Liver Cirrhosis and/or Hepatocellular Carcinoma Occurring Late After the Fontan Procedure
— A Nationwide Survey in Japan —

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**Background:** Fontan-associated liver disease (FALD) is an important late complication involving liver dysfunction, such as liver cirrhosis (LC) and hepatocellular carcinoma (HCC), in patients undergoing the Fontan procedure. However, the prevalence, clinical manifestation, and methods of diagnosis of FALD are still not well established.

**Methods and Results:** This study comprised 2 nationwide surveys in Japan. First, the prevalence of LC and/or HCC in patients undergoing the Fontan procedure was determined. Second, clinical manifestations in patients with LC and/or HCC were analyzed, along with data from blood tests, echocardiography, and right heart catheterization. In the 1st survey, of the 2,700 patients who underwent the Fontan procedure, 31 were diagnosed with LC and/or HCC (1.15%), and 5 died due to liver diseases (mortality: 0.19%). In the 2nd survey, data were collected from 17 patients (12 with LC, 2 with HCC, and 3 with LC+HCC). Of these 17 patients, 5 died (mortality: 29.4%). The mean age at diagnosis of LC and HCC was 23 and 31 years, respectively. Computed tomography followed by ultrasound was most frequently used for diagnosis. Blood tests revealed low platelet counts, increased hemoglobin, aspartate aminotransferase, γ-guanosine triphosphate, and total bilirubin levels, and an elevated international normalized ratio of prothrombin time.

**Conclusions:** LC and/or HCC in patients undergoing the Fontan procedure were not rare late complications and were associated with high mortality rates.

**Key Words:** Diagnosis; Fontan-associated liver disease (FALD); Hepatocellular carcinoma; Liver cirrhosis; Risk factors

The Fontan procedure is currently accepted as the final palliative surgery in patients with single ventricle physiology. However, the lack of a subpulmonary ventricle alters static resistance and dynamic impedance, resulting in a profound effect on the hepatic circulation. Long-term hepatic dysfunction is a significant late complication in patients undergoing the Fontan procedure and is known as Fontan-associated liver disease (FALD). Hepatic complications, such as hepatic fibrosis or cirrhosis, develop as a result of increased hepatic venous pressure, tissue hypoxia, and decreased cardiac output. There are many case reports on hepatocellular carcinoma (HCC) in patients undergoing the Fontan procedure. It has been estimated that, annually, 1.5–5.0% of patients with liver cirrhosis (LC) may develop HCC. However, the appropriate interval for screening of liver function is unknown.

A long duration after the Fontan procedure (>20 years) is one of the risk factors for LC, and hyaluronic acid and γ-guanosine triphosphate (γ-GTP) have been reported to be useful markers to evaluate the progression of liver fibrosis in patients undergoing the Fontan procedure. The aim of the present study was to clarify the prevalence of LC and/or HCC after the Fontan procedure and to elucidate...
Table 1. Characteristics of the 17 Patients With LC and/or HCC After the Fontan Procedure

<table>
<thead>
<tr>
<th></th>
<th>LC</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1st diagnosis (years)</td>
<td>23 (13–34)</td>
<td>31 (22–44)</td>
</tr>
<tr>
<td>Age at 1st Fontan procedure* (years)</td>
<td>8.2 (1–15)</td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis from the 1st Fontan procedure (years)</td>
<td>14.5 (5–24)</td>
<td>21.6 (7–31)</td>
</tr>
</tbody>
</table>

Primary congenital heart disease diagnoses (n)

- Tricuspid atresia: 6
- Complete atrioventricular septal defects: 3
- Complete corrected transposition of the great arteries: 3
- Others: 6

Hepatitis virus infection (n)

- HBV: 0
- HCV: 3

Mean NYHA heart failure classification (n=16): 2.1

NYHA heart failure classes (n)

- Class I: 3
- Class II: 9
- Class III: 4

SpO2 (%; n=16): 88±6

Other Fontan procedure-related complications (n)

- Atrial tachyarrhythmia: 10
- PAVFs: 4
- Venovenous collateral: 4
- Protein losing enteropathy: 1

Data are given as the median (interquartile range), number of patients, or as the mean±SD. Of the 17 patients with liver cirrhosis (LC) and/or hepatocellular carcinoma (HCC), 12 had LC, 2 had HCC, and 3 had LC+HCC. *Ten patients had a 2nd operation (8 undergoing total cavopulmonary connection conversion). HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association; PAVF, pulmonary arteriovenous fistula; SpO2, peripheral oxygen saturation.

specific clinical manifestations of FALD.

Methods

Study Design and Study Subjects

This study comprised 2 nationwide surveys in Japan conducted by the Research Committee of Japanese Society of Pediatric Cardiology and Cardiac Surgery (JPCCS). The 1st survey was conducted in 2008 and the 2nd survey was conducted in 2009.

LC is defined as an irreversible condition of liver dysfunction due to long-term damage. HCC is a cancerous state diagnosed by a doctor with imaging modalities or biopsy.

In the 1st survey, questionnaires were sent to 175 facilities belonging to the JPCCS. The questionnaires contained 3 questions: (1) the number of patients undergoing the Fontan procedure; (2) the number of patients undergoing the Fontan procedure diagnosed with or suspected of LC and/or HCC; and (3) whether routine diagnostic imaging for liver dysfunction was performed and, if so, what imaging modalities were used?

In the 2nd survey, questionnaires were sent to the facilities where patients with LC and/or HCC after the Fontan procedure were followed-up. These questionnaires contained 7 questions: (1) basic diagnosis of congenital heart disease (CHD); (2) history of cardiac surgery; (3) history of viral hepatitis infections; (4) date and method of diagnosis and treatment of liver disease; (5) laboratory data, including blood tests, echocardiography, and heart catheterization; (6) performance status, as per the New York Heart Association (NYHA) heart failure classification, and cardiac function; and (7) outcome or death.

Statistical Analysis

Unless stated otherwise, data are expressed as the mean±SD or as percentages. All statistical analyses were performed using SPSS version 22 for Windows (IBM, New York, NY, USA). However, because the study involved a nationwide survey, no comparison analysis was conducted.

Ethical Considerations

In the present study, we adhered to the principles of the Declaration of Helsinki. All surveys were collected as anonymized data, and no personal information was identified. The study protocol was approved by the Ethics Committee of Chiba Cardiovascular Center and St. Luke’s International Hospital.

Results

The 1st Survey

Effective answers were received from 97 of 175 institutes (55%). Of these 97 institutes, 72 were registered and followed-up 2,700 patients who underwent the Fontan procedure. Of these 2,700 patients, 31 (1.15%) were diagnosed with LC and/or HCC, and 5 patients died due to liver diseases (mortality: 0.19%). Of the 72 institutes conducting routine diagnostic imaging to detect liver dysfunction, 17 (24%) used ultrasound, 9 (13%) used computed tomography (CT), and 4 (6%) used magnetic resonance imaging (MRI). In institutes using one or more imaging modalities, all methods were counted.

The 2nd Survey

Seventeen patients had LC and/or HCC after the Fontan procedure: 12 had LC, 2 had HCC, and 3 had LC+HCC. The mean (range) age at first diagnosis of LC and HCC was 23 (13–34) and 31 (22–44) years, respectively. The mean (range) age at the first Fontan procedure was 8.2 (1–15) years. The mean (range) period from the first Fontan procedure until the diagnosis of LC and/or HCC was 14.5 (5–24) and 21.6 (7–31) years, respectively. Ten patients had Fontan conversion (8 with total cavopulmonary connection [TCPC] conversion and 2 with no detailed information regarding the method of Fontan conversion). The primary diagnosis revealed CHD with cases of tricuspid atresia (n=6), complete atrioventricular septal defects (n=3), congenital corrected transposition of the great arteries (n=2), and others (n=6). There were 3 patients who were positive for hepatic virus C (HCV) infection: 1 was HCV-RNA negative, and 1 had a history of interferon treatment. Only 1 patient with HCV had HCC and was alive. The other patients with LC and/or HCC after the
Liver Disease After the Fontan Procedure

Characteristics and examination results for the 5 patients with HCC are given in Table 4.

Discussion

In 2014, 397 Fontan procedures were performed in Japan. We can estimate that the number of Fontan procedures over a recent 10-year period is approximately 400/year. The present study covered a 10-year period, and therefore this nationwide survey covered approximately 60% of patients undergoing the Fontan procedure in Japan. From...
KUWABARA M et al.

Table 4. Detailed Characteristics of 5 Cases With HCC After the Fontan Procedure

A. Patients’ characteristics

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Age at 1st Fontan procedure (years)</th>
<th>Age at 1st diagnosis of HCC (years)</th>
<th>Time from 1st Fontan procedure to 1st diagnosis of HCC (years)</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>5</td>
<td>22</td>
<td>17</td>
<td>Negative</td>
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<tr>
<td>2</td>
<td>41</td>
<td>9</td>
<td>39</td>
<td>29</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>22</td>
<td>15</td>
<td>22</td>
<td>7</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>29 (death)</td>
<td>5</td>
<td>29</td>
<td>24</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>43 (death)</td>
<td>12</td>
<td>42</td>
<td>31</td>
<td>Negative</td>
<td>Negative</td>
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</table>

B. Results of heart catheterization

<table>
<thead>
<tr>
<th>Case no.</th>
<th>CVP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>Cardiac index (L/min/m²)</th>
<th>EDP (mmHg)</th>
<th>SaO₂ (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>17</td>
<td>3.2</td>
<td>9</td>
<td>95</td>
</tr>
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<td>2</td>
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<td>3</td>
<td>19</td>
<td>19</td>
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<tr>
<td>4</td>
<td>21</td>
<td>21</td>
<td>3.1</td>
<td>14</td>
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<tr>
<td>5</td>
<td>13</td>
<td>13</td>
<td>–</td>
<td>12</td>
<td>–</td>
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C. Blood test results

<table>
<thead>
<tr>
<th>Case no.</th>
<th>WBC (×10⁹/L)</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>Platelet (×10⁹/L)</th>
<th>TP (g/dL)</th>
<th>Albumin (g/dL)</th>
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<tr>
<td>1</td>
<td>4.02</td>
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<tr>
<td>2</td>
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<td>73</td>
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<td>4.20</td>
<td>15.1</td>
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<td>4</td>
<td>3.82</td>
<td>13</td>
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<td>102</td>
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<td>5.00</td>
<td>13.2</td>
<td>40.2</td>
<td>162</td>
<td>7.2</td>
<td>4.3</td>
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</table>

*Warfarin usage. –, missing data; CT, computed tomography; γ-GTP, γ-glutamyltransferase; PAP, pulmonary artery pressure; SaO₂, arterial oxygen saturation; TAE, transcatheter arterial embolization. Other abbreviations as in Tables 1–3.

(this viewpoint, the primary finding of the present cross-sectional study was that the prevalence of HCC was estimated to be 0.18%, and the mortality of HCC was as high as 40% among patients undergoing the Fontan procedure. Moreover, more than 1% of patients who underwent the Fontan procedure had LC and/or HCC. Blood tests confirmed low platelet, increased hemoglobin, γ-GTP, and total bilirubin, and an elevated PT-INR. However, these blood tests were not sufficient to confirm the diagnosis of LC and/or HCC. These results suggest that hepatic imaging modalities are essential for the detection of liver disease in patients undergoing the Fontan procedure. Previous studies showed that LC may develop into HCC in 1.5–5.0% of cases per year, and the prevalence of HCC in our study population could increase in the future.

The main causes of HCC are HCV infection (70–75%) and hepatitis B virus infection (15%). The prevalence of HCC after the Fontan procedure was lower (0.18%) than that from HCV infection. If 40-year-old patients infected with HCV do not receive treatment for over 30 years, it is estimated that approximately 20–25% will have HCC. In the present study, the mortality of HCC after the Fontan procedure was high (40%). However, treatment for HCC after the Fontan procedure has not been established, and further studies are required.

The mechanisms of FALD are different from those of LC and HCC caused due to hepatitis virus infection or fatty liver. Low cardiac output in CHD decreases the hepatic blood supply, which induces a hepatic hypoxic state and results in damage in Zone 3 of the liver. Damaged hepatocytes induce fibrosis, which leads to LC. Moreover, the follow-up of patients undergoing the Fontan procedure revealed that the systemic venous pressure was 3- to 4-fold higher than normal, which leads to chronically elevated right atrial pressure, which, in turn, increases hepatic vein pressure. Increased hepatic vein pressure is also a cause of FALD. A recent study confirmed that time after the Fontan procedure was the only factor significantly associated with collagen deposition, which suggested that liver fibrosis was an inherent feature of Fontan physiology. However, no inflammation or hepatocellular damage was evident in patients undergoing the Fontan procedure, suggesting that fibrosis may be mediated by a non-inflammatory mechanism.

We could not determine the most reliable marker for the detection of liver disease in patients undergoing the Fontan procedure in the present study. However, although the mean ALT level was within the normal range, the mean AST level was higher than the normal range, suggesting that the AST/ALT ratio may be a suitable marker to detect liver disease in patients undergoing the Fontan procedure. Moreover, we should pay attention to low platelet counts, increased hemoglobin, γ-GTP, and total bilirubin, and elevated PT-INR. These laboratory data may indicate liver disease in patients undergoing the Fontan procedure.

In the present study, the mortality of liver diseases in patients who underwent the Fontan procedure was very low (5/2,700; 0.19%). However, the mortality was nearly
Liver Disease After the Fontan Procedure

Conclusions

LC and/or HCC in patients undergoing the Fontan procedure were not rare late complications. The mortality of liver diseases in these patients was only 0.19%, but if the patients had LC and/or HCC, the mortality increased to nearly 30%. Liver disease was a primary cause of death in 17.6% of the patients. Imaging modalities, especially CT, should be recommended owing to the difficulty in diagnosing LC and HCC using blood tests only. Further studies are required to establish accurate diagnostic methods for LC and/or HCC and to clarify the risk factors for liver disease and mortality in patients undergoing the Fontan procedure.

Acknowledgments

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Liver Disease After the Fontan Procedure

30% after patients were diagnosed with LC and/or HCC. TCPC conversion for patients with LC could be an extreme risk for death because 2 such patients died during the perioperative period (11.8%) in the present study. Death due directly to liver disease occurred in 17.6% of the patients. Our results suggest that patients with LC and HCC after the Fontan procedure are at high risk of mortality. However, viral HCC and LC alone may not be associated with high mortality. We should pay attention to emerging HCC in patients with LC.

Study Limitations

First, although we show detailed characteristics of the 5 patients with HCC in Table 4, the diagnosis of HCC in patients undergoing the Fontan procedure was difficult because these patients often show hyperenhancing nodules.3 A 7-year-old girl who underwent the Fontan procedure was diagnosed with hepatic adenomatosis based on MRI and MRI-guided liver biopsy,22 which suggests that the diagnosis of HCC is very difficult. Most patients with HCC did not undergo biopsy owing to the risk of bleeding, and it is a limitation of the present study that these patients may not have been accurately diagnosed with HCC. Second, the present study used questionnaire-based surveys, which could be inaccurate. The questionnaires used in the present study focused primarily on adult patients, but some pediatric patients were also included. Third, some patients who underwent the Fontan procedure were not followed-up because some pediatricians could not follow-up patients continuously after they were 16 or 18 years of age, so the prevalence of LC and/or HCC (1.15%) in the present study could be underestimated. In addition, not all patients were examined for liver disease using imaging modalities. However, the findings of the present study indicate that the number of patients with LC and/or HCC after the Fontan procedure is not small.

<table>
<thead>
<tr>
<th>Diagnostic methods</th>
<th>CT, echo</th>
<th>TAE, chemotherapy</th>
</tr>
</thead>
<tbody>
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<td>CT, echo</td>
<td>TAE</td>
<td>No indication</td>
</tr>
<tr>
<td>CT, echo, biopsy</td>
<td>TAE, chemotherapy</td>
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</table>

<table>
<thead>
<tr>
<th>BNP (pg/mL)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>Y-GTP (U/L)</th>
<th>T-Bil (mg/dL)</th>
<th>D-Bil (mg/dL)</th>
<th>BUN (mg/dL)</th>
<th>Cre (mg/dL)</th>
<th>PT-INR</th>
</tr>
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<tbody>
<tr>
<td>34</td>
<td>26</td>
<td>41</td>
<td>148</td>
<td>2.6</td>
<td>–</td>
<td>12.6</td>
<td>0.9</td>
<td>1.2</td>
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<td>206</td>
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<td>1.35</td>
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<td>46.3</td>
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<td>86</td>
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<td>55</td>
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<td>0.7</td>
<td>11</td>
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<td>404</td>
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<td>0.2</td>
<td>19</td>
<td>0.7</td>
<td>1.96*</td>
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Nosaka (National Center for Children Health and Development); Eiichi Kohda and Tsutomu Saji (Toho University); Arata Murakami (Tokyo University); Makoto Nakazawa (Minami Tohoku Hospital); Shigeyuki Echigo (Echigo Clinic); Kisaburo Sakamoto (Shizuoka Children’s Hospital); Takuya Ueda (St. Luke’s International Hospital); and Hideshi Yamamura and Mikiko Shimizu (Tokyo Women’s Medical University).

Sources of Funding / Disclosures

None.

References


