ORIGINAL RESEARCH

Incidence, Predictors, and Mortality in Patients With Liver Cancer After Fontan Operation

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BACKGROUND: Liver cancer (LC) is a serious late complication after the Fontan operation. However, the incidence, predictors, and prognosis remain unknown. The purpose of our study was to determine these clinical characteristics.

METHODS AND RESULTS: We assessed liver function in 339 consecutive patients who had undergone the Fontan procedure from 2005 to 2019. LC was histologically diagnosed in 10 patients after a median period of 2.9 years (range: 0.3–13.8; median age: 29.9 years [range: 14.4–41.5 years]; overall median post–Fontan procedure follow-up: 25.6 years [range: 13–32.1 years]), and the annual incidence was 0.89%. Over the entire post-Fontan follow-up period, the annual incidences of new-onset LC in the second, third, and fourth decades were 0.14%, 0.43%, and 8.83%, respectively. The patients with LC had longer follow-up periods, higher levels of AFP (α-fetoprotein), and higher values of liver fibrosis indices (*P*<0.01–0.0001). Moreover, all indices were predictive of new-onset LC (*P*<0.01–0.0001). The LC treatments were surgical resection (n=3), transarterial chemoembolization (n=3), radiofrequency ablation (n=2), and hospice care (n=2). During a median follow-up of 9.4 months, 4 patients died; the survival rate at 1 year was 60%, and it was better among asymptomatic patients (*P*<0.01).

CONCLUSIONS: The LC incidence rapidly increased ≥30 years after the Fontan procedure, and liver fibrosis indices and AFP were predictive of new-onset LC. These LC-predictive markers should be monitored closely and mandatorily for early LC detection and better prognosis.

Key Words: cancer ■ Fontan procedure ■ liver ■ mortality ■ predictors

The majority of adult survivors of the Fontan procedure have good functional status with an acceptable 5-year survival rate.[1] However, the significant prevalence and complications of noncardiac mortality indicate that the pathophysiology of the Fontan procedure constitutes a multiorgan disease that can have deleterious effects on quality of life and lifespan.[1] These complications include heart failure, arrhythmias, protein-losing enteropathy, and thromboembolic disorder and have been described in a large-scale study.[2] Recently, besides these complications, more attention has been given to issues of Fontan-associated liver disease (FALD).[3] FALD can be characterized by subclinical progression of liver fibrosis and ultimately leads to liver cirrhosis, liver cancer (LC), or both, and these late complications, particularly LC, are now recognized as among the major factors in all-cause mortality.[1,4] Because of the unique Fontan hemodynamics and diagnostic challenges of liver fibrosis, clinical information about LC remains limited. Therefore, on the basis of our unique follow-up management strategy of patients who have undergone the Fontan procedure,[5] we sought to clarify the following issues: (1) incidence of LC, (2) predictors of new-onset LC, (3) current management of LC, and (4) prognosis after diagnosis of LC.

CLINICAL PERSPECTIVE

What Is New?
- The incidence rate markedly increases late after the Fontan operation, especially 30 years or more after the operation.
- In addition to hepatocellular carcinoma, rare types of liver cancer, such as intrahepatic cholangiocarcinoma and combined hepatocellular cholangiocarcinoma, could develop after the Fontan operation.
- Liver fibrosis indices and the annual change, as well as AFP (α-fetoprotein) level, are predictive of new-onset liver cancer.

What Are the Clinical Implications?
- Routine surveillance with liver fibrosis indices, as well as ultrasonography and AFP measurement, could help in the early detection of liver cancer and thus better survival in long-term survivors of the Fontan operation.

Nonstandard Abbreviations and Acronyms

APRI	ratio of aspartate aminotransferase level to platelets
CHC	combined hepatocellular cholangiocarcinoma
FALD	Fontan-associated liver disease
Fib-4	fibrosis-4 index
HCC	hepatocellular cholangiocarcinoma
ICC	intrahepatic cholangiocarcinoma
LC	liver cancer
SOL	space-occupying lesion

METHODS

The data for this study may be made available for scientific purposes from the corresponding author on reasonable request.

Participants

This study was a retrospective review of our experience with a large Fontan cohort. Of the 500 patients who had undergone Fontan procedures at our institution from October 1979 to February 2019, 443 were admitted for postoperative status evaluation at least 6 months after any cardiac operation. Our management strategy has been based on routine periodic comprehensive assessment of patients who have undergone the Fontan procedure; this assessment includes catheterization, cardiopulmonary exercise testing, hepatorenal function tests, and other metabolic assessments at 1 year after the operation and every 5 years thereafter.[5] Of the 443 patients, 12 patients died, 74 patients moved to other institutions, and 18 patients dropped out during the follow-up period before the study's inception in October 2005. The final sample included 339 consecutive patients who were then evaluated at the end of July in 2019. This study had no other exclusion criteria (Table 1). As of October 1, 2005, LC had not been histologically diagnosed in any patients at our or other institution, including the study participants. We provided patients with the appropriate opportunity to decline consent under the opt-out method on the institutional website and the written informed consent was waived. The Ethics Committee of the National Cardiovascular Center approved the study protocol (M23-002-4).

Hemodynamics

Intracardiac pressure and blood oxygen saturation were measured during catheterization as previously described.[5] Catheterization was performed at least 6 months after any operation. Simpson's rule was used to estimate morphological right and left ventricular

Table 1. Latest Clinical Characteristics of Fontan Patients

Cases	339
Age, y	17 (11–25)
Male sex, %	59
Body mass index, kg/m^2	17.9 (15.8–20.1)
Follow-up after Fontan, y	17.7 (13.4–23.4)
Age at first Fontan operation, y	2.3 (1.4–4.8)
Left ventricle type systemic ventricle, %	41
Heterotaxy	26
New York Heart Association class	1 (1–2)
Hemodynamics, n	
Central venous pressure, mm Hg	10 (8–11)
Cardiac index, L/min per m^2	2.9 (2.4–3.4)
Systemic ventricular end-diastolic volume index	72 (61–86)
Systemic ventricular ejection fraction	55 (49–61)
Hemoglobin, g/dL	14.7 (13.6–16)
Arterial oxygen saturation (%)	95 (93–96)
Neurohumoral factors	
Norepinephrine, pg/mL	382 (257–577)
Brain natriuretic peptide, pg/mL	13 (7–30)
Renin activity, ng/mL per h	7 (3–16)
Medications, %	
Diuretics	38
Anticoagulant	78
Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker	39
Beta blocker	31

Values are expressed as a median with interquartile range.

volumes in patients who underwent cineventriculography. The end-diastolic ventricular volume was divided by body surface area to obtain the end-diastolic volume index and ejection fraction of the systemic ventricle.

Plasma Neurohormonal Activities and Biochemical Variables

After the patients rested in the supine position for at least 15 minutes, plasma norepinephrine level was determined in 328 patients, brain natriuretic peptide level in 337, and renin activity in 326.

Assessment of Fontan-Associated Liver Disease

Liver Ultrasonography

After patients fasted for 6 hours, experienced sonographers obtained and evaluated liver images (Aplio i900 with low-frequency curved-array transducers [5.5 MHz] and high-frequency linear-array transducers [8.5 MHz]; Canon Medical Systems Corporation, Otawara, Japan) under the supervision of physicians considered experts in the field of ultrasonography. To date, no guidelines based on ultrasonography findings for assessing FALD have been established. Therefore, we focused on the following 5 findings by binary scoring and then arbitrarily rated the abnormal liver image as a total ultrasonography score: parenchymal echotexture (normal=0, coarse=1), surface irregularity (smooth=0, irregular=1), ascites (non-small=0, moderate or larger=1) (if ascitic fluid accumulated in both Morison's pouch and the pouch of Douglas, the ascites was graded as moderate), number of hyperechoic spots (≥3 mm in diameter; none to a few=0, larger number ≥ moderate=1; if several hyperechoic spots were observed in a particular parenchymal area, the scale was arbitrarily graded as moderate), and space-occupying lesions (SOLs; no=0, yes=1). After comparisons of these ultrasonography findings between patients with and without LC, only statistically significant findings were used to calculate the total ultrasonography score.

Liver Fibrosis Indices, α-Fetoprotein, and Other Biomarkers

We calculated liver fibrosis indices, including the ratio of aspartate aminotransferase level to platelets (APRI) in 337 patients,[6] Fibrosis-4 Index for Liver Fibrosis (Fib-4) score in 337,[7] and the Forns index in 333.[8] Next, we categorized the patients into 3 groups according to whether they were at low, intermediate, or high risk for advanced fibrosis for each score according to the following cutoff values: APRI (lower cutoff of 0.50, upper cutoff of 1.50), Fib-4 score (lower cutoff of 1.30, upper cutoff of 2.67), and Forns index (lower cutoff of 4.2, upper cutoff of 6.9).[9] At the beginning of this study, these indices could be determined in 267 patients (79%), and we were thus able to calculate annual changes in these markers with a median follow-up of 5.0 years (range: 4.4–5.3 years). The plasma levels of AFP (α-fetoprotein) were measured in 286 patients, who were categorized into 2 groups according to the traditional cutoff value of 10.0 ng/mL. We also measured the plasma levels of albumin, total bilirubin, creatinine, alanine aminotransferase, and γ-glutamyltransferase and calculated a model for end-stage liver disease, excluding the international normalized ratio score in 336 patients, and all patients were assessed for the presence of concomitant viral hepatitis infection.

Liver Cancer

LC was diagnosed based on the histopathological findings of board-certified pathologists at the time of liver biopsy, surgical resection, and autopsy. We excluded patients in whom LC was diagnosed solely on the basis of image findings.

Statistical Analysis

Clinical variables that were present at the time of the most recent evaluation before the onset of LC were used for the prediction of new-onset LC. For patients without LC, the most recent variables were also used. Data were calculated as medians with interquartile ranges. The Wilcoxon test was used to evaluate differences in demographics, functional capacity, hemodynamics, neurohormonal variables, and liver variables between patients with and without LC. Comparisons of the prevalence of medications and liver ultrasonography abnormalities were evaluated using chi-square tests or Fisher's exact test if appropriate. Univariate Cox's proportional hazards model was used to predict the associations of clinical factors with new-onset LC. For statistically significant variables, receiver operating characteristic curve analysis was applied to determine cutoff values for identifying an efficient predictor of new-onset of LC. The Kaplan–Meier method was used to estimate survival rate, and log-rank tests were used to assess differences between groups. Analyses were performed using JMP 12 Pro software (SAS Institute, Cary, NC, USA). All P values of <0.05 were considered statistically significant.

RESULTS

Of the 339 consecutive patients, 14 patients underwent evaluation for the presence of LC because of

symptoms in 3 patients (abdominal pain in 1, malaise in 2), significant size of SOL in 6, and high plasma levels of AFP in 5. Of these, after denying the possibility of LC based on histological examination in 4 patients with significant size of SOL, 10 patients were finally histologically diagnosed with LC, and their clinical features are shown in Table 2.

Incidence of LC

Among the 339 patients, free rates from new-onset LC at 10, 20, and 30 years after the initial Fontan operation were 100%, 98.4%, and 94.3%, respectively (Figure 1A). The annual incidences of new-onset LC were 0.14% in the second decade after the Fontan procedure (among 294 patients), 0.43% in the third decade (among 130 patients), and 8.83% in the fourth decade (among 21 patients); this indicates a marked increase in the fourth decade (ie, ≥30 years after the operation). When we focused on a median follow-up of 2.9 years (range: 1.6–4.4 years) after October 2005, the annual incidence was 0.89% (Figure 1B). Of these 10 patients, the histopathological diagnosis were hepatocellular carcinoma (HCC) in 8, intrahepatic cholangiocarcinoma (ICC) in 1, and combined hepatocellular cholangiocarcinoma (CHC) in 1. Three patients had symptoms related to LC at the time of diagnosis; 2 experienced general malaise and loss of weight, and 1 patient experienced abdominal pain. LC rupture occurred in 1 of the 2 patients with malaise and weight loss. Of the remaining 7 patients who developed LC without symptoms, 5 (50%) had high AFP plasma levels and 2 (20%) had abnormal ultrasonography findings (SOLs ≥10 mm).

Clinical Characteristics of Patients Before Onset of LC

The clinical characteristics of patients who did and did not develop LC are summarized in Table 3. Patients with LC were older, had higher body mass indices, had longer postoperative follow-up, and had disease in higher New York Heart Association classes. In contrast, there were no differences in hemodynamics or neurohumoral activities. Patients with LC had some abnormalities in liver function, especially the liver fibrosis indices, including annual changes in the APRI and Fib-4 scores.

Rates of all abnormal ultrasonography findings, except for number of hyperechoic spots, were higher in the patients with LC than in those without LC. Therefore, we calculated a total ultrasonography score by using parenchymal echotexture, surface irregularity, ascites, and SOLs. Thus, the ultrasonography score ranged from 0 to 4. The total ultrasonography scores were higher in patients with LC than in those without LC. AFP levels were also higher in the patients with LC than in those without LC.

Predictors of New-Onset LC

Cox's proportional hazards model showed that older age, higher body mass index, longer follow-up duration, higher New York Heart Association class, poorer results on liver function tests (especially liver fibrosis indices, including annual changes in APRI and Fib-4 score), total ultrasonography score, and AFP were predictive of new-onset LC (Table 4). We did not perform multivariable analysis because of the small number of cases[10] of new-onset LC. Receiver operating characteristic analysis revealed that the cutoff values for efficient LC prediction were 0.66 for APRI, 0.89 for Fib-4 score, 6.33 for the Forns index, 5.5 for AFP level, and 2 for total ultrasonography score. The cutoff values of annual changes in APRI and Fib-4 were 0.052 and 0.082, respectively. When our patients were divided into 2 subgroups according to these cutoff values, the hazard ratios in the subgroup with values higher than the cutoff were 7.54 (95% CI, 1.89–50.0; P=0.0033) for APRI, 18.2 (95% CI, 3.42–336; P=0.0002) for Fib-4 score, 10.9 (95% CI, 3.10–42.6; P=0.0003) for the Forns index, and 24.0 (95% CI, 3.86–460; P=0.0004) for AFP. Similarly, the hazard ratios in the subgroup with values lower than the cutoff were 8.0 (95% CI, 2.28–31.5; P=0.0015) for the annual change in APRI and 7.35 (95% CI, 2.04–34.1; P=0.0022) for the annual change in Fib-4 score. Kaplan–Meier curves for each subgroup are shown in Figure 2. For the annual changes in APRI and Fib-4, the Kaplan–Meier curves for each subgroup are shown in Figure 3.

When the traditional cutoff values of the 3 fibrosis indices were applied to divide the patients into subgroups at low, intermediate, or high risk at the time of entry into the study, percentages of each subgroup were 42%, 55%, and 3%, respectively, for APRI; 83%, 12%, and 5%, respectively, for Fib-4 score; and 60%, 30%, and 10%, respectively, for the Forns index. Cox's proportional hazards model revealed that in comparison with the low-risk groups, each high-risk group for APRI, Fib-4 score, and Forns index was at a significantly higher risk for new-onset LC: 15.7 for APRI (95% CI, 1.88–131; P=0.0146), 28.6 for Fib-4 score (95% CI, 6.29–145; P<0.0001), and 10.1 (95% CI, 2.22–51.4; P=0.0153) for the Forns index. As for application of traditional cutoff value of AFP (≥10 ng/mL) to our patients, 12 patients (4.2%) who showed high plasma levels were at high risk for new-onset LC (hazard ratio, 25.9; 95% CI, 4.80–140; P=0.0006).

Treatment and Prognosis After Diagnosis of LC

The outcomes after a diagnosis of LC are summarized in Figure 4 and Table 2. After LC diagnosis, 4 patients underwent surgical resection, 3 underwent

Table 2. Cases of Liver Cancer After Fontan Operation

No.	Case	Age at LC Diagnosis (y)	Sex	Cardiac Diagnosis	Age at First Fontan Operation (y)	Years After Fontan Operation	Histological Diagnosis of LC	1st Sign of LC	LC Size at Diagnosis (mm)	AFP at LC Diagnosis (ng/mL)	Hepatic Disease at LC	Symptom at LC Diagnosis	Hepatitis	Treatment	Outcome
1	S T	14.4	M	CIRV	1.4	13	HCC	SOL	33	6	NA	No	No	TACE	Alive
2	M T	19.2	F	CIRV	2.0	17	Combined hepatocellular cholangiocarcinoma	SOL	18	154	Cirrhosis	No (HF)	No	TACE	Died
3	A H	21.2	F	TA	2.9	18	Intrahepatic cholangiocarcinoma	Symptom	50	NA	NA	Abdominal pain	No	Surgical resection	Died
4	H S	22.7	M	CIRV	1.6	21	HCC	AFP	18	48.9	NA	No	No	RFA+TACE	Alive
5	N K	29.5	M	Double inlet left ventricle	5.2	24	HCC	AFP	18	79.3	Precirrhosis	No	No	Surgical resection	Alive
6	M C	30.2	F	Atrioventricular septal defect	3.3	27	HCC	AFP	15	17.2	Cirrhosis	No	No	Surgical resection	Alive
7	C S	34.5	F	TA	3.4	31	HCC	Symptom	NA	52 333	Cirrhosis	Malaise	No	Hospice	Died
8	H S	34.6	M	TA	4.4	30	HCC	AFP	15	22.3	Cirrhosis	No	C	Surgical resection	Alive
9	K Y	35.8	M	Transposition of the great arteries	5.0	31	HCC	AFP	9	17	Cirrhosis	No (HF)	B	RFA	Alive
10	Y F	41.5	M	TA	9.4	32	HCC	Symptom	63	538 883	Precirrhosis	Malaise	No	Hospice	Died

AFP indicates α-fetoprotein; CIRV, common inlet right ventricle; HCC, hepatocelluar carcinoma; HF, heart failure; LC, liver cancer; NA, not available; RFA, radiofrequency ablation; TA, tricuspid atresia; and TACE, transarterial chemoembolization.
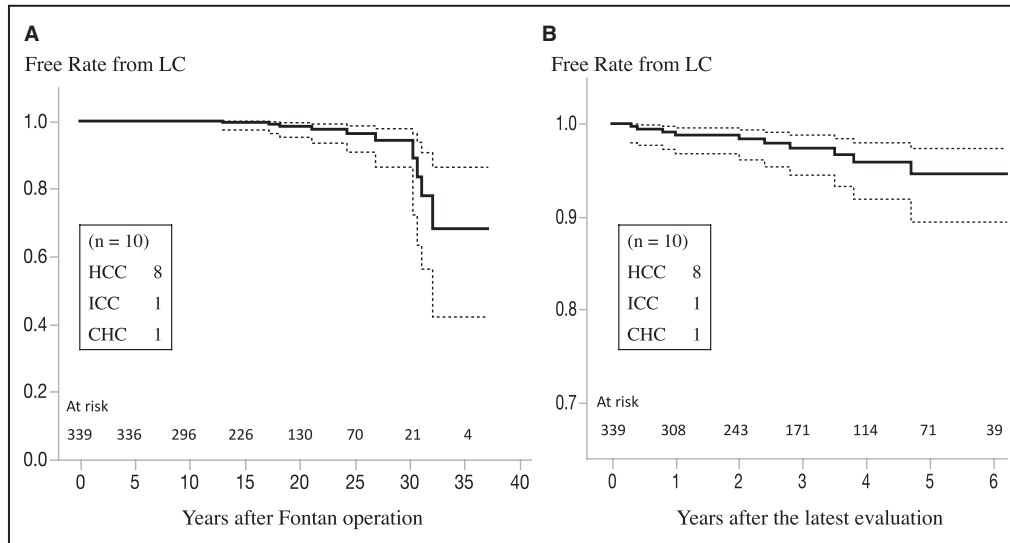
Figure 1. **Kaplan–Meier curve showing the rate of new-onset of liver cancer (LC) after the Fontan operation (A) and during the most recent evaluation (B).**
CHC indicates combined hepatocellular cholangiocarcinoma; HCC, hepatocellular carcinoma; and ICC, intrahepatic cholangiocarcinoma.

transarterial chemoembolization, and 2 underwent radiofrequency ablation. Of the 4 patients who underwent LC resection, 3 patients had no symptoms and no recurrence, whereas 1 patient with symptoms and a diagnosis of ICC died. Of the 3 patients who underwent transarterial chemoembolization, 1 also underwent radiofrequency ablation; the other 2 patients received hospice care; 1 patient with a diagnosis of CHC died from a cerebellar hemorrhage, which was not related to the treatment, and another patient who had initially received radiofrequency ablation had a recurrence and underwent transarterial chemoembolization. The third patient to undergo transarterial chemoembolization and only 1 patient who underwent radiofrequency ablation survived without recurrence for 8 and 2 years, respectively. Patients who received hospice care were those with symptoms of general malaise, weight loss, or abdominal pain at the time of LC diagnosis. One patient in hospice died soon after the onset of LC. Survival rates during the 1 and 2 years after a LC diagnosis were 60% and 40%, respectively (Figure 5A). All 3 patients with symptoms at the time of LC diagnosis died within 1 year, whereas all patients without symptoms survived, except for the 1 patient with CHC who died of a cerebellar hemorrhage. There was a statistical difference in rates of survival of patients with and without symptoms at the time of LC diagnosis (P=0.0057; Figure 5B).

DISCUSSION

This is the first study to address predictive values of hepatic biomarkers, as well as ultrasonography findings, of new-onset LC in a large cohort of patients who have undergone the Fontan procedure, and the results provide new information about FALD. Our findings can be summarized as follows. First, LC incidence increased late after Fontan operation, especially 30 years or more afterwards. In addition, rare LCs (ie, ICC and CHC) sometimes developed after the operation. Second, traditional liver fibrosis indices and the annual changes in APRI and Fib-4 scores, in addition to older age and high plasma levels of AFP, could be useful predictors of new-onset LC in patients who have undergone Fontan operations. Third, we reconfirmed that the rate of mortality after the onset of LC was high and the rate of survival was better among patients without symptoms. Thus, these results reemphasize the importance of routine FALD surveillance for a better prognosis.

Prevalence and Incidence of LC Development After Fontan Operation

Several LC-related studies after Fontan operation were cross-sectional, and the annual incidence was estimated to be between 1.5% and 5.0%.[10] One multicenter study showed that the prevalence of HCC was 1.3% (n=2470).[4] In our study, the prevalence of all LCs was 2.9% (10/339), and the annual incidence over a median follow-up period of 2.9 years was 0.89%. Moreover, the annual incidences of LC were 0.14% in the second decade after the Fontan operation, 0.43% in the third decade afterwards, and 8.83% in the fourth decade afterwards; thus, there was a rapid rise in the fourth decade (ie, ≥30 years after the operation).

Table 3. Latest Clinical Characteristics of Fontan Patients With and Without Liver Cancer

	Cancer (+)	Cancer (−)	*P* Value
Cases	10	329	
Age, y	27 (18–34)	17 (11–25)	0.0099*
Male sex, %	60	59	0.9415
Body mass index, kg/m^2	20.8 (18.4–23.1)	17.9 (15.8–20)	0.0188*
Follow-up after Fontan, y	25.6 (18.0–30.8)	17.6 (13.3–23.2)	0.0083*
Age at first repair, y	3.3 (1.9–5.1)	2.2 (1.4–4.8)	0.2469
Left ventricle type systemic ventricle, %	40	41	0.9477
Heterotaxy	39	26	0.2505
New York Heart Association class	2 (1–2)	1 (1–2)	0.0426*
Hemodynamics, n			
Central venous pressure, mm Hg	10 (9–12)	10 (8–11)	0.3459
Cardiac index, L/min per m^2	2.8 (2.5–3.5)	2.9 (2.4–3.4)	0.9201
Systemic ventricular end-diastolic volume index	73 (61–107)	72 (61–85)	0.5738
Systemic ventricular ejection fraction	56 (49–59)	55 (49–62)	0.7349
Hemoglobin, g/dL	15.1 (13.8–16.4)	14.7 (13.6–16)	0.5106
Arterial oxygen saturation (%)	94 (89–95)	95 (93–96)	0.175
Neurohumoral factors			
Norepinephrine, pg/mL	419 (300–600)	379 (257–578)	0.4769
Brain natriuretic peptide, pg/mL	19 (14–34)	12 (7–30)	0.1623
Renin activity, ng/mL per h	14 (2–24)	7 (3–16)	0.5373
Liver function tests			
Albumin, g/dL	4.5 (4.4–4.5)	4.6 (4.3–4.8)	0.1235
Total bilirubin, mg/mL	1.2 (1.0–2.2)	0.9 (0.6–1.3)	0.0177*
Aspartate aminotransferase, U/L	31 (28–39)	28 (23–34)	0.1463
Alanine aminotransferase, U/L	21 (15–38)	21 (16–27)	0.6694
Cholinesterase, IU/L	247 (199–276)	269 (236–319)	0.0665
γ-glutamyltransferase, U/L	87 (73–149)	63 (41–100)	0.0411*
Platelets, 10^3/μL	8.9 (7.1–17)	15.8 (12.2–20.3)	0.0106*
Model for end-stage liver disease, excluding the international normalized ratio	9.8 (9.4–11.1)	9.4 (9.4–10)	0.0936
Fibrosis indices			
APRI	0.94 (0.62–1.64)	0.53 (0.41–0.73)	0.0072*
d–APRI (per year) (n=267)	0.06 (−0.01 to 0.14)	0.00 (−0.02 to 0.03)	0.0344*
Fib-4	1.91 (0.99–3.20)	0.62 (0.40–1.08)	0.0007*
d-Fib-4 (per year) (n=267)	0.11 (0.02–0.32)	0.04 (0.02–0.07)	0.0319*
Forns	6.39 (3.67–8.38)	3.25 (1.18–5.19)	0.003*
d-Forns (per year) (n=257)	0.45 (0.10–0.67)	0.30 (0.16–0.50)	0.8028
α-fetoprotein, ng/mL	9.0 (5.5–22.3)	2.9 (1.9–4.6)	0.0036*
Liver ultrasonography	(n=10)	(n=304)	
Parenchymal coarse (yes=1)	100 (%)	71 (%)	0.009*
Surface irregularity (yes=1)	20 (%)	2.6 %	0.0319*
High-echoic spot (≥ several=1)	20 (%)	18 (%)	0.8907
Space occupying lesion ≥10 mm (yes=1)	30 (%)	10 (%)	0.0912
Ascites (≥ moderate=1)	20 (%)	3 (%)	0.0393*
Ultrasonography score	1.5 (1–2.3)	1 (0–1)	0.0013*
Medications, %			
Diuretics	60	38	0.1589
Anticoagulant	60	79	0.1837

(Continued)

Table 3. Continued

	Cancer (+)	Cancer (–)	P Value
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	40	39	0.9565
Beta blocker	50	31	0.2162

APRI indicates aspartate aminotransferase to platelet ratio; d-APRI, d-Fib-4, and d-Forns are annual changes in each fibrotic index, respectively; and Fib-4, fibrosis-4 score.

*indicates statistically significant.

Of interest was the finding, for the first time, that rare forms of LC (ie, ICC and CHC) could develop even after Fontan operation. In general, of all LCs, the prevalence of ICC and CHC was 10% to 20% and 0.4% to 14.2%, respectively.[11,12] The association of Fontan circulation with onset of these rare LCs and their exact incidence were unknown in this study. However, clinicians should be aware that these rare LCs could develop after Fontan operation because the clinical characteristics are somewhat different from HCC: for example, the rate mortality from these LCs is higher.[11,12]

Predictors of New-Onset LC After Fontan Operation

In general, prevalence of LC is higher among patients with liver cirrhosis than in those without,[11,13] and prediction of new-onset LC is important for a better prognosis. Similarly, because both liver cirrhosis and LC are

Table 4. Predictors of Liver Cancer in Fontan Patients

	Hazard Ratio	95% CI	P Value
Cases			
Age, y	1.08	1.02–1.14	0.0074
Body mass index, kg/m^2	1.25	1.05–1.48	0.0125
Follow-up after Fontan, y	1.13	1.04–1.25	0.0062
New York Heart Association class	2.43	1.02–5.11	0.0457
Liver variables			
Aspartate aminotransferase, U/L	1.04	1.00–1.07	0.0499
Cholinesterase (per 10 IU/L)	0.90	0.82–0.99	0.0306
Platelets, 10^3/μL	0.84	0.72–0.95	0.0042
Fibrotic markers			
APRI	3.38	1.71–5.71	0.0018
d-APRI per year (per 0.01)	1.08	1.02–1.15	0.0175
Fib-4	2.15	1.44–3.01	0.0007
d-Fib-4 per year (per 0.01)	1.07	1.02–1.11	0.0045
Forns index	1.54	1.19–2.04	0.0006
Ultrasonography score	5.99	2.48–15.0	<0.0001
Tumor marker			
α-fetoprotein	1.16	1.08–1.24	0.0006

APRI indicates aspartate aminotransferase to platelet ratio; d-APRI, d-Fib-4, and d-Forns are annual changes in each fibrotic index, respectively; and Fib-4, fibrosis-4 score.
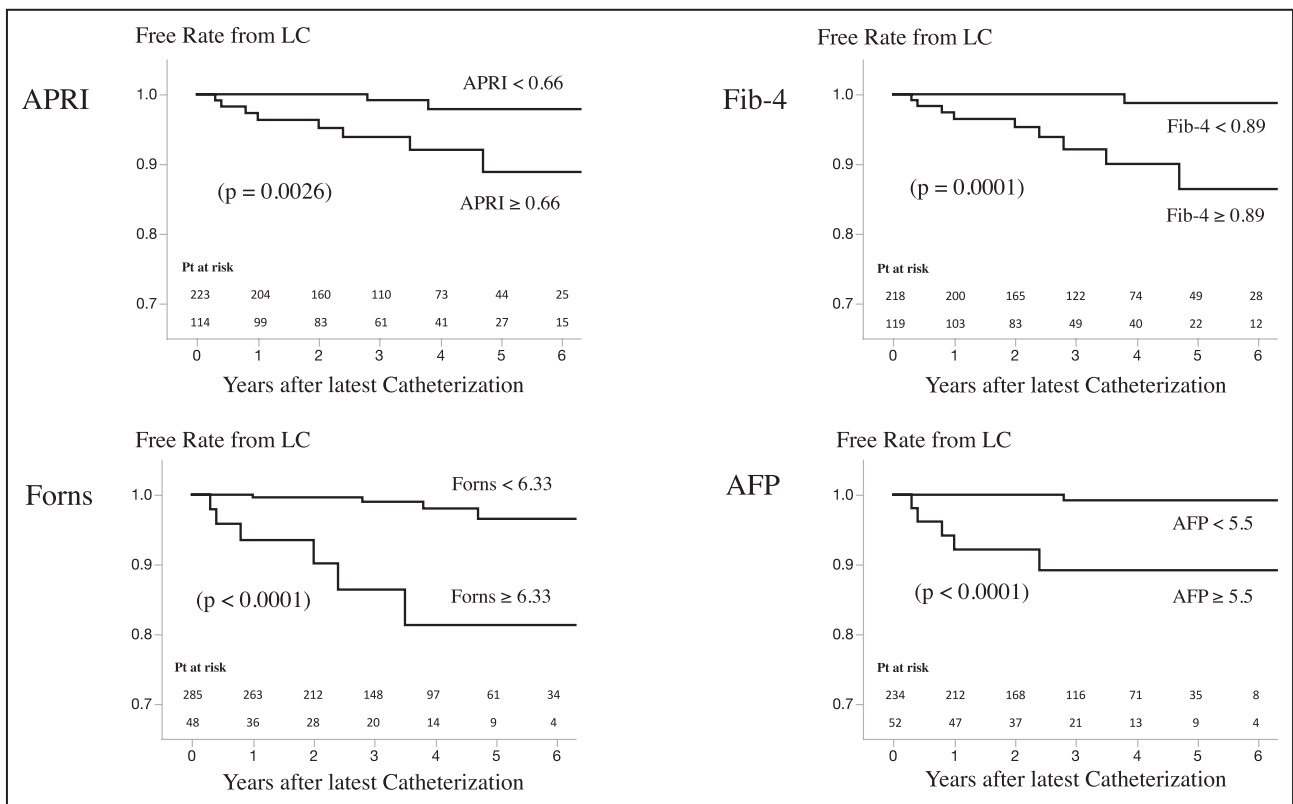
associated with poor prognosis,[4,14] the screening and prediction of new-onset LC are also important for better prognosis. As in patients with chronic liver disease, biopsy is not always feasible diagnostic tool for stratification of FALD[15]; therefore, noninvasive modalities, such as ultrasonography and evaluation of biomarkers, may be useful alternatives.

Abnormal Ultrasonography Finding

We found that patients who had a high rate of abnormal ultrasonography findings were at high risk for new-onset LC. In particular, a coarse appearance of the liver parenchyma and an irregular liver surface were observed in all patients before LC development; both are indicative of presence of severe liver fibrosis.[16] The presence of ascites or SOL might be associated with progression of liver fibrosis because the prevalence of these findings is also associated with longer follow-up duration after Fontan operation.[17] In patients with liver cirrhosis, SOLs 10 mm or larger have a substantial likelihood of being malignancies.[18] In fact, ultrasonography findings of SOLs 10 mm in size or larger was the trigger of LC diagnosis in 2 of our patients. However, because some SOLs are not detectable by ultrasonography, further studies with other additional imaging modalities, such as computed tomography or magnetic resonance imaging, may be necessary. Of interest was that grading of hyperechoic spots, which are often observed in long-term survivors of Fontan operations,[19,20] was not associated with new-onset LC.

AFP Level

The clinical significance of AFP levels, including their prognostic value, has been repeatedly validated despite its uncertainty in terms of the sensitivity and specificity for early detection of LC.[21] A cutoff AFP value of 20 ng/mL or higher is generally considered effective in predicting the presence of LC. In this study, because the number of patients with new-onset LC was small, our cutoff value was 5.5 ng/mL, which is within normal range, and this value may not be generalized. However, if we change our perspective, we found that patients who did not develop LC had a substantially low value of AFP (median: 2.9 ng/mL), and this may also support its value in predicting

Figure 2. Comparisons of Kaplan–Meier curves between 2 groups of Fontan operation survivors, divided by cutoff values of liver fibrosis markers (ratio of aspartate aminotransferase to platelets [APRI], fibrosis-4 index of liver fibrosis [Fib-4] score, and Forns index) and α-fetoprotein (AFP) for predicting new onset of liver cancer (LC).

new-onset LC even in patients who have undergone Fontan procedures. Actually, the risk of new-onset LC was 25.9 times higher in patients with a high AFP level (≥10 ng/dL). Serial assessment could improve the sensitivity[22,23]; unfortunately, we did not have enough serial data on AFP in this study.

Liver Fibrosis Indices

Our notable finding in this study is that conventional fibrosis indices were predictive of new-onset LC. In general, advanced liver fibrosis is a risk factor for LC development,[11,13,24] and the annual incidence of LC in patients with liver cirrhosis ranges from 1% to 8%.[13] In fact, of the 7 patients with LC whose histological diagnosis of a non-LC lesion was available, 5 (71%) had a diagnosis of liver cirrhosis and the remaining 2 had a diagnosis of pre–liver cirrhosis (fibrotic stage F3 in the METAVIR staging system). There have been significant debates whether these fibrosis indices reflect actual histologic changes in the liver.[16,25] However, because our and conventional cutoff values were associated with new-onset LC, it is likely that these fibrosis indices, to some extent, reflect the degree of liver fibrosis.

We also found that these cutoff values were somewhat lower than the traditional cutoff value for predicting severity of liver fibrosis.[9,26] We speculate that values of APRI and Fib-4 scores were low because aspartate aminotransferase and alanine aminotransferase values were normal and most of our patients were relatively young; moreover, Forns index values were low because of low cholesterol levels[27] and younger age. In addition, and of more importance, a significant proportion of patients (65 [19%]) had right-sided heart isomerism (ie, asplenia syndrome), which could have been responsible for the low values of all liver fibrosis indices, inasmuch as asplenic patients have higher platelet counts. In fact, platelet count was significantly higher in the asplenic patients (20.5 [range: 14.7–27.1] than in the nonasplenic patients (15.1 [range: 11.2–19.1]; $P<0.0001$). Patients who were asplenic also tended to exhibit lower APRIs (0.48 [0.37–0.71] versus 0.55 [0.41–0.74]; $P=0.18$), Fib-4 scores (0.56 [0.36–1.05] versus 0.66 [0.41–1.16]; $P=0.08$), and Forns indices (3.12 [0.99–4.37] versus 3.52 [1.36–5.38]; $P=0.08$). Therefore, comprehensive FALD assessment with multiple modalities is mandatory in these patients.
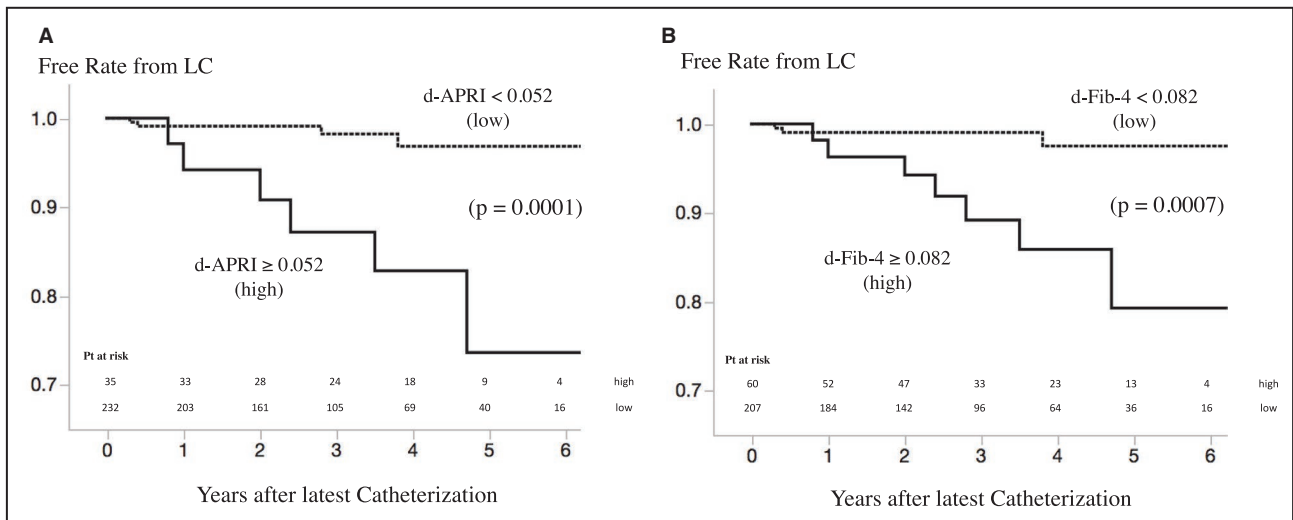
Figure 3. Comparisons of Kaplan–Meier curves between 2 groups of Fontan procedure survivors, divided by cutoff values of annual changes in liver fibrosis indices (ratio of aspartate aminotransferase to platelets [APRI] (A), fibrosis-4 index of liver fibrosis [Fib-4] (B)) for predicting new-onset liver cancer (LC).
d-APRI and d-Fib-4 indicates annual change in APRI and Fib-4, respectively.

Treatment and Prognosis After LC Diagnosis

In general, the 5-year survival rate among patients with LC is ≈20%; in Japan, it has reached 43%. However, it still remains high among patients with several types of cancers.[28,29] Among our patients, the mortality rate was similar to that in Western countries,[4] and we reconfirmed that in patients without symptoms in whom LC was detected during routine LC surveillance, the prognosis was significantly better than in those with symptoms at the time of diagnosis. This finding emphasizes the importance of LC surveillance in our practice for long-term survivors of Fontan procedures. Our shortest post-Fontan follow-up at the time of LC diagnosis was 13 years, but a patient with a diagnosis of LC after a much shorter follow-up has been described.[4] Various conventional treatments have been applied without any guidelines specific to survivors of Fontan operations. Thus, it remains too early to conclude which treatment is efficacious for such patients who develop LC.
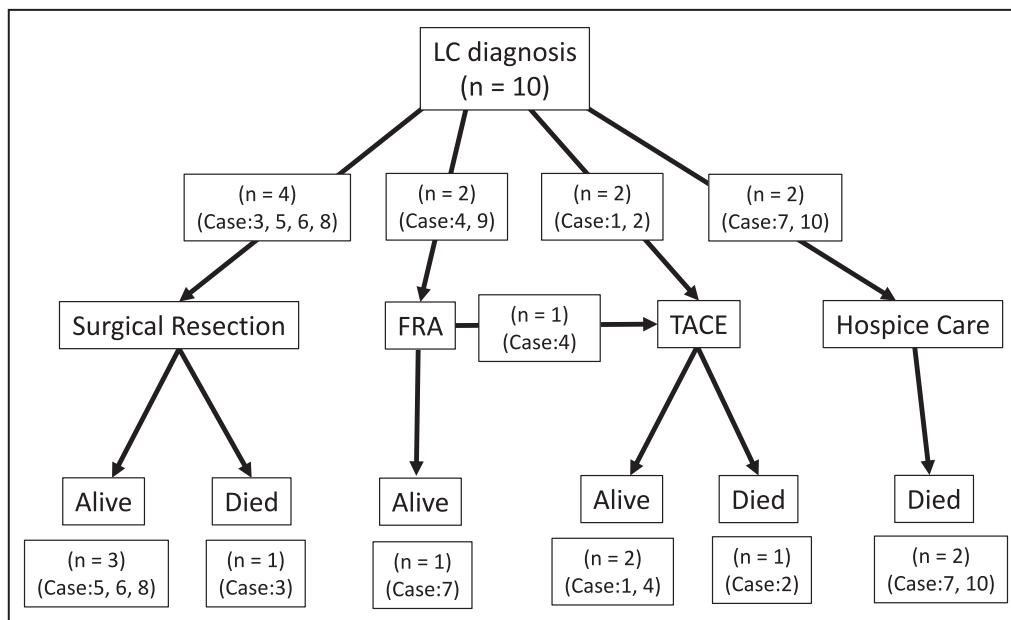

Figure 4. Flow chart of liver cancer (LC) therapy after the diagnosis.
Numbers of cases correspond to those in Table 2. FRA indicates radiofrequency ablation; and TACE, transarterial chemoembolization.
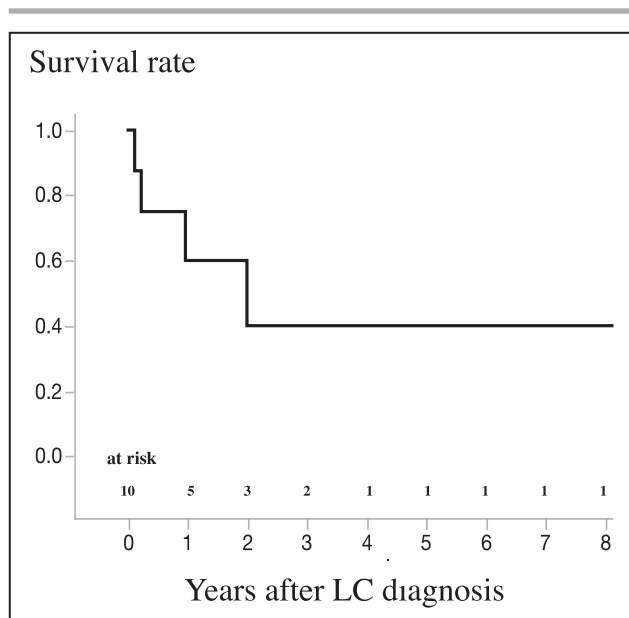
Figure 5. **Rate of survival after a diagnosis of liver cancer (LC) in all cases.**

Study Limitations

This study had several limitations. First, the number of patients with LC[10] was quite low for statistical analysis, although our cohort was large (n=339). Second, in addition to a lack of information about LC-related issues in patients whom we could not monitor, we may have underestimated the prevalence or incidence of LC because we focused on histologically proven cases; it is possible that some patients had undetectable asymptomatic LC. Third, we did not check the influence of alcohol consumption or smoking on FALD; these behaviors might have some effect on the incidence of new-onset LC. Fourth, we acknowledged that estimation of ejection fraction with cineventriculography may be inaccurate. However, along with no effect of ejection fraction on our results, cardiac magnetic resonance imaging is not yet versatile enough for routine use in all follow-up studies. Finally, although ICC may be biologically distinct from HCC, we thought that ICC was surely a primary LC and one of the manifestations of FALD, and most risk factors of HCC, such as fibrosis and hepatic virus infection, as well as obesity, are the same as those of ICC.[11] In order to overcome these limitations, large-scale multicenter prospective study must address these issues.

CONCLUSIONS

The incidence of LC increases late after the Fontan operation, especially 30 years or more after the operation. Moreover, rare types of LCs (ie, ICC and CHC) could develop in long-term survivors of the Fontan

procedure. Conventional liver fibrosis markers, older age, high AFP plasma levels, and abnormal ultrasonography findings could be useful predictors of new-onset LC, even in patients who have undergone the Fontan procedure. We reconfirmed the high mortality rate after new onset of LC in such patients, along with a better survival rate among patients without symptoms. Therefore, we reemphasize the importance of routine FALD surveillance with liver fibrosis markers, as well as ultrasonography and AFP measurement, for a better prognosis.

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