acid levels more frequently than controls, and less frequently than Fontan patients (22% *vs.* 0% *vs.* 38%, respectively, $p < 0.05$). Multivariate analyses indicated a positive association of right atrial pressure with type IV-collagen or hyaluronic acid levels (each, $p < 0.001$, $p = 0.003$). Abdominal ultrasonography revealed hepatic congestion in 50% of rTOF patients tested. Liver biopsy of the two rTOF patients with highest hyaluronic acid levels showed pathological evidence of moderate and severe (F2 and F3) liver fibrosis and one had combined hepatocellular and cholangiocarcinoma.
Conclusions: We first demonstrated elevated liver fibrosis markers in adult patients with rTOF. These levels may help to predict the progressive liver disease as well as consider the timing of pulmonary valve replacement.

1. Introduction

Tetralogy of Fallot is the most common type of cyanotic congenital heart disease with an incidence of 3.5% of congenital heart diseases [1]. Improvements in the diagnosis, management and surgery have led to increased population of repaired Tetralogy of Fallot (rTOF) patients in adulthood. However, most of the patients have pulmonary regurgitation and/or stenosis (PR/PS) even after intracardiac repair, which cause pressure and volume overload to the right ventricle (RV) resulting in elevated right atrial (RA) pressure.

In patients after Fontan procedure, systemic venous pressure is persistently elevated. This elevated central venous pressure and reduced cardiac output result in hepatic fibrosis, and most of the patients after Fontan procedure show abnormal results of liver function tests. Hepatic fibrosis, cirrhosis and hepatocellular carcinoma may develop as a result of the high venous pressures. This complication is well known as Fontan-associated liver disease (FALD) [2,3]. Even in patients who have structurally normal heart, cardiohepatic interaction is an important concern especially in patients with heart failure [4]. Hepatic venous flow velocity is reported to decrease in patients with RV hypertension [5]. Chronic RV dysfunction and hepatic congestion may also develop over time in patients with rTOF. This condition may lead to liver fibrosis, and subsequent development of liver cirrhosis and hepatocellular carcinoma late after repair of TOF [6]. However, there is little information about the incidence and severity of liver fibrosis in patients with rTOF.

Circulating hyaluronic acid and type IV collagen are useful indicators for evaluation of liver fibrosis or cirrhosis, especially in viral hepatitis.

Abbreviations: rTOF, repaired tetralogy of Fallot; RV, right ventricular; RA, right atrial; FALD, Fontan-associated liver disease; CMR, cardiac magnetic resonance; LV, left ventricular; ALT, alanine aminotransferase.

☆ Each author listed on the manuscript takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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These levels reflect the severity of liver fibrosis and are utilized in non-invasive screening for the indication of liver biopsy [7,8]. There are several studies reporting elevated serum levels of hyaluronic acid and type IV collagen in patients after Fontan procedure [9]. However, clinical significance of these non-invasive biomarkers for the development of progressive liver disease in patients with rTOF remains elusive.

The present study aimed to elucidate the incidence and severity of liver fibrosis in patients with rTOF by evaluating these liver fibrosis markers, and also to investigate its association with hemodynamic risk factors assessed by magnetic resonance imaging (CMR) and cardiac catheterization parameters.

2. Methods

2.1. Patients

From the 168 patients with rTOF treated at the adult congenital heart disease clinic of Kyushu University Hospital between 2009 and 2016, 50 consecutive patients with rTOF were evaluated as possible candidates for pulmonary valve replacement due to significant pulmonary regurgitation/stenosis. This study included these 50 TOF patients with PR/PS, 50 age-matched patients with single ventricle after Fontan procedure, and 11 control subjects who had cardiac surgery but did not have right side heart sequelae. Patients who had other forms of liver diseases, such as viral hepatitis or alcoholic liver disease were excluded from the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in an approval by our institutional review board (29-605).

2.2. Data collection

We retrospectively reviewed the medical records of patients and investigated (i) liver fibrosis markers (hyaluronic acid and type IV collagen) and other liver function tests in all the subjects, (ii) hemodynamic parameters obtained from cardiac magnetic resonance (CMR) imaging and cardiac catheterization, (iii) abdominal ultrasonography and liver biopsy data in patients after repair of TOF, if available. The results of liver fibrosis markers and other liver function tests were compared among the groups of subjects. In patients with rTOF, we studied the association of hemodynamic risk factors with elevated liver fibrosis markers by univariate and multivariate analysis.

CMR studies were performed with 3-Tesla MR imaging (Achieva 3.0T or Ingenia 3.0T, Philips Healthcare, Best, The Netherlands). We measured RV and left ventricular (LV) volumes using a work-station (Extended Workspace; Philips Healthcare, Cleveland, OH, USA). CMR images were analyzed semi-automatically, followed by manual correction. RV volumes were measured based on axial images, as previously reported [10]. LV volumes were measured based on short-axis images. Papillary muscles, moderator bands and trabeculations were assigned to the intracavitary lumen of the ventricles. We utilized phase contrast velocity mapping to assess the pulmonary regurgitant fraction.

Right cardiac catheterization was performed *via* femoral or internal jugular vein approach employing a standard methodology. Abdominal ultrasonography was performed for patients with suspicion of hepatic congestion using Prosound SSD-α10 (Aloka Co. Ltd., Japan) with a standard manner.

2.3. Statistical analysis

Continuous variables were presented as median and range/interquartile range (IQR). Statistic comparison of continuous variables was performed using the Student's *t*-test or Mann-Whitney *U* test as appropriate. Categorical variables were analyzed using chi-square test or Fisher's exact test. Kruskal-Wallis test was used to compare the variables in the three groups. In patients with rTOF, univariate and multivariate linear regression analyses were performed to determine the hemodynamics predictors of elevated liver fibrosis markers. The correlations with hemodynamic predictors and liver fibrosis markers were analyzed with Spearman's rank-sum test. Two-tailed p values of <0.05 were considered significant. All statistical operations were performed by using the JMP 13 statistical software package (SAS Institute Inc., Cary, NC).

3. Results

3.1. Study population

The median age of TOF, Fontan, Control group were 26.1, 27.0, and 25.5 years old, respectively ($p = 0.927$). No sex or body surface areas differed between the three groups. The demographic information including the anatomical diagnosis, and the previous cardiac operations are summarized in Table 1. Among the 50 patients after repair of TOF, 39, 6, and 5 subjects had significant PR, PR + PS, and PS, respectively. Ten patients had moderate tricuspid regurgitation (TR), and three patients had severe TR. Two patients had history of heart failure. Nineteen patients had end-diastolic forward flow in the RV outflow tract on echocardiogram, which indicates the presence of restrictive RV physiology.

Table 1
Patient characteristics.

	TOF		Fontan		Control		p value[a]
	n = 50		n = 50		n = 11		
Age#, years	26.1, 21.4–40.7		27.0, 24.0–29.0		25.5, 23.9–30.5		0.927
Sex	M/F = 24/26		M/F = 25/25		M/F = 4/7		0.635
BSA#, m^2	1.53, 1.42–1.69		1.56, 1.36–1.72		1.47, 1.37–1.71		0.862
Anatomy	TOF	44	TA	17	TGA	5	
	TOF, PA	4	SRV	13	AS/AR	3	
	TOF, absent PV	2	DILV	5	MR	2	
			AVSD	4	VSD, ASD	1	
			PA, IVS	2			
			Others	9			
Operation	Transannular	33	Extracardiac TCPC	30	Jatene	5	
	Non-transannular	11	including TCPC conversion or fenestration	4 or 1	AVR, AVP	3	
	Rastelli	6	Lateral tunnel	17	MVR	2	
			APC	3	VSD, ASD closure	1	

Each value represents the median and interquartile ranges (IQR).
TOF, tetralogy of Fallot; BSA, body surface area; PA, pulmonary atresia; PV, pulmonary valve; TA, tricuspid atresia; SRV single right ventricle.
AVSD, atrioventricular septal defect; DILV, double inlet left ventricle; IVS, intact ventricular septum; TCPC, total cavopulmonary connection.
APC, atriopulmonary connection; TGA, transposition of the great arteries; AS, aortic stenosis; AR, aortic regurgitation; MR, mitral regurgitation.
VSD, ventricular septal defect; ASD, atrial septal defect; AVR, aortic valve replacement; AVP, aortic valve plasty; MVR, mitral valve replacement.
[a] Kruskal-Wallis test or chi-square test was used to analyze the differences among group medians.

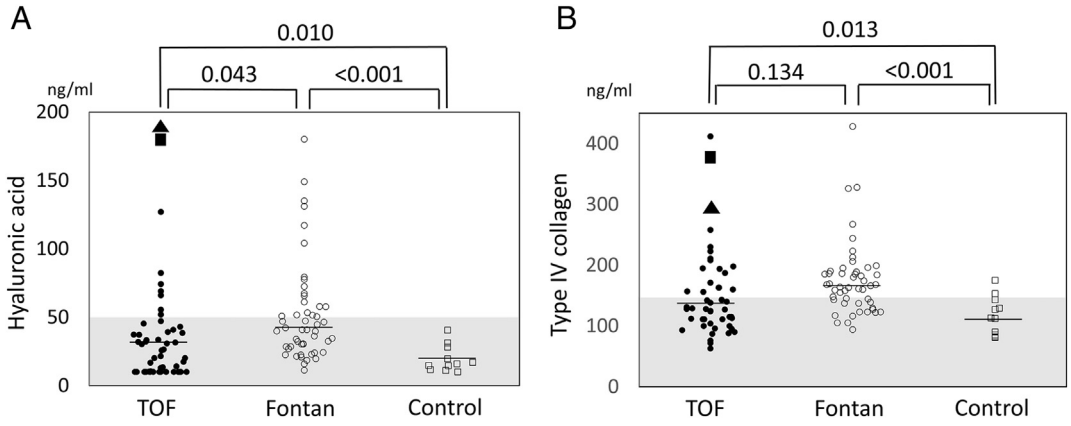

Fig. 1. Serum levels of hyaluronic acid (A) and type IV collagen (B) in TOF, Fontan and control groups. Each bar indicates the median value. Shaded areas represent values below the reference ranges (hyaluronic acid: <50 ng/mL, type IV collagen: <140 ng/mL). Square marker indicates the patient who had liver cancer and triangle marker indicates the patient who had pathological evidence of F2 liver fibrosis. The respective median and ranges (ng/mL) among the groups of TOF, Fontan, and control are hyaluronic acid: 25.8, 10.0–189.0 *vs.* 40.8, 11.2–180.0 *vs.* 15.9, 10.0–40.5, type IV collagen: 129, 63–412 *vs.* 166, 94–428 *vs.* 113, 81–175 ng/mL. TOF, tetralogy of Fallot.

3.2. Liver fibrosis markers and hemodynamic predictors

Hyaluronic acid levels in patients with rTOF were significantly higher than controls (median, 25.8 *vs.* 15.9 ng/mL, $p = 0.01$), and were lower than those after Fontan procedure (median, 25.8 *vs.* 40.8 ng/mL, $p = 0.043$, Fig. 1). Type IV-collagen levels in patients with rTOF were higher than controls (median, 129 *vs.* 113 ng/mL, $p = 0.013$), and tended to be lower than those after Fontan procedure (median, 129 *vs.*166, ng/mL, $p = 0.134$). Patients with rTOF showed abnormal hyaluronic acid levels more frequently than controls, and less frequently than those after Fontan procedure (22% *vs.* 0% *vs.* 38%, respectively, $p < 0.05$). Among the other laboratory data of biochemistry (Table 2), alanine transaminase, brain natriuretic peptide, total bilirubin and aspartate transaminase are significantly higher in patients with rTOF than the controls ($p = 0.001$, 0.016, 0.037, 0.045, respectively).

Median RV end-diastolic index by CMR was 155 mL/m^2 and median pulmonary regurgitant fraction was 45% in patients with rTOF. Median RA pressure measured by cardiac catheterization is 6 mm Hg in patients with rTOF and median central venous pressure was 10 mm Hg in patients after Fontan procedure. On univariate analysis in patients with rTOF, time after initial repair and RA pressure had significant association with hyaluronic acid ($p < 0.05$, respectively). RA pressure, RV end-diastolic pressure, RV-EF, RVESVi, time after initial repair, RVEDVi, and pulmonary regurgitant fraction had a significant association with elevated type IV collagen ($p < 0.05$, respectively). On multivariate analysis, only RA pressure had a significant association with hyaluronic acid ($\beta = 0.88$, $p = 0.002$). RA pressure and pulmonary regurgitant fraction had significant association with elevated type IV collagen ($\beta = 0.67$, $p = 0.003$; $\beta = 0.12$, $p = 0.018$, respectively, Supplementary Table 1).

Type IV-collagen levels in patients with rTOF with moderate or severe TR ($n = 13$) was higher than those with less than moderate TR ($n = 37$) (median, 197 *vs.* 125 ng/mL, $p = 0.005$). Other than that, there was no difference in type IV-collagen or hyaluronic acid levels among patients with PR, PR + PS, and PR, between patients with and without moderate or severe TR, between patients with and without restrictive RV physiology ($p > 0.05$, respectively).

The correlations between liver fibrosis markers and time after surgery and RA pressure in rTOF and Fontan patients are shown in Fig. 2. In patients with rTOF, hyaluronic acid levels positively correlated with time after repair ($r = 0.39$, $p = 0.005$) and type IV collagen levels positively correlated with RA pressure ($r = 0.42$, $p = 0.007$). On the other hand, in patients after Fontan procedure, liver fibrosis markers showed no significant correlation with time after surgery, or central venous pressure.

In this study, 23 patients with rTOF underwent PVR and 13 of them received the assessment of fibrosis markers after PVR. Liver fibrosis markers did not show statistically significant decrease after PVR in this small number of subjects (hyaluronic acid: median, 32 to 28 ng/mL, $p = 0.588$; type IV collagen: median 145 to 124 ng/mL, $p = 0.105$). However, 12 patients (92%) and 10 patients (77%) had normalization of the hyaluronic acid and type IV collagen levels after PVR.

3.3. Abdominal ultrasound and liver biopsy

In patients with rTOF, abdominal ultrasonography revealed hepatic congestion (dilated inferior vena cava and hepatic veins, diminished respiratory variation) in 11 (50%) patients, fatty liver in 7 (32%) patients, nodular liver surface and round edge suggesting liver cirrhosis in 2 (8%)

Table 2
Serum laboratory data including liver function tests in each group.

	Normal range	TOF	Fontan	Control	p value	
		n = 50	n = 50	n = 11	TOF *vs.* control	Fontan *vs.* control
Aspartate transaminase, U/L	13–33	21, 13–52	25, 11–47	18, 3–28	0.045*	0.008*
Alanine transaminase, U/L	6–30	17, 8–77	22, 6–61	13, 10–19	0.001*	<0.001*
γ-Glutamyltransferase, U/L	10–47	27, 11–783	57, 18–719	20, 12–47	0.064	<0.001*
Total bilirubin, mg/dL	0.3–1.2	0.8, 0.3–2.9	1.1, 0.4–3.1	0.6, 0.2–1.3	0.037*	<0.001*
Total cholesterol, mg/dL	128–219	153, 118–264	154, 116–259	149, 115–194	0.501	0.901
Total protein, g/dL	6.7–8.3	7.4, 6.4–9.3	7.3, 6.1–8.6	7.2, 6.8–7.8	0.190	0.777
Albumin, g/dL	4.0–5.0	4.7, 3.8–6.8	4.7, 3.0–6.4	4.6, 4.2–5.6	0.745	0.722
Platelet count, /10^9/L	140–440	194, 58–347	170, 73–317	204, 166–291	0.201	0.009*
Brain natriuretic peptide, pg/mL	<18.4	39.4, 5.1–315.8	29.0, 4.1–366.0	24.7, 4.0–66.2	0.016*	0.101

Each value represents the median and range.
* $p < 0.05$.

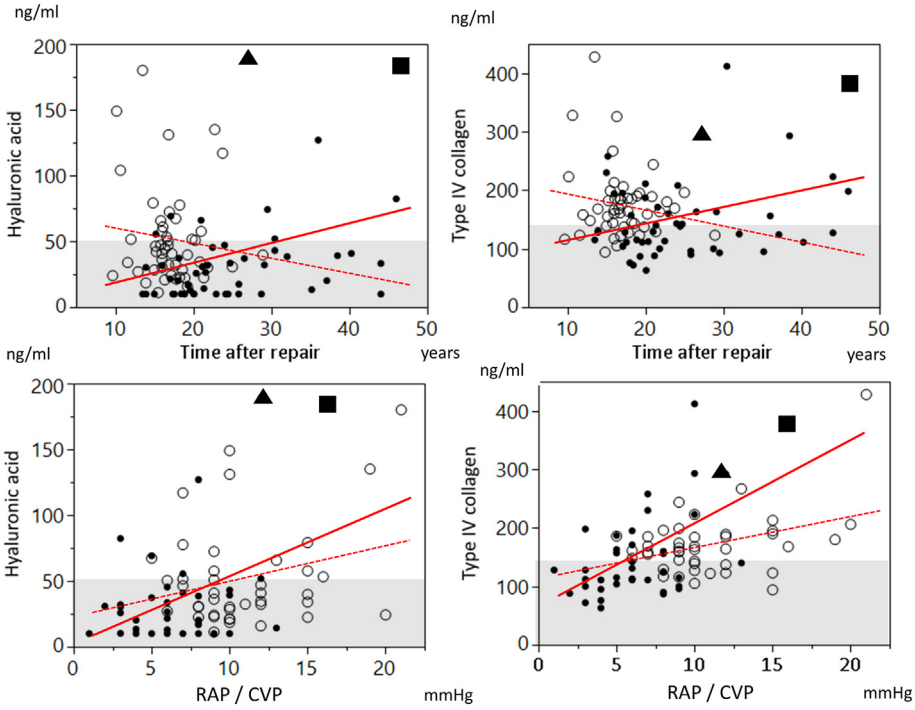

Fig. 2. The correlations between liver fibrosis markers and time after surgery and RA pressure in rTOF and Fontan patients. Closed symbols indicate patients after rTOF and open ones indicate patients after Fontan procedure. Squares indicate the patient who had liver cancer and triangles indicate the patient who had pathological evidence of F2 liver fibrosis. Hyaluronic acid levels positively correlated with time after repair ($r = 0.39$, $p = 0.005$), and type IV collagen levels positively correlated with RA pressure/CVP ($r = 0.40$, $p = 0.007$) in patients with rTOF. Liver fibrosis markers showed no significant correlation with time after surgery, or central venous pressure in Fontan patients. Solid lines indicate the correlation in patients after rTOF, and dotted lines indicate correlation in patients after Fontan procedure.

patient, and liver mass suggesting hepatocellular carcinoma in 1 (4%) patient. Patients with hepatic congestion on abdominal ultrasound had significantly higher type IV collagen, higher total bilirubin, lower total protein, lower platelet count and higher RV end-diastolic pressure than those without hepatic congestion ($p < 0.05$, respectively, Supplementary Table 2).

Liver biopsy was performed in two patients after repair of TOF with highly elevated liver fibrosis markers. The first patient was a 50 year-old female patient who was suspected of hepatocellular carcinoma with liver cirrhosis from the abdominal computed tomography (Supplementary Fig. 1A). Her RA pressure was 16 mm Hg, hyaluronic acid was 180 ng/mL, and type IV collagen was 377 ng/mL. She had pathological diagnosis of combined hepatocellular and cholangiocarcinoma with severe liver fibrosis (METAVIR criteria F3 [11], Supplementary Fig. 2A–E). She underwent surgical resection of the liver cancer. The second patient was a 32 year-old male who had received the clinical diagnosis of liver fibrosis or cirrhosis assessed by the abdominal computed tomography (Supplementary Fig. 1B). His RA pressure was 12 mm Hg, hyaluronic acid was 189 ng/mL, and type IV collagen was 292 ng/mL. He had the pathological evidence of moderate congestive liver fibrosis (METAVIR criteria F2, Supplementary Fig. 2F, G). There was no patient after Fontan procedure who underwent liver biopsy.

4. Discussion

This is the first report that demonstrated the presence of elevated liver fibrosis markers not only in adult patients after Fontan procedure but also after TOF repair. In addition, this is the second report of liver cancer associated with congestive liver fibrosis in patients with rTOF. Liver fibrosis due to hepatic congestion is an important complication in patients with elevated right atrial pressure, which is often seen in patients with rTOF. Liver fibrosis and cirrhosis considerably elevate the risk of cardiac operation with cardiopulmonary bypass especially if it is associated with thrombocytopenia and/or coagulopathy. Also, liver cancer is a severe and possibly fatal complication of congestive hepatopathy. A cohort study showed patients with heart failure have a 1.6 times higher hazard ratio for developing liver/biliary system cancer [12]. The incidence of liver cancer does not seem to be very high in patients with rTOF at present [13,14]. However, considering the fact that elderly patients with ACHD is increasing, we might experience more cases in the future. Liver fibrosis might be an underestimated but possibly important factor in considering the adequate timing of pulmonary valve replacement, which is still controversial and the most vital topic in the management of patients with rTOF.

The etiology of liver fibrosis after Fontan procedure is not fully understood [15]. However, there are several reports describing that it is due to both elevated central venous pressure and diminished cardiac index, which are typical of this circulation. Postmortem studies showed that these patients exhibited passive congestion, cardiac cirrhosis and hepatic adenoma [16,17]. Sinusoidal or portal fibrosis, correlated with time since Fontan surgery, was described at hepatic biopsy [18]. In patients after repair of TOF, central venous pressure is often elevated because of chronic RV volume overload and eventually RV failure. Patients after repair of TOF often have RV restrictive physiology, and it will also contribute to the elevation of central venous pressure [19]. However, cardiac index is usually maintained even in patients with significant pulmonary stenosis and/or regurgitation [20]. Maintained cardiac index might be one of the reasons for relatively mild liver fibrosis in rTOF, along with the relatively mild elevation of the central venous pressure. We chose patients who had cardiac surgery but did not have right side heart sequelae as control subjects. They had only subtle elevation of liver fibrosis markers or other liver function tests. The impact of cardiopulmonary bypass or surgery itself on liver fibrosis is considered to be negligibly small in patients who had undergone cardiac surgery. It is of interest that our patient had combined hepatocellular and cholangiocarcinoma. This is a rare cancer that consists about 1.0% to 4.7% of the primary liver cancer. Compared with hepatocellular carcinoma, the relationship between HBV or HCV and combined hepatocellular

and cholangiocarcinoma incidence is relatively weak. Previous studies reported other risk factors such as male gender, cirrhosis, family history of liver cancer, heavy alcohol consumption and diabetes mellitus, but there is no report highlighted congestive liver [21]. Liver congestion due to right heart failure in congenital heart disease such as TOF could be an important risk factor of developing this rare liver cancer.

Liver dysfunction is also frequently observed in patients with anatomically normal heart complicated with chronic heart failure. It has been attributed to hepatic congestion and/or impaired arterial perfusion [22,23]. Elevation of both transaminases and cholestatic enzymes was reported in several cohorts across the full spectrum of heart failure severity [24–27]. Also, transaminases and to total bilirubin as well as gamma-glutamyltranspeptidase have been associated with poor outcome in heart failure [26–28]. Patients with rTOF having severe PR/PS are a typical phenotype of RV dysfunction. Levels of hyaluronic acid, type IV collagen, transaminases, and total bilirubin were higher in rTOF patients than in controls in the present study. The association of these elevated biomarkers and the prognosis should be elucidated in further studies.

In the present study, elevated RA pressure and pulmonary regurgitant fraction had an association with elevated type IV collagen. Although the predictive value of serum markers for liver fibrosis is not completely validated with comprehensive imaging tests or liver biopsy in this population, this association indicates the fibrosis markers should reflect the degree of liver fibrosis due to elevated RA pressure. Actually, the patient who had combined hepatocellular and cholangiocarcinoma in the present study had the highest RA pressure (16 mm Hg). Similarly, the patient who had hepatocellular carcinoma in the previous report had extremely elevated RA pressure (19–35 mm Hg) [5]. Elevated RA pressure resulting from RV failure due to pulmonary regurgitation and/or tricuspid regurgitation for years may be the most contributing risk factor of the liver fibrosis in patients with rTOF. In the present study, time after surgery was correlated with hyaluronic acid in rTOF but not in Fontan patients. This difference might be due to the relatively short history of Fontan procedure compared with repair of TOF. As the present study showed, the incidence and severity of liver dysfunction in patients after repair of TOF is relatively mild compared to patients after Fontan procedure. However, RV dysfunction and liver congestion could be resolved more easily by pulmonary valve replacement in patients after repair of TOF than in patient after Fontan procedure. This study emphasizes the importance of liver fibrosis as one of the possible factors in considering the timing of pulmonary valve replacement.

Hyaluronic acid levels exceeded the reference range only in 22%, while type IV collagen was abnormal in 44% of TOF patients in the present study. In addition, type IV collagen levels were higher in patients who showed liver congestion in abdominal ultrasonography, while hyaluronic acid levels did differ between patients with and without liver congestion. In general, hyaluronic acid is elevated only in patients with severe liver fibrosis or liver cirrhosis. Type IV collagen, which was elevated in patients with evidence of hepatic congestion on abdominal ultrasound, may be more useful to detect early fibrotic changes of the liver than hyaluronic acid in patients after rTOF. On the other hand, the patients with pathological evidence of liver cancer and F2 liver fibrosis had the first and second highest hyaluronic acid levels among the 50 patients. Elevated hyaluronic acid levels might be a critical sign of cirrhotic change of the liver in patients with rTOF. Regular noninvasive monitoring with type IV collagen and hyaluronic acid with abdominal ultrasonography may be helpful in rTOF patients with elevated RA pressure to detect liver fibrosis, and enables adequate pulmonary valve replacement before the progression of liver cirrhosis and cancer.

There are several limitations about this study. First, the study population is relatively small, especially in patients who underwent imaging tests and biopsy of the liver. We investigated only patients with significant PR and/or PS, who do not represent all the patients after repair of TOF. All of those facts might be a cause of selection bias. In addition, we cannot be too conclusive about the cause and results relation between liver cancer and liver fibrosis with only one case in this series. Second, cardiac catheter data in the controls and CMR data in the Fontan patients and controls were not available in the majority of subjects because of the retrospective data collection. Lastly, we do not have the data to investigate the relationship between elevated liver fibrosis markers and prognosis. A prospective study with a larger population is needed to determine the clinical impact of elevation of these fibrosis markers.

5. Conclusions

Out study demonstrated the presence of elevated liver fibrosis markers and the possibility of liver cancer not only in adult patients after Fontan procedure but also in TOF repair. The liver fibrosis in patients after repair of TOF is less severe than that in patients after Fontan procedure. However, RV dysfunction and liver congestion could be resolved by pulmonary valve replacement. Careful monitoring of the liver fibrosis markers and reoperation at an adequate timing may be beneficial to improve the long-term outcomes in rTOF patients with elevated right atrial pressure.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.032.

Conflict of interest disclosure

H. Tsutsui received consultancy fees from Novartis Pharma K.K., Pfizer Japan Inc., Bayer Yakuhin, Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Ono Pharmaceutical Co., Ltd.; received the speakers' bureau and/or honoraria from Daiichi Sankyo Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corp., Teijin Pharma Ltd., Bristol-Myers Squibb Company, Takeda Pharmaceutical Co., Ltd., Nippon Boehringer, Ingelheim Co., Ltd., and Bayer Yakuhin, Ltd.; received research funds from Takeda Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Nippon Boehringer Ingelheim Co., Ltd., Mitsubishi Tanabe Pharma Corp., Sanofi K.K., and Daiichi Sankyo Co., Ltd.; and is affiliated with an endowed department sponsored by Acterion Pharmaceuticals Japan Ltd. The other authors have no conflicts of interest to disclosure. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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