Introduction

Type 2 diabetes mellitus (DM) consists of impaired insulin secretion and/or resistance and therefore causes hyperglycemia. Patients who have liver disease often have concurrent insulin resistance. DM is known to cause complications such as cardiovascular disease, neuropathy, retinopathy and chronic renal failure (1). Furthermore, the number of patients with DM is markedly increasing every year (2). Indeed, the International Diabetes Federation reported that there were 387 million patients with DM worldwide in 2014 and that this number may increase to 592 million by 2035 (3). DM is also a known risk factor for

Original Article

High HbA1c is a risk factor for complications after hepatectomy and influences for hepatocellular carcinoma without HBV and HCV infection

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Background: Currently, the population with type 2 diabetes mellitus (DM) is increasing worldwide. However, the influence of DM or hyperglycemia on the outcome of resected hepatocellular carcinoma (HCC) is unclear.

Methods: We analyzed 756 patients with HCC who underwent hepatectomy. These patients were assigned to an HbA1c ≥7.0% (H-A1c; n=100) or HbA1c <7.0% (L-A1c; n=656) group depending on their HbA1c level at admission. We investigated prognoses, clinicopathological characteristics and surgical outcomes including morbidities of HCC patients with high HbA1c, prognoses according to the treatment for DM were also investigated.

Results: Among all patients and those with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, overall survival (OS) and relapse-free survival (RFS) did not differ significantly between the H-A1c and L-A1c groups. In contrast, the five-year OS rate of the H-A1c group was 55% and that of the L-A1c group 71% among patients without HBV and HCV (NBNC patients) (P=0.03). Among NBNC patients, the median RFS of the H-A1c group was 13 months, and that of the L-A1c group was 26 months (P=0.02). In addition, metformin use was an independent favorable factor for both OS and RFS. The H-A1c group had significantly higher rates of hyperbilirubinemia, wound infection, and pneumonia.

Conclusions: HCC patients with high HbA1c might have poor prognoses for both survival and recurrence in NBNC-HCC. High HbA1c may also be a risk factor for morbidities after hepatectomy. Metformin use may constitute a good option for NBNC patients with HCC.

Keywords: Hepatocellular carcinoma (HCC); HbA1c; diabetes mellitus (DM); hepatectomy; metformin

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malignancies, such as pancreatic cancer, lung cancer, colon cancer, and hepatocellular carcinoma (HCC) (2,4,5).

Hyperinsulinemia contributes to hepatocarcinogenesis via cell division and proliferation (6,7). Niwa et al. reported that hyperinsulinemia is more strongly related to HCC development than to high blood glucose (8).

Treatment for DM, such as metformin and sodium glucose cotransporter 2 (SGLT2), has been reported to inhibit HCC (9,10).

Hemoglobin A1c (HbA1c) is a biomarker of blood glucose levels over the previous 3 months and is an indicator of diabetes control. However, the impact of HbA1c on the prognosis of resected HCC remains controversial.

Thus, in our current study, we investigated the prognoses and clinicopathological characteristics of HCC patients with high HbA1c levels. We also investigated the surgical outcomes and morbidities of these patients.

Methods

Between January 2001 and December 2018, 771 consecutive patients with HCC underwent primary liver resection at the Gastroenterological Surgery I Unit of the Hokkaido University Hospital in Sapporo, Japan. As we excluded 15 cases with both hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, we analyzed 756 cases.

For stratification, we assigned patients to an HbA1c ≥7.0% group (H-A1c; n=100, 100/756, 13.2%) or an HbA1c <7.0% group (L-A1c; n=656, 656/756, 86.8%) depending on their HbA1c at admission. The Japan Diabetes Society recommends maintaining HbA1c <7.0% to prevent complications (11); thus, we chose an HbA1c of 7 as the cutoff.

We compared prognoses for survival, recurrence, clinicopathological characteristics, surgical outcomes and morbidities between the H-A1c and L-A1c groups. In addition, we evaluated the impact of treatment for DM on the prognoses of HCC patients without HBV and HCV (NBNC-HCC patients). HBV included patients with HBV infection alone, HCV included patients with HCV infection alone, and NBNC included patients without HBV and HCV infection.

The indications for hepatic resection and the type of operative procedures were usually determined based on the patients’ liver function reserve, i.e., the results of the indocyanine green retention test at 15 min (ICGR15) (12). Anatomical resection, defined as a resection in which the lesions were completely removed anatomically on the basis of Couinaud’s classification (segmentectomy, sectionectomy, and hemihepatectomy or more), was performed on patients in whom ICGR15 was lower than 25%. Non-anatomical partial but complete resection was achieved in other cases. For all patients, surgery was performed in which the resection surfaces were found to be histologically and macroscopically free of HCC. Follow-up analyses after liver resection were conducted at 3-month intervals, including physical, serological [liver function test, serum alpha-fetoprotein (AFP) level, and serum protein induced by vitamin K absence-II (PIVKA-II)], and radiological [ultrasound sonography (US) and contrast-enhanced computed tomography (CT) scan or contrast-enhanced magnetic resonance imaging (MRI)] examinations. Recurrence was diagnosed on the basis of the results of contrast-enhanced CT and elevation of serum levels of AFP and/or PIVKA-II. Extrahepatic metastasis (lung, lymph node, adrenal gland, brain, and bone) was diagnosed by contrast-enhanced chest and abdominal CT, contrast-enhanced head MRI, and bone scintigram. The median follow-up period was 32 months (range, 1.0-172 months).

Postoperative morbidity was assessed using the validated classification system by Clavien-Dindo (13). Serious complications were categorized as grades III-V and defined as morbidity requiring surgical or radiological intervention. This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee and was performed in accordance with the Helsinki Declaration guidelines.

Statistical analysis

The clinicopathological characteristics of the H-A1c group were compared with those of the L-A1c group. Univariate analyses between two groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test for noncontinuous variables. Multivariate analyses were performed using logistic regression model analysis. Overall survival (OS) and relapse-free survival (RFS) were determined via the Kaplan-Meier method and analyzed with the log-rank test or Cox proportional hazard model. Statistical analyses were performed using JMP Pro 14.0.0 for Windows (SAS Institute, Cary, NC, USA). Significance was defined as a P value of <0.05.

Results

Clinicopathological characteristics of the patients

The NBNC patients with HCC had larger tumor sizes
and relatively better liver function than the other patients; in addition, a larger proportion of these patients were undergoing treatment for DM with metformin or other oral drugs (Table 1). In this study, patients using insulin only or insulin combined with other oral drugs except for metformin were defined as the insulin group. Patients using metformin only or metformin combined with other oral drugs were defined as the metformin group. Patients using other oral drugs with neither insulin nor metformin were defined as the other group.

**HbA1c and prognoses in HCC patients in relation to HBV, HCV, and NBNC status**

The five-year OS rates and median survival times (MSTs) of all cases were 65% and 94 months, respectively. The median RFS time was 20 months. Specifically, the underlying liver condition was as follows: 267 cases of HBV, 203 cases of

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**Table 1** Clinicopathological characteristics of the patients in this study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=756)</th>
<th>HBV (n=267)</th>
<th>HCV (n=203)</th>
<th>NBNC (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex male:female</td>
<td>629:127</td>
<td>222:45</td>
<td>153:50</td>
<td>254:32</td>
</tr>
<tr>
<td><strong>Biochemical factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (10^4/mm³)</td>
<td>17.5±10.6</td>
<td>16.4±6.5</td>
<td>15.8±7.0</td>
<td>20.3±14.6</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0±0.4</td>
<td>4.1±0.4</td>
<td>4.0±0.4</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>PT (%)</td>
<td>92.5±14.2</td>
<td>90.0±12.8</td>
<td>92.6±13.8</td>
<td>94.6±16.9</td>
</tr>
<tr>
<td>ChE (IU/L)</td>
<td>253±81</td>
<td>261±79</td>
<td>237±72</td>
<td>261±86</td>
</tr>
<tr>
<td>ICGR15 (%)</td>
<td>16.1±10.6</td>
<td>15.4±10.3</td>
<td>17.2±10.2</td>
<td>15.1±8.9</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>14.9 (1.0–5,986,980)</td>
<td>32.9 (1.7–5,986,980)</td>
<td>19.3 (1.0–471,725)</td>
<td>7.7 (1.0–186,518)</td>
</tr>
<tr>
<td>PIVKA-II (mAU/mL)</td>
<td>187 (2.3–928,799)</td>
<td>222 (6.0–664,680)</td>
<td>74 (8.0–245,630)</td>
<td>333 (2.3–928,799)</td>
</tr>
<tr>
<td><strong>Tumor factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>5.8±4.5</td>
<td>6.1±4.4</td>
<td>4.3±3.1</td>
<td>6.8±4.5</td>
</tr>
<tr>
<td>Tumor number: multiple</td>
<td>273 (36%)</td>
<td>112 (42%)</td>
<td>82 (40%)</td>
<td>79 (28%)</td>
</tr>
<tr>
<td>Except simple nodular type</td>
<td>428 (57%)</td>
<td>171 (64%)</td>
<td>95 (47%)</td>
<td>162 (57%)</td>
</tr>
<tr>
<td><strong>Histological factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vp positive</td>
<td>192 (25%)</td>
<td>88 (33%)</td>
<td>32 (16%)</td>
<td>72 (25%)</td>
</tr>
<tr>
<td>vv positive</td>
<td>85 (11%)</td>
<td>34 (13%)</td>
<td>12 (6%)</td>
<td>39 (14%)</td>
</tr>
<tr>
<td>Differentiation: poor</td>
<td>322 (43%)</td>
<td>131 (49%)</td>
<td>89 (44%)</td>
<td>102 (36%)</td>
</tr>
<tr>
<td>Fibrosis F3/F4</td>
<td>325 (43%)</td>
<td>148 (55%)</td>
<td>110 (54%)</td>
<td>67 (23%)</td>
</tr>
<tr>
<td><strong>Treatment for DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>524 (69%)</td>
<td>233 (87%)</td>
<td>134 (66%)</td>
<td>157 (55%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>53 (7%)</td>
<td>11 (4%)</td>
<td>18 (9%)</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>Metformin</td>
<td>67 (9%)</td>
<td>9 (3%)</td>
<td>18 (9%)</td>
<td>40 (14%)</td>
</tr>
<tr>
<td>Others</td>
<td>112 (15%)</td>
<td>14 (5%)</td>
<td>33 (16%)</td>
<td>65 (23%)</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, NonBNonC; PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; vp, portal venous invasion; vv, hepatic venous invasion; DM, diabetes mellitus.
HCV, and 286 cases of NBNC.

Among all cases, the five-year OS rates of the H-A1c and L-A1c groups were 65% vs. 65% (P=0.51). For the HBV, HCV, and NBNC groups, the five-year OS rates of the H-A1c and L-A1c groups were 70% vs. 63% (P=0.78), 48% vs. 66% (P=0.37), and 55% vs. 71% (P=0.03), respectively (Figure 1).

Regarding recurrence, the median RFS time of the H-A1c and L-A1c groups was 16 vs. 21 months (P=0.28) in all cases. In patients with HBV, HCV, and NBNC, the median RFS times of the H-A1c and L-A1c groups were 13 vs. 16 months (P=0.34), 28 vs. 25 months (P=0.62), and 13 vs. 26 months (P=0.02), respectively (Figure 2).

Although both OS and RFS were not significantly different for all cases, HBV cases, and HCV cases, the rates for those in the H-A1c group were significantly more unfavorable in NBNC patients with HCC.

**Clinicopathological features of the H-A1c group among NBNC patients with HCC**

Table 2 presents the clinicopathological characteristics of the H-A1c and the L-A1c groups of NBNC patients with HCC determined by univariate analyses. No factor except treatment for DM differed between the two groups.

**Univariate and multivariate analyses of OS and RFS among NBNC patients with HCC**

Table 3 shows the factors found to influence the OS and RFS in the NBNC cases. Univariate analysis revealed that OS was significantly related to the following: HbA1c ≥7.0%; prothrombin time (PT) <80%; cholinesterase (ChE) <250 IU/L; albumin (Alb) <3.5 g/dL; AFP ≥20 ng/mL; PIVKA-II ≥100 mAU/mL; tumor size ≥5 cm; multiple tumors, except the simple nodular type; poor differentiation; portal venous invasion (vp); hepatic venous invasion (vv); and lack of metformin use. These analyses also indicated that RFS was significantly related to HbA1c ≥7.0%, PT <80%, ChE <250 IU/L, Alb <3.5 g/dL, AFP ≥20 ng/mL, PIVKA-II ≥100 mAU/mL, tumor size ≥5 cm, multiple tumors, except the simple nodular type, poor differentiation, vp, vv, insulin use, and lack of metformin use. Multivariate
analysis indicated that ChE <250 IU/L, tumor size ≥5 cm, multiple tumors, vp, and lack of metformin use were independent unfavorable prognostic factors for OS and that PT <80%, ChE <250 IU/L, tumor size ≥5 cm, multiple tumors, vp, vv, insulin use, and lack of metformin use were independent unfavorable prognostic factors for RFS among the patients with NBNC-HCC. HbA1c ≥7.0% was not an independent significant factor for OS or RFS based on multivariate analysis.

**Prognoses based on treatment for DM in NBNC patients with HCC**

Figure 3 shows OS and RFS depending on the treatment for DM.

According to univariate analysis, the patients treated with insulin had significantly poorer RFS rates than the patients treated without insulin (P=0.01) (Table 3); OS was not significantly different. Additionally, the patients treated with metformin showed significantly favorable OS and RFS rates compared with those treated without metformin (P=0.01 and <0.01, respectively). Metformin use was an independent favorable factor for both OS and RFS, whereas insulin use was an independent unfavorable factor for RFS (Table 3). Significant differences were not observed for OS and RFS in patients treated with sulfonylurea (SU), α-glucosidase inhibitor (α-GI), thiazolidine (TZD), and dipeptidyl
peptidase 4 inhibitor (DPP-4i).

**Surgical outcome and morbidities in all cases**

The 30-day and 90-day mortalities of the H-A1c group were 0%; those of the L-A1c group were 0% and 0.1%, respectively. The complications of the patients in the H-A1c group included pleural effusion (5.0%), ascites (7.0%), postoperative bleeding (4.0%), bile leakage (7.0%), hyperbilirubinemia (7.0%), wound infection (4.0%), pneumonia (5.0%), and ileus (2.0%). The complications of the patients in the L-A1c group included pleural effusion (32.0%), ascites (24.0%), postoperative bleeding (22.0%), bile leakage (24.0%), hyperbilirubinemia (18.0%), wound infection (8.0%), pneumonia (10.0%), and ileus (8.0%).
The H-A1c group showed significantly higher rates of hyperbilirubinemia ($P=0.02$), wound infection ($P=0.03$), and pneumonia ($P=0.02$). Other complications did not differ significantly. The median postoperative stay times were 15 [3–297] and 15 [5–380] days ($P=0.80$) for the H-A1c and L-A1c groups, respectively.

The median blood loss was 355 [0–20,190] mL and the median operative time 312 [121–612] minutes in patients with H-A1c; these values were 375 [0–35,820] mL and 312 [78–911] minutes, respectively, for the L-A1c patients. There were no significant differences between the H-A1c and L-A1c groups (Table 4).

**Discussion**

The results of our univariate analysis indicate that high HbA1c is a significantly unfavorable factor for survival and recurrence in NBNC patients with HCC. However, there were no differences between patients with HBV or HCV. In this cohort of NBNC patients, those treated with insulin showed significantly poorer RFS than those treated without insulin. Conversely, the patients treated with metformin showed significantly favorable OS and RFS rates compared

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**Table 4** Surgical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>H-A1c (n=100)</th>
<th>L-A1c (n=656)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median blood loss [range] in mL</td>
<td>355 [0–20,190]</td>
<td>375 [0–35,820]</td>
<td>0.44</td>
</tr>
<tr>
<td>Median operative time [range] in minutes</td>
<td>312 [121–612]</td>
<td>312 [78–911]</td>
<td>0.99</td>
</tr>
<tr>
<td>Postoperative stay time</td>
<td>15 [3–297]</td>
<td>15 [5–380]</td>
<td>0.80</td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>5 (5.0%)</td>
<td>32 (4.9%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ascites</td>
<td>7 (7.0%)</td>
<td>24 (3.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>4 (4.0%)</td>
<td>22 (3.4%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Bile leakage</td>
<td>7 (7.0%)</td>
<td>42 (6.4%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>7 (7.0%)</td>
<td>18 (2.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4 (4.0%)</td>
<td>8 (1.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (5.0%)</td>
<td>10 (1.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ileus</td>
<td>2 (2.0%)</td>
<td>8 (1.2%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>–</td>
</tr>
<tr>
<td>90-day</td>
<td>0 (0%)</td>
<td>1 (0.2%)</td>
<td>–</td>
</tr>
</tbody>
</table>
with the patients treated without metformin. Regarding postoperative morbidities, there were significantly higher rates of hyperbilirubinemia, wound infection, and pneumonia in the H-A1c group than in the L-A1c group.

Type 2 DM is known as a risk factor for several malignancies (2,4,5). In particular, there have been many reports showing a correlation between type 2 DM and HCC. Li et al. reported that DM was associated with an increased risk for HCC in HCV patients (14), and DM was found to be a risk factor for HCC in patients with HCV who had mild (not severe) fibrosis and a sustained virologic response (15). Huang et al. also reported that metabolic risk factors such as fatty liver, high triglyceride levels and a history of DM are significantly associated with NBNC-HCC (16).

In a meta-analysis, Wang et al. found that DM was independently associated with poorer survival and recurrence in HCC (17), whereas Howell et al. reported that DM did not negatively impact the prognosis of HCC (18). Whether DM is a prognostic factor for resected HCC remains controversial. In this study, high HbA1c was a significantly unfavorable factor for survival and recurrence in NBNC-HCC, as based on univariate analysis. However, it was not an independent factor according to multivariate analysis. Shau et al. reported that DM is an independent factor for poorer prognosis in patients who received curative therapy for HCC, such as surgery or ablation, but these authors did not mention recurrence (19). Additionally, Wang et al. showed that DM did not significantly affect the disease-free survival of patients with HCC after curative hepatectomy but that DM was associated with significantly lower OS (20). Our study showed no significant difference in OS and RFS among all cases. This discrepancy may be due to the status of the hepatitis virus (HBV and HCV) infection. These studies, including ours, included different proportions of HBV, HCV, and NBNC cohorts. Kawamura et al. reported that DM is a significant predictor of tumor recurrence after curative therapy for HCC in patients with nonviral hepatitis (21), consistent with the findings in our study. He et al. also indicated that the HbA1c-based score model can be used to predict death risk in patients with HCC and type 2 DM (22). Among patients with nonalcoholic fatty liver disease (NAFLD), insulin resistance influences inflammation, from which HCC may develop (23). Thus, high HbA1c might more strongly influence the prognosis of patients with NBNC-HCC than those with viral hepatitis.

Exogenous insulin is thought to promote oncogenesis by increasing insulin-like growth factor 1 (IGF-1) activity. A meta-analysis by Singh et al. showed that the use of insulin was associated with a statistically significant (161%) increase in the risk of HCC (24). Regarding the mechanism of DM development in HCC, several studies have advocated that hyperinsulinemia contributes to hepatocarcinogenesis via cell division and proliferation (6,7). Insulin promotes the phosphorylation of insulin receptor substrate-1 (IRS-1) and transmission of the insulin signal through the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cascades (6), possibly leading to abnormal cell proliferation and metabolism (25). Nonetheless, it remains unclear how those factors can affect HCC after curative therapy. Zheng et al. revealed that the activation of AMPK by metformin inhibits NF-kB and STAT3 signaling and thus suppresses HCC cell growth (26). Additionally, metformin is able to inhibit HCC cell growth by regulating cell-cycle regulatory proteins, such as cyclin D1 and cyclin E. Metformin may also inhibit c-myc expression by upregulating the let-7 family (27). Some researchers have reported that metformin might reduce the risk of recurrence or cancer-related mortality after curative resection of HCC (28,29). Tseng et al. also reported that metformin was associated with a reduced risk of HCC, depending on the cumulative duration of use (30). In the present study, the use of insulin had an unfavorable impact on recurrence, though the use of metformin had a favorable impact on both recurrence and survival. Thus, we might consider the use of metformin for patients with NBNC-HCC after hepatectomy.

Lee et al. reported that DM was a risk factor for major complications after hepatectomy (31), yet their study did not show the details of these complications. A meta-analysis by Li et al. revealed no significant difference in total complications after hepatectomy between patients with DM and those without DM, but liver failure, ascites, and postoperative infection were significantly higher in patients with DM (32). In line with these findings, in the present study, there was no significant difference in total complications after hepatectomy, whereas the rates of hyperbilirubinemia, wound infection, and pneumonia were significantly higher in the H-A1c group than in the L-A1c group. Patients with DM are susceptible to infection (33), and the higher rates of wound infection and pneumonia appear to be reasonable findings. DM has been suggested to exacerbate existing liver fibrosis, resulting in severe liver failure via increased expression of connective tissue growth factor or the production of reactive oxygen species (20).
Thus, hyperbilirubinemia might be highly prevalent in the H-A1c group. However, there are some limitations of this study, which was a completely retrospective study. The number of H-A1c patients was also low compared with the total number of patients.

**Conclusions**

High HbA1c alone may not be an independent prognostic factor for HCC. Maintaining goal blood glucose levels over the 3 months prior to surgery might be favorable for the prognosis of NBNC patients with HCC, and metformin might be a beneficial drug for patients with HCC after hepatectomy. In addition, high HbA1c may be a risk factor for morbidities after hepatectomy.

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**Footnote**

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee and was performed in accordance with the Helsinki Declaration guidelines.

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