TABLE 4. Risk Factors for 6-Month Graft Mortality After LDLT: A Univariate Analysis

Variable	Graft Survival (%) 1 Month	3 Months	6 Months	*P* Value
Recipients				
Age				NS
≥60 years (n = 70)	95.7	95.7	92.5	
<60 years (n = 147)	98.6	96.6	95.1	
Sex				NS
Male (n = 96)	99.0	97.9	94.6	
Female (n = 121)	96.7	94.9	94.1	
Etiology				NS
FHF (n = 22)	95.2	95.2	95.2	
Other (n = 195)	97.9	96.4	94.2	
Admission on foot				NS
Yes (n = 29)	96.6	93.0	88.9	
No (n = 188)	97.9	96.8	95.1	
BMI				<0.001
≥30 kg/m^2 (n = 7)	57.1	57.1	57.1	
<30 kg/m^2 (n = 210)	99.0	97.6	95.5	
Diabetes mellitus				NS
Yes (n = 29)	96.6	93.0	88.9	
No (n = 188)	97.9	96.8	95.1	
Splenectomy				NS
No (n = 34)	97.1	94.0	94.0	
Yes (n = 183)	97.8	96.1	94.4	
Portal pressure				NS
≥20 mm Hg (n = 27)	92.6	88.9	88.9	
<20 mm Hg (n = 190)	98.4	97.3	95.0	
Enteral nutrition				NS
No (n = 14)	100	92.9	92.9	
Yes (n = 203)	97.5	96.5	94.4	
Donors/grafts				
Sex				NS
Male (n = 138)	97.1	94.9	92.6	
Female (n = 79)	98.7	98.7	97.4	
Graft type				NS
Left and caudate lobes (n = 126)	98.4	95.9	94.2	
Other (n = 91)	96.7	96.7	94.4	
Donor-recipient matching				
ABO-incompatible				NS
Yes (n = 17)	100	100	100	
No (n = 200)	97.5	96.0	93.8	
Consanguinity				0.066
No (n = 45)	93.3	91.1	88.8	
Yes (n = 172)	98.8	97.6	95.7	
Predictive score				<0.001
<1.15 (n = 18)	83.3	77.8	71.8	
≥1.15 (n = 199)	99.0	97.9	96.3	

(Table 4). An absence of consanguinity had a *P* value 0.066 according to the univariate analysis. A multivariate analysis that included these variables showed that a predictive score < 1.15 (odds ratio = 7.87, $P = 0.006$) and a BMI ≥ 30 kg/m^2 (odds ratio = 13.3, $P = 0.0003$) were independent risk factors for 6-month graft mortality after LDLT (Table 5).

DISCUSSION

Predictive scores calculated with our proposed formula have proved to be extremely useful for predicting the probability of 6-month graft survival. A crucial feature of this formula is that it uses variables that can be obtained before LDLT. Using data from technetium-99m galactosyl human serum albumin liver scintigraphy, we previously set the cutoff value at 1.30.[4] When the preoperatively calculated score was ≥1.15, the 6-month graft survival rate was 96.3% in this study. This rate was better than our previously reported rate,[4] probably because of the introduction of simultaneous splenectomy[5] and early enteral nutrition[14] and because of changes attributable to the greater experience that we have amassed since our

TABLE 5. Risk Factors for Graft Mortality After LDLT: A Multivariate Analysis

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Predictive score < 1.15: yes versus no	7.87	1.81-34.5	0.006
BMI ≥ 30 kg/m^2: yes versus no	13.3	3.32-55.6	<0.001
Consanguinity: no versus yes	1.25	0.29-5.40	0.76

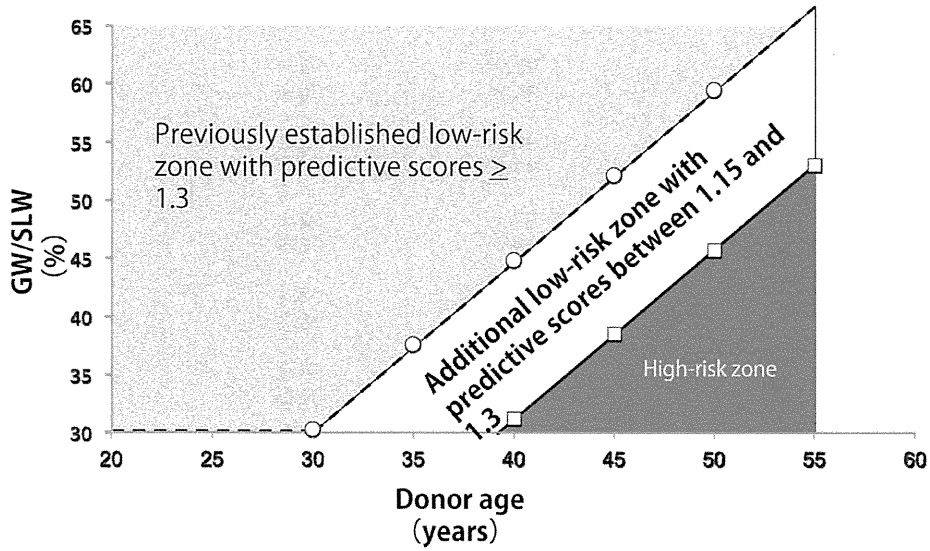

Figure 2. Representative scheme for selecting grafts. For a patient with a MELD score of 20 and a huge portosystemic shunt, a partial hepatic graft with a 45% GW/SLW ratio from a ≤40-year-old donor is needed to achieve a predictive score ≥ 1.30 (light gray space). A 35% GW/SLW ratio with a 40-year-old donor is enough to achieve a score ≥ 1.15 (white space). Our present treatment strategy, which includes simultaneous splenectomy and enteral nutrition, has widened the safety range for donor ages and graft sizes.

previous report. Splenectomy is routinely performed at our center for patients undergoing LDLT, but this is not standard in most of the world; this practice has a potential influence on our outcomes and predictive scores. Some hold the reservation that splenectomy during liver transplantation is closely associated with septic complications and a poorer prognosis.[22,23] However, the incidence of septic complications in the present study did not differ significantly from the incidence in our previous study (data not shown). We have previously speculated that because whole grafts have a greater liver mass than partial liver grafts, the former may not lead to excessive portal vein flow into the graft. It has been suggested that splenectomy during whole liver graft transplantation may lead to insufficient portal flow, which would induce hepatic atrophy and liver failure.[5] Such inadequate portal flow might lead to septic complications. Improvements in posttransplant care, such as enteral nutrition, may also have contributed to a decrease in the occurrence of sepsis in our study.

A predictive score < 1.15 is an independent risk factor for 6-month graft mortality. MELD scores and/or the presence of a huge portosystemic shunt cannot be easily changed, whereas the graft size (ie, graft type; particularly left lobe versus right lobe) is modifiable and can be selected on the basis of the patient's condition. For example, when a patient's MELD score is 20 and the patient has a huge portosystemic shunt, a partial hepatic graft with a 45% GW/SLW ratio from a ≤40-year-old donor is needed to achieve a predictive score ≥ 1.30 (Fig. 2). Indeed, a 35% GW/SLW ratio from a 40-year-old donor is enough to achieve a score ≥ 1.15. Furthermore, we should consider that the risk of using an older donor is ameliorated by a larger graft, which is likely to leave the donor with a small remnant; this is not the best for an older patient.

Some may object that according to the formula, the presence of a shunt negatively affects the prognosis. The presence of shunts may be very protective against the occurrence of SFSG syndrome. Furthermore, several published reports have described the salvage of small grafts with portosystemic shunts.[24,25] Another report recommends not touching already existent portosystemic shunts.[26] Our basic strategy when we perform LDLT is to close any shunts whenever possible to obtain adequate portal flow.[27] Huge patent shunts

often steal portal flow, and decreases in portal flow beyond a certain point negatively affect graft function. Thus, it makes sense that the presence of shunts negatively affects the outcome. The need to close portosystemic shunts may be created by removal of the spleen. A loss of splenic vein flow may increase the fraction of portal blood flow that leaves the portal system via the portosystemic shunt.

Another new finding in this study is that our modified predictive score is applicable to FHF. We excluded patients with FHF from the previous study[4] because their predictive scores did not correlate with their prognosis. When we started the LDLT program, FHF was the leading indication for adult LDLT. In the early phase of our program, 3 cases of hepatic artery thrombosis that led to graft loss occurred in patients with FHF. Our predictive formula works only with constant use of the same technique because a major vascular or biliary complication leads to a poor prognosis. We excluded 2 cases of apparent technical failure (excessive intraoperative bleeding) from this study. We also excluded 2 cases of irreversible brain damage, which definitely adversely influences the prognosis and can occur after untimely transplantation for FHF.

The recipient BMI was one of the independent risk factors for 6-month graft survival. Therefore, a recipient BMI ≥ 30 kg/m^2 is a contraindication to LDLT regardless of the predictive score. Whether obesity affects short-term survival after liver transplantation remains controversial.[28,29] It is possible that obese patients have more postoperative complications than nonobese patients and that this contributes to their poorer outcomes. Furthermore, the expression of adipokines reportedly increases in obese patients because adipose tissue induces their expression, and this leads to an accumulation of inflammatory cytokines.[30] A recent report has suggested that obesity has a proinflammatory effect on adipose tissue macrophages and enhances the secretion of tumor necrosis factor α and interleukin-6.[31] Further study is needed to clarify the role of adipose tissue in inflammation in obese patients.

In conclusion, predictive scores calculated with our formula, which incorporates the graft size, donor age, MELD score, and portosystemic shunt status, reliably predict 6-month graft survival. Furthermore, our treatment strategy has widened the safety range for donor ages and graft sizes.

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Decreased immunoglobulin G levels after living-donor liver transplantation is a risk factor for bacterial infection and sepsis

T. Yoshizumi, K. Shirabe, T. Ikegami, N. Yamashita, Y. Mano, S. Yoshiya, R. Matono, N. Harimoto, H. Uchiyama, T. Toshima, Y. Maehara. Decreased immunoglobulin G levels after living-donor liver transplantation is a risk factor for bacterial infection and sepsis. Transpl Infect Dis 2014: **16**: 225–231. All rights reserved

Abstract: *Background.* Several studies have suggested an association between post-transplant immunoglobulin (Ig) levels and the development of infection in solid organ transplantation. We therefore conducted exploratory analyses of potential factors associated with bacterial infection/sepsis after living-donor liver transplantation (LDLT).
Methods. Blood samples from 177 recipients who received primary LDLT between September 1999 and November 2011 were available for study. Hypogammaglobulinemia was defined as having at least 1 IgG level <650 mg/dL within 7 days after LDLT. Risk factors for developing post-transplant bacterial infection and sepsis within 3 months after LDLT were analyzed.
Results. Fifty (28.2%) recipients experienced bacterial infection within 3 months of LDLT. Eighty-four (47.5%) recipients had hypogammaglobulinemia, although no recipients had hypogammaglobulinemia before LDLT. Hypogammaglobulinemia, undergoing hepaticojejunostomy, and portal pressure at closure >15 mmHg were independent risk factors for developing bacterial infection within 3 months of LDLT ($P < 0.0001$ $P = 0.0008$, and $P = 0.011$, respectively). The odds ratio (OR) and confidence interval (CI) for hypogammaglobulinemia were 4.79 and 2.27–10.7, respectively. Twenty-four (13.6%) recipients developed bacterial sepsis within 3 months. Hypogammaglobulinemia, operative time >14 h, model for end-stage liver disease score >15, and no mycophenolate mofetil use were independent risk factors for developing bacterial sepsis ($P = 0.009$, $P = 0.001$, $P = 0.003$, and $P = 0.005$, respectively). The OR and CI for hypogammaglobulinemia were 3.83 and 1.38–12.0, respectively.
Conclusions. Hypogammaglobulinemia within 7 days of LDLT was a significant risk factor for post-transplant bacterial infection and sepsis.

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Key words: living-donor liver transplantation; hypogammaglobulinemia; sepsis

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Immunoglobulin G (IgG) is synthesized by B cells, and IgG levels are elevated in patients with liver cirrhosis as a non-specific response to bacteremia, increased Ig production, or portal systemic shunting. Increased numbers of plasma cells in the bone marrow and liver may be the source of increased IgG (1). Previous studies suggested an association between post-transplant Ig levels and the development of infection in solid organ transplantation (2, 3). Most studies focused on cytomegalovirus or opportunistic infection at a relatively late term after organ transplantation (4, 5). However, very few studies have focused on bacterial

Abbreviations: CI, confidence interval; CT, computed tomography; CyA, cyclosporine; FHF, fulminant hepatic failure; GW, graft weight; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; LDLT, living-donor liver transplantation; LL+C, left lobe with caudate lobe; LT, liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; OR, odds ratio; POD, postoperative day; SFS, small-for-size; SLW, standard liver weight.

sepsis and Ig levels in the early phase after liver transplantation (LT). Following the release of a report in 1994 that demonstrated successful living-donor liver transplantation (LDLT) between adults, living donors have been increasingly used because of the disparity between demand and supply of deceased donors (6). However, to our knowledge, no published reports have described the incidence and impact of IgG levels before and after LDLT. The small graft size is the main disadvantage of adult-to-adult LDLT, because it results in increased portal venous pressure, impaired bowel motility, bacterial translocation, ascites production, and hyperbilirubinemia, although it does not necessarily lead to graft loss (7). Recently, we reported the impact of bacterial sepsis on the survival of patients who received LDLT (8). Intraoperative blood loss >10 L and no enteral feeding started within 48 h after LDLT were independent risk factors for bacterial sepsis. No data for IgG levels have been reported. Therefore, we retrospectively analyzed IgG levels from stored blood specimens in an effort to assess whether a decreased IgG level (hypogammaglobulinemia) was an independent risk factor for developing bacterial infection and sepsis after LDLT. The aim of this study was to explore the impact of decreased IgG levels on developing bacterial infection and sepsis after LDLT.

Study design

We conducted exploratory analyses of potential factors associated with bacterial infection and sepsis after LDLT. Stored samples from 177 recipients who received primary LDLT between September 1999 and November 2011 were available and were used in the study. IgG levels and potential factors associated with infection and sepsis, such as operative time, blood loss, model for end-stage liver disease (MELD) score, and graft weight (GW), were retrospectively collected from the database and analyzed.

Patients and methods

Patients

Graft types included left lobe with caudate lobe (LL+C) graft (n = 100), right lobe graft without the middle hepatic vein (n = 73), and posterior segment graft (n = 4). The etiology of liver cirrhosis was hepatitis C (n = 88), primary biliary cirrhosis (n = 22), fulminant hepatic failure (FHF, n = 16), hepatitis B (n = 17), alcohol abuse (n = 9), cryptogenic (n = 8), primary sclerosing cholangitis (n = 6), autoimmune hepatitis (n = 5), Wilson's disease (n = 2), biliary atresia (n = 1), Alagille syndrome (n = 1), hemangioma (n = 1), and epithelioid hemangio endothelioma (n = 1) (Table 1). ABO incompatible cases who received exogenous intravenous Ig (IVIG) to prevent humoral rejection (9) were excluded. Serum samples were collected before LDLT, on postoperative day (POD) 1, POD 3, and POD 7, and were used for IgG measurement.

Donor and graft selection

Donors were selected from candidates who volunteered to be living donors (6, 10). Donors were required to be within the third degree of consanguinity with recipients or spouses, and to be between 20 and 65 years of age. For a donor who was not within the third degree of consanguinity, individual approval was obtained from the Ethics Committee of Kyushu University Hospital. Altruistic donations were not used.

Eligible donors underwent imaging studies, including chest and abdominal x-rays and 3-mm-slice computed tomography (CT) scans for graft volumetric analysis. Three-dimensional CT was introduced for volumetric analysis and delineation of vascular anatomy. The standard liver weight (SLW) of recipients was calculated according to the formula of Urata et al. (11). GW was predicted by CT volumetric analysis. Decisions regarding graft type for recipients were based on the preoperatively predicted GW-to-SLW ratio. LL+C graft was used when the preoperatively predicted GW-to-SLW ratio was >35%. When GW-to-SLW ratio with LL+C graft was <35% and remnant donor liver volume after right lobectomy was >35%, a right lobe graft was used. Posterior segment graft was considered when the donor's vascular anatomy was suitable to accept a posterior segment. We previously reported a formula (7), which consisted of GW-to-SLW ratio, MELD score, donor age, and the presence of huge portcaval shunt, to predict early graft function. This formula was not fully used to select the graft type during this study.

Surgery and postoperative management

The graft retrieval technique, recipient surgery, and perioperative management of the recipients, including immunosuppression regimens were described previously (12). Simultaneous splenectomy was performed in 95 recipients for decreasing portal vein pressure or for improving pancytopenia (13). Five recipients

Risk factors for developing infection within 3 months after living-donor liver transplantation (LDLT): univariate analysis

Variables	Total (n = 177)	Infection within 3 months		P-value
		Yes (n = 50)	No (n = 127)	
Recipient				
Gender (Male/Female, %)	49.7/50.3	48.0/52.0	50.4/49.6	0.77
Age (years)	53.7 ± 10.8	52.9 ± 11.4	54.0 ± 10.5	0.57
Etiology				
Postnecrotic cirrhosis (%)	127 (71.8)	35 (70.0)	92 (72.5)	0.56
Cholestatic cirrhosis (%)	30 (16.9)	10 (20.0)	20 (15.7)	
Fulminant hepatic failure (%)	16 (9.0)	3 (6.0)	13 (10.2)	
Others (%)	4 (2.3)	2 (4.0)	2 (1.6)	
IgG pre-LDLT	2316 ± 823	2356 ± 840	2230 ± 820	0.68
IgG on POD 1	820 ± 331	731 ± 265	855 ± 348	0.023
IgG on POD 3	856 ± 350	784 ± 333	884 ± 354	0.087
IgG on POD 7	781 ± 327	687 ± 251	818 ± 346	0.020
Hypogammaglobulinemia (Yes/No, %)	47.5/52.5	72.0/28.0	37.8/62.2	<0.0001
MELD score	14.4 ± 7.1	15.4 ± 7.7	14.0 ± 6.9	0.26
Pre-LDLT ICU bound (Yes/No, %)	10.2/89.8	12.0/88.0	9.4/90.6	0.61
Diabetes mellitus (Yes/No, %)	16.9/83.1	18.0/82.0	16.5/83.5	0.82
Operative time >14 h (Yes/No, %)	31.6/68.4	46.0/54.0	26.0/74.0	0.009
Operative blood loss >10 L (Yes/No, %)	8.5/91.5	18.0/82.0	4.7/95.3	0.005
Biliary reconstruction (D-D/H-J, %)	88.1/11.9	74.0/26.0	93.7/6.3	0.0003
Splenectomy (Yes/No, %)	58.8/41.2	54.0/46.0	60.6/39.4	0.42
Portal pressure at closure (mmHg) >15 (Yes/No, %)	56.5/43.5	72.0/28.0	50.4/49.6	0.009
CNI (TAC/CyA/None, %)	55.9/42.9/1.2	56.0/40.0/4.0	55.9/44.1/0	0.77
MMF use (Yes/No, %)	81.9/10.1	78.0/22.0	83.5/16.5	0.40
Enteral nutrition started within 48 h (Yes/No, %)	51.4/48.6	44.0/56.0	54.3/45.7	0.22
Donor				
Gender (Male/Female, %)	66.1/33.9	74.0/26.0	63.0/37.0	0.16
Age (years)	35.2 ± 10.9	36.1 ± 11.8	34.8 ± 10.5	0.49
Graft (Left/Right/Posterior, %)	56.5/41.2/2.3	62.0/34.0/4.0	54.3/44.1/1.6	0.33
GW-to-SLW ratio (%)	41.5 ± 8.2	41.1 ± 7.8	41.6 ± 8.3	0.74
ABO (identical/compatible/incompatible)	71.8/22.6/5.6	78.0/20.0/2.0	69.3/23.6/7.1	0.33

IgG, immunoglobulin G; POD, postoperative day; MELD, model for end-stage liver disease; ICU, intensive care unit; D-D/H-J, duct-to-duct/hepaticojejunostomy; CNI, calcineurin inhibitor; TAC, tacrolimus; CyA, cyclosporine; MMF, mycophenolate mofetil; GW, graft weight; SLW, standard liver weight.

Table 1

underwent splenectomy before LDLT. Since 2001, duct-to-duct anastomosis has been preferred to Roux-en-Y hepaticojejunostomy for bile duct reconstruction (14). Hepaticojejunostomy was performed when duct-to-duct anastomosis could not be applied, such as in those with biliary atresia or primary sclerosing cholangitis. Duct-to-duct or hepaticojejunostomy was performed over a 2.0-mm C-tube with intermittent 6-0 PDS-II sutures (8, 14). Perioperative anti-microbial prophylaxis consisted of IV cefotaxime (4 g/day) and ampicillin sulbactam (6 g/day) 4 times/day for 3 days after LDLT, and was started 30 min before surgery. Once bacterial sepsis was clinically suspected, broad-spectrum antibiotics were administered empirically (8). IVIG was not

exogenously infused until the development of sepsis. Immunosuppression was initiated using a protocol based on either tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine (CyA) (Neoral; Novartis Pharma K.K., Tokyo, Japan) with steroids. Tacrolimus was used in 108 recipients, and CyA in 90 recipients. Two recipients did not receive calcineurin inhibitors owing to poor postoperative course. A target trough level of tacrolimus was set at 10 ng/mL for 3 months after LDLT, followed by 5–10 ng/mL thereafter. A target trough level of CyA was set at 250 ng/mL for 3 months after LDLT, followed by 150–200 ng/mL thereafter. Methylprednisolone was initiated on the day of LDLT, tapered, and converted to prednisolone 7 days after LDLT. Prednisolone treatment was tapered and discontinued 6 months after LDLT. Mycophenolate mofetil (MMF) was used in 145 recipients and was started at 1 g/day on the day after LDLT, tapered, and discontinued until 6 months after LDLT. A trough level was not measured for MMF. All patients had monthly follow-ups, and the median follow-up period was 1491 days, with 700 days and 2345 days as the 25th and 75th percentiles, respectively.

Post-LDLT infection and bacterial sepsis

Incidence of bacterial sepsis was set as the primary end-point. Bacterial sepsis was defined as the isolation of bacteria other than common skin contaminants from a single blood culture within 3 months after LDLT, along with clinical symptoms, including high fever, shivering, dyspnea, altered mental status, tachycardia, or hypotension (8). Infections included pneumonia, cholangitis, peritonitis, urinary tract infection, and wound infection. Pneumonia was defined as the isolation of bacteria from cultured sputum accompanied by radiological infiltration. Cholangitis was defined when patients had clinical symptoms including high fever, right upper quadrant pain, and elevated serum biliary enzymes. Peritonitis was defined as the isolation of bacteria from ascites culture and clinical symptoms including abdominal pain and fever. The definition of urinary tract infection was the isolation of bacteria from urine culture, along with urodynia or pollakiuria. Wound infection was defined as the isolation of bacteria from culture of effusion from skin redness.

Statistical analysis

Hypogammaglobulinemia was defined as having at least 1 IgG level <650 mg/dL (15) within 7 days after LDLT. Data were expressed as means ± standard deviation. Logistic regression analysis was applied to the multivariate analyses. Variables that were used for the univariate analysis included recipient age, donor age, GW-to-SLW ratio, MELD score, the presence of diabetes mellitus, recipient gender, donor gender, Intensive Care Unit stay before LDLT, serum IgG level before and after LDLT, blood loss during LDLT, bile duct reconstruction method, graft type, tacrolimus or CyA use, and MMF use. Multiple logistic regression analysis was performed with selected predictors by a stepwise procedure from variables with a P-value <0.10 by univariate analysis. The significance levels for the procedure were 0.05, to add variables into the method, and 0.08, to keep variables in the model. All statistical analyses were performed using JMP 9.0 software (SAS, Inc., Cary, North Carolina, USA).

Results

In this study, 50 (28.2%) recipients experienced bacterial infection after LDLT. Table 1 shows the characteristics of the recipients and donors. Mean serum IgG levels of pre-LDLT, POD 1, POD 3, and POD 7 were 2316 ± 823, 820 ± 331, 856 ± 350, and 781 ± 327, respectively. Serum IgG levels at POD 1, POD 3, or POD 7 were significantly lower compared with that of pre-LDLT ($P < 0.0001$). Serum IgG levels of pre-LDLT in patients with cirrhosis (2393 ± 727) were significantly higher than in patients with FHF (1469 ± 327, $P < 0.0001$). Serum levels of IgG at POD 1, POD 3, or POD 7 were not different between recipients with cirrhosis and recipients with FHF. Finally, 84 (47.5%) recipients developed hypogammaglobulinemia within 7 days after LDLT, although no recipients had hypogammaglobulinemia before transplantation. Risk factors for developing hypogammaglobulinemia were a preoperative value of IgG ($P = 0.002$), operative bleeding ($P = 0.003$), and operative time ($P = 0.002$). Mean operative bleeding in recipients with hypogammaglobulinemia was significantly greater compared with recipients without hypogammaglobulinemia (5525 mL vs. 3618 mL). Recipients with hypogammaglobulinemia had a longer operative time compared with recipients without hypogammaglobulinemia (832 min vs. 755 min). Univariate analysis revealed that recipients who experienced bacterial infection within 3 months after LDLT developed hypogammaglobulinemia, had an operative time >14 h, had more operative blood loss, were more likely to have received hepaticojejunostomy for biliary reconstruction, and had high portal venous pressure at the end of LDLT (Table 1).

Risk factors for developing infection within 3 months after living-donor liver transplantation: multivariate analysis

Variables	Odds ratio	95% CI	*P*-value
Hypogammaglobulinemia	4.79	2.27–10.7	<0.0001
Hepaticojejunostomy	5.81	2.06–17.7	0.0008
Portal vein pressure at closure >15 mmHg	2.63	1.24–5.85	0.011

CI, confidence interval.

Table 2

The selected variables as predictors in the model by a stepwise procedure were hypogammaglobulinemia, receiving hepaticojejunostomy, and portal pressure at closure >15 mmHg. Multivariate logistic regression analysis revealed that hypogammaglobulinemia (odds ratio [OR]; 4.79, $P < 0.0001$), receiving hepaticojejunostomy (OR; 5.81, $P = 0.0008$), and portal pressure at closure >15 mmHg (OR; 2.63, $P = 0.011$) were independent risk factors for developing bacterial infection within 3 months after LDLT in this study (Table 2).

Twenty-four (13.6%) recipients developed bacterial sepsis within 3 months after LDLT. The mean onset day was POD 16 (range 4–84 days).

Univariate analysis revealed that hypogammaglobulinemia, receiving hepaticojejunostomy, portal pressure at closure >15 mmHg, MELD score >15, operative time >14 h, operative blood loss >10 L, and no MMF use were risk factors for developing bacterial sepsis within 3 months after LDLT ($P = 0.004$, $P = 0.005$, $P = 0.049$, $P = 0.025$, $P = 0.0005$, $P = 0.002$, and $P = 0.037$, respectively) (Table 3). The selected variables as predictors in the model by a stepwise procedure were hypogammaglobulinemia, operative time >14 h, MELD score >15, and no MMF use. Multivariate analysis revealed that hypogammaglobulinemia (OR; 3.83, $P = 0.009$), an operative time >14 h (OR; 5.17, $P = 0.001$), MELD score >15 (OR; 5.67, $P = 0.003$), and no MMF use (OR; 5.49, $P = 0.005$) were independent risk factors for developing bacterial sepsis within 3 months after LDLT (Table 4).

Discussion

This is the first report to our knowledge to identify a correlation between serum IgG levels and bacterial sepsis development after LDLT. Multivariate analysis revealed that hypogammaglobulinemia within 7 days after LDLT was an independent risk factor for developing bacterial sepsis, which caused higher mortality rates. Data from this study demonstrated that 6-month survival in patients who developed bacterial sepsis within 3 months ($n = 24$) was significantly worse than in patients who did not develop sepsis ($n = 153$, $P < 0.0001$, data not shown). Monitoring IgG levels may aid in clinical management of LDLT recipients (3). The present study suggested that IgG levels dramatically decreased during surgery. Patients with liver failure can develop major coagulation abnormalities, splenomegaly, portal hypertension, and nutritional deficiencies can result in associated thrombocytopenia (16). Such coagulopathy sometimes causes massive bleeding during LT and can cause longer surgery time. Thus, recipients with hypogammaglobulinemia had more operative bleeding and longer operative times compared with recipients without hypogammaglobulinemia. This suggested that IgG levels were reduced during surgery, as well as after surgery owing to increased capillary permeability and increased catabolism.

This study had some limitations including the use of stored samples. In addition, IgG concentrations were not measured at the onset of sepsis. Furthermore, we divided septic recipients according to the presence of hypogammaglobulinemia within 7 days after LDLT, but no significant difference was seen in any variables between patients with hypogammaglobulinemia and patients without hypogammaglobulinemia. This result may have been because of the small number of patients in both groups (data not shown). In addition, samples were only obtained from half of the patients in the study. These concerns might lead to a potential bias. Further additional studies are required to explain these concerns fully.

Hypogammaglobulinemia had a negative impact on the development of infections in patients undergoing heart (5) or lung (17) transplantation. Size mismatch is a major obstacle in LDLT between adults, and small-for-size (SFS) graft syndrome after LDLT remains a major complication of the procedure. Most surgeons believe that SFS graft syndrome can induce postoperative hyperbilirubinemia, intractable ascites, and prolonged coagulopathy, which ultimately lead to septic complication and liver failure (7, 13). Polyclonal IVIG can modulate the host immune response and may improve outcomes in patients who develop septic shock (15). IVIG can neutralize endotoxins, limit the production of cytokines, increase serum bactericidal activity, and block the complement cascade (18, 19). IVIG has been administered to various categories of patients regardless of their baseline IgG levels. This approach carries the possibility of using IVIG in patients with normal

Risk factors for developing sepsis within 3 months after living-donor liver transplantation (LDLT): univariate analysis

Variables	Sepsis within 3 months		
	Yes (n = 24)	No (n = 153)	P-value
Recipient			
Gender (Male/Female, %)	41.7/58.3	51.0/49.0	0.40
Age >55 years (Yes/No, %)	66.7/33.3	77.1/22.9	0.27
Etiology			
Postnecrotic cirrhosis (%)	16 (66.7)	111 (72.5)	0.20
Cholestatic cirrhosis (%)	4 (16.7)	26 (17.0)	
Fulminant hepatic failure (%)	2 (8.3)	14 (9.2)	
Others (%)	2 (8.3)	2 (8.3)	
Hypogammaglobulinemia (Yes/No, %)	75.0/25.0	43.1/56.7	0.004
MELD score >15 (Yes/No, %)	37.5/62.5	17.6/83.3	0.025
Pre-LDLT ICU bound (Yes/No, %)	20.8/79.2	8.5/91.5	0.063
Diabetes mellitus (Yes/No, %)	16.7/83.3	17.0/83.0	0.97
Operative time >14 h (Yes/No, %)	62.5/37.5	26.8/73.2	0.0005
Operative blood loss >10 L (Yes/No, %)	25.0/75.0	5.9/94.1	0.002
Biliary reconstruction (D-D/H-J, %)	70.8/29.2	90.8/9.2	0.005
Splenectomy (Yes/No, %)	54.2/45.8	59.5/40.5	0.62
Portal pressure at closure >15 mmHg (Yes/No, %)	75.0/25.0	53.6/46.4	0.049
CNI (TAC/CyA/None, %)	66.7/25.0/8.3	54.2/45.8/0	0.102
MMF use (Yes/No, %)	66.7/33.3	84.3/15.7	0.037
Enteral nutrition started within 48 h (Yes/No, %)	37.5/62.5	53.6/46.4	0.14
Donor			
Gender (Male/Female, %)	75.0/25.0	64.7/35.3	0.32
Age >45 years (Yes/No, %)	37.5/62.5	21.6/78.4	0.088
Graft (Left/Right/Posterior, %)	54.2/37.5/8.3	56.9/41.8/1.3	0.098
GW-to-SLW ratio >40% (Yes/No, %)	66.7/33.3	49.0/51.0	0.11
ABO (identical/compatible/incompatible, %)	79.2/20.8/0	70.6/22.9/6.5	0.40

MELD, model for end-stage liver disease; ICU, intensive care unit; D-D/H-J, duct-to-duct/hepaticojejunostomy; CNI, calcineurin inhibitor; TAC, tacrolimus; CyA, cyclosporine; MMF, mycophenolate mofetil; GW, graft weight; SLW, standard liver weight.

Table 3

IgG levels who would not benefit from a further increase in plasma IgG concentrations. Monitoring IgG level could help to select recipients that have developed sepsis who might benefit from IVIG administration. A preemptive use of IVIG replacement may serve as a new strategy for managing LDLT recipients with hypogammaglobulinemia. Thus, a prospective study is necessary to evaluate the impact of IVIG on recipients with hypogammaglobulinemia after LDLT.

Splenectomy did not cause hypogammaglobulinemia, infection, or sepsis in this study. Previous studies suggested that splenectomy in liver transplantation is closely associated with septic complications and a poorer prognosis, because the spleen is a huge source of B cells (20, 21). Splenectomy is commonly performed at our medical center, as we reported favorable outcomes of splenectomy for overcoming SFS graft syndrome in LDLT recipients (13, 22). IgG levels in recipients a long time after LDLT with splenectomy may decrease compared with recipients who did not undergo the procedure. Further immunological studies are required to determine how splenectomy affects the incidence of hypogammaglobulinemia in liver transplantation.

Risk factors for developing sepsis within 3 months after living-donor liver transplantation: multivariate analysis

Variables	Odds ratio	95% CI	*P*-value
Hypogammaglobulinemia	3.83	1.38–12.0	0.009
Operative time >14 h	5.17	1.94–14.9	0.001
MELD score >15	5.67	1.86–18.2	0.003
No MMF use	5.49	1.71–18.3	0.005

CI, confidence interval; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

Table 4

In conclusion, nearly half of the recipients in this study developed hypogammaglobulinemia within 7 days after LDLT. Hypogammaglobulinemia was a risk factor for post-transplant infection and sepsis. A prospective study in LDLT is necessary to evaluate the impact of IVIG for recipients with hypogammaglobulinemia after LDLT.

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Conflict of interest: The authors declare no conflict of interest.

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14(IX)-49 脳死ドナー多臓器摘出手術の教育に向けた 3DCGによるeラーニングコンテンツの構築

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E-learning contents using 3DCG animations for surgical education of multi-organ harvesting from brain-dead donor

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Abstract: As the number of organs harvested from brain-dead donors increase, there is an urgent need to educate surgeons. It is difficult to create teaching material for multi-organ transplantations because observing the surgical process is difficult as the transplantations are performed rapidly by a large number of surgical staff. Furthermore, the video recording of surgeries presents ethical concerns. Therefore, to create an educational program for multi-organ transplantations from brain-dead donors, the authors developed an e-learning content prototype using 3D computer graphics (3DCG) animation. The 3DCG animation focused on visually representing the coordination between each surgeon's hand movements. Transplant surgeons evaluated this prototype content. The evaluations by the surgeons indicated that a more detailed visual expression of the 3DCG animation is needed for the representation of surgical techniques and cooperation between each surgeon.
Keywords: Multi organ harvesting, Brain-dead donor, e-Learning

1. 序論

2010年に改正臓器移植法が実施されてから，脳死ドナーからの臓器提供件数が急速に増加してきた[1]（**Fig. 1**）．脳死下における臓器提供は，良好な状態で複数の臓器を提供できることから，重要性が高い．そのため，臓器の提供および移植を行う医療体制の確立が求められている．特に日本においては，1ドナーから多くの臓器を摘出することが多く，難度の高い多臓器摘出手術を行える医師の教育が急務となっている．

多臓器摘出手術の教育においては，通常の外科手術とは異なり，多人数の手術となるため供覧による教育が困難である．さらに，ビデオ撮影による手技の記録についても，死の過程を記録しているとも受け取れるため，倫理的な問題が存在する．仮に撮影が可能だとしても，術野が深部にある，迅速な手技が求められるため動作の記録が難しい，といったことから映像での記録は大きな困難を伴う．ブタなどの大動物を用いたシミュレーションによる教育も行われるが，コストがかかることが問題となる．

こうした問題に対して本研究では，3次元コンピュータグラフィクス(3DCG)アニメーションによる多臓器同時摘出手術手技の教育コンテンツ構築を目指し，3DCGアニメーションの制作とeラーニングコンテンツの試作を行った．

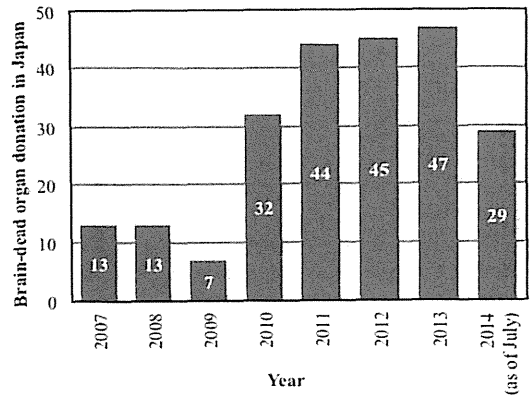

Figure 1 Number of brain-dead organ donation in Japan from 2007 to 2014[1]

2. 医学教育におけるeラーニング

医学教育分野におけるeラーニングについての取り組みとしては，国内にもいくつか事例が散見される[2][3]．海外においては，特に先進的な取り組みとしてE-learning MOD procurement surgeryが例に挙げられる[4]．オランダでは，このeラーニング受講と，指導医のもとでの執刀経験，ドナー手術トレーニングコースの終了によって技術認定を受けることができるなど，公式の教育システムとしてeラーニングが組み込まれている．

本研究でのｅラーニングコンテンツの試作にあたっては，上記のオランダの事例を参考とした．具体的には，Web 上におけるページ単位に適した手術手技の手順説明の分割や，使用する映像メディアの選定などの検討を行った．

検討から，アニメーションによるビジュアル表現を多用することや，手技の構成を教材に合わせて分割することが重要であると考えられた．

3. 3DCG アニメーションによる教材制作

多臓器摘出手術の手技理解のために最適なビジュアル表現の一つとして，3DCG を選択した．コンテンツを試作するにあたり，肝単独摘出，肝膵同時摘出の術式を対象とした．

3DCG 作成にあたっては，術式過程を医師の作業毎にシーケンスという単位で分類した．術式における一つのシーケンスは，複数の動作によって遂行されるため，医師による一つの動作をステップと定義して分類した．

これらの情報を元に3DCGアニメーションの作成を行った．臓器と手のモデルの形状や大きさ，色調，他臓器との位置関係など，医師の確認を得ながらクリエータが修正を加えていった．特に複数の術者が協調して行う動作などの表現については，それぞれの立場での学習が行われることを考慮し，各助手の位置関係や手の方向などを再現に注力した（**Fig. 2**）．

一方で，細かい手の動作の再現については，医師も普段意識せずに行っている動作も多く，簡略化した表現となる場面も多く存在した．

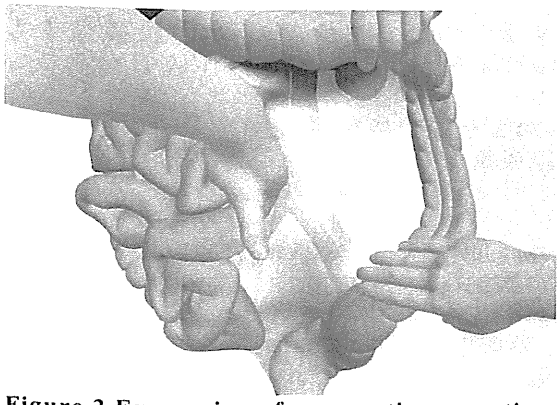

Figure 2 Expression of cooperation operation

4. ｅラーニングコンテンツの試作

上記 3DCG をｅラーニングコンテンツとして閲覧できるテストサイト（**Fig. 3**）を制作し，実際に Web 上で試験公開した．制作にあたっては，一般のｅラーニングサイトの構成を参考にし，レイアウトや機能の選定を行った．

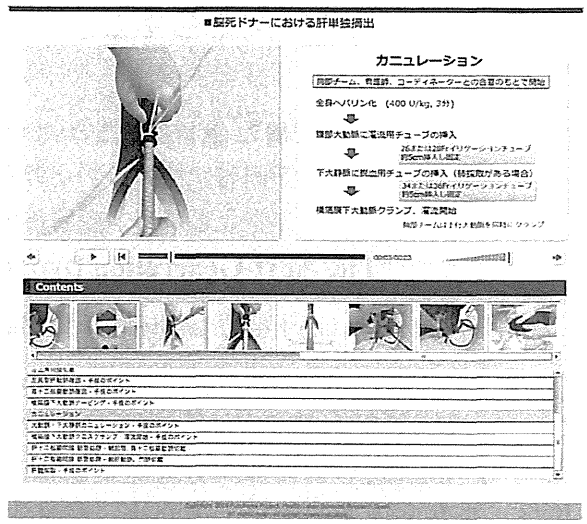

Figure 3 Prototype of e-learning content

5. 評価と考察

実際に移植手術の執刀を行った経験のある医師に試作したサイトの閲覧を求め，教材としての構成について意見を収集した．その結果，音声による説明とアニメーションとの同期が，内容の理解に有効であるとの意見が得られた．

3DCG アニメーションの制作において得られた知見として，場の展開をはじめ，普段は意識せずに行っている手術の動作が，実際には非常に複雑なパターンの組み合わせで構成されていることが明らかになった．このような医師のスキルを，3DCG アニメーションにより分かりやすく可視化することで，手技の習得を越えて，動作の最適化といった，より高度なノウハウの習得にも活用が期待されると考えられる．

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文献

1) 日本臓器移植ネットワークホームページ
http://www.jotnw.or.jp/index.html
2) 日本消化器外科学会 e教育講座
http://www.jsgs.or.jp/el/
3)国際協力型がん臨床指導者養成拠点　がんプロ全国e-learning クラウドについて
http://kanto-kokusai-ganpro.md.tsukuba.ac.jp/gnavi-catei d-2/gaiyo002
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https://www.mod-surgery.org/website/

日本膵・膵島移植研究会

Japanese Pancreas and Islet Transplantation Association

福島県立医科大学臓器再生外科　後藤 満一、斎藤 拓朗、穴澤 貴行

インスリン分泌能が廃絶した糖尿病患者の日常生活に、著しい障害を来す血糖不安定性からの解放を目指し、血糖感受性にインスリン分泌を可能にする治療として、膵臓移植と膵島移植という移植医療が位置づけられている。これらの移植に関する諸問題の研究とその進歩を目的に活動している日本膵・膵島移植研究会（http://plaza.umin.ac.jp/~jpita/）は、1982年に発足した膵移植談話会から発展し、1995年に設立された。以後、年に一度の学術集会、年に2回の各種会議を開催し、基礎的研究のみならず臨床における膵・膵島移植の実施と成績向上に向けて、学術的検討を重ねてきた。これまで、4名の歴代会長のもと（表1）、表2に示すような活動成果をあげている。膵臓移植あるいは膵島移植の適応となるインスリン依存状態糖尿病患者への移植医療は、単一な専門診療科のみの対応では不十分で、専門診療科を越えた医師の連携や、移植コーディネーターおよびナースの協力が不可欠である。このため会員は、外科医、内科医、小児科医、病理医、基礎研究者、移植コーディネーター、ナースなど、膵・膵島移植のレシピエント、ドナー、コーディネーションにかかわる多くの職種で構成されており、2014年1月現在、施設会員数55施設、会員数219名を有する。

本邦の膵臓移植は、1984年の膵・腎同時移植実施により幕を開けたが、その後は脳死状態からの提供による移植が困難で、しばらくは心停止ドナーからの膵臓移植が行われた。その成績は欧米と比して必ずしも良好とは言えず、脳死下提供による膵臓移植の実施が望まれていた。1997年に臓器移植法が制定され、臓器移植に関する環境が大きく変化したことを受けて、本研究会に加え、日本移植学会・日本糖尿病学会・日本腎臓学会より委員を選出した膵臓移植特別委員会を発足させ、適応基準や移植施設の選定を担うこととした。この委員会は1999年に膵臓移植中央調整委員会（http://www.ptccc.jp/）へと発展し、1999年10月に「膵臓移植に関する実施要綱」[1]を発刊し、本邦での実施体制を整備した。2000年に臓器移植法施行後本邦初の膵腎同時移植[2]が行われ、その後、2010年の改正臓器移植法施行を経て、現在は年間数十例の脳死臓器提供があり、本格的に脳死膵臓移植が行われている。2014年1月現在、全国で17施設が膵臓移植実施施設として認められている。膵臓移植実施のためには、レシピエント候補者の主治医が地域の膵臓移植適応評価委員会にデータを添えて申請し、その結果が膵臓移植中央調整委員会へ送付さ

表 1. 歴代会長

氏名	任期	所属
出月康夫	1982. 1. 1-1984. 2. 18 1984. 2. 18-2000. 3. 3	聖マリアンナ医科大学第一外科 東京大学医学部第二外科（現 肝胆膵・人工臓器移植外科）
井上一知	2000. 3. 3-2005. 3. 18	京都大学再生医科学研究所再生医学応用研究部門
寺岡　慧	2005. 3. 18-2008. 3. 7	東京女子医科大学腎臓病総合医療センター外科
後藤満一	2008. 3. 7-2014. 3. 7	福島県立医科大学医学部臓器再生外科学講座
伊藤壽記	2014. 3. 7-	大阪大学大学院医学系研究科生体機能補完医学寄附講座

表 2. 研究会の活動

1982 年	膵移植談話会の発足。会則発行
1984 年	聖マリアンナ医科大学第一外科から東京大学医学第 2 外科（現 肝胆膵・人工臓器移植外科）に事務局移転
1992 年	膵移植談話会から膵移植研究会に改称
1995 年	膵移植研究会から膵・膵島移植研究会に改称
1997 年	「膵島移植班」発足
1998 年	「膵島移植の指針」発行
1999 年	「膵島移植知っていますか？」、「膵島移植のための膵臓提供について」、「膵島移植の概要」を発行
2000 年	東京大学医学第 2 外科（現 肝胆膵・人工臓器移植外科）から京都大学再生科学研究所再生応用講座に事務局移転 「膵島移植実施合意事項」発行
2002 年	「膵島移植実施マニュアル」（初版）発行
2003 年	心停止ドナーから提供された膵臓による膵島分離を実施
2004 年	日本初の膵島移植が実施された。「膵島移植実施マニュアル」（第 2 版）発行
2005 年	京都大学再生科学研究所再生応用講座から東京女子医科大学腎臓病総合医療センター外科に事務局移転
2006 年	「膵島移植実施マニュアル」（第 3 版）発行
2007 年	膵・膵島移植研究会．本邦膵移植症例登録報告．移植 2007; 42(5): 433-438 膵・膵島移植研究会．膵島移植症例登録報告．移植 2007; 42(5): 439-447
2008 年	東京女子医科大学腎臓病総合医療センター外科から福島県立医科大学臓器再生外科学講座に事務局移転 膵・膵島移植研究会．本邦膵移植症例登録報告．移植 2008; 43(6): 477-481 膵・膵島移植研究会．膵島移植症例登録報告．移植 2008; 43(6): 482-485
2009 年	膵・膵島移植研究会から日本膵・膵島移植研究会に改称
2013 年	脳死ドナーからの初の膵島移植を実施

2014年	福島県立医科大学臓器再生外科講座から大阪大学大学院医学系研究科生体機能補完医学寄附講座に事務局移転

れる。膵臓移植中央調整委員会から移植施設に対して、移植可能の是非が確認され、日本臓器移植ネットワークへ登録となる。ドナー（脳死下、心停止下）発生時には、選択基準に従ってレシピエントが選択され、膵臓移植実施施設で移植が実施される。膵腎同時移植の場合の手術手技としては、ドナーから全膵を十二指腸とともに摘出し、レシピエントの右腸骨窩に膵臓を移植し、腎臓は左側に移植する方法が一般的である。免疫抑制法は、抗IL-2レセプター抗体による導入療法に、タクロリムス、ミコフェノール酸モフェチル、ステロイドによる維持療法を行う4剤併用療法が主流である。本邦で実施される膵臓移植には、本研究会の会員を中心とした「膵臓移植実務者委員会」が膵臓移植支援体制（ナショナルチーム）を構築し、支援チームが、当該施設のスタッフと協働するという特色がある。これは移植手術を、全ての施設で共通の経験とするとともに、移植医療の質を保持・向上させることを目的としたシステムで、症例数は少なくとも、移植した膵臓の生着率・患者の生存率を世界のトップレベルに遜色ないものとして維持することに貢献している[3]。

臓器移植である膵臓移植は、1型糖尿病の治療の一選択肢としてすでに確立しているが、血管吻合を伴う難易度の高い開腹手術を必要とし、移植手術そのものに起因する合併症も少なくない。一方、組織移植に分類される膵島移植は、提供された膵臓から分離された膵島組織を、点滴の要領で門脈内に輸注する先進的な低侵襲治療である。しかし、膵島分離の困難性、移植効率や生着率の改善が望まれていることなど解決すべき課題が多く、本研究会内の膵島移植班が中心となり課題解決に努めてきた。1997年に発足した膵島移植班は、移植医や糖尿病内科医、腎臓内科医などにより構成され、日本組織移植学会および日本移植学会と連携しながら臨床膵島移植の準備を進めてきた。開始当初の事務局は国立病院機構千葉東病院にあり、『膵島移植の指針（1998年）』、『膵島移植実施マニュアル第1版（2002年）・第2版（2004年）』などの編集・刊行をはじめとして臨床膵島移植開始へ向けての礎が形作られた。2004年7月に事務局が福島県立医科大学外科学第一講座（現臓器再生外科学講座）へ移転し、臨床膵島移植の実施に伴う問題点を修正した『膵島移植実施マニュアル第3版（2006年）』が発刊された。

膵島移植の実施施設は、日本膵・膵島移植研究会内の施設認定委員会で審査・認定を行っている。2014年7月現在、膵島分離・凍結・移植施設として、10施設が認定されている。膵島分離・移植の実施にあたっては、本研究会内のシェアリング委員会における協議決定に従い、その施設が存在する地域および隣接する地域を担当する形で地域を分担しブロック体制を形成している。

本邦での膵島移植は、2000年代に入り報告された「エドモントン・プロトコール」[4]によるインスリン離脱の達成率の改善を受けて、2003年に初のヒト膵島分離が実施され、2004年に初の膵島移植が実施された。その後症例を重ね、内因性インスリン産生と血糖安定性の回復に成功し、重症低血糖からの解放が得られる可能性が示されたものの、長期的な生着を得ることは難し

いとされた[5,6]。それを受けて、本研究会では、欧米で成功をおさめた新たな免疫抑制プロトコール[7]を導入した臨床試験を計画した。先進医療Bとしての承認も得て、試験は現在進行中である。膵グラフトのドナーとしては脳死・心停止ドナーを想定されていたが、本邦では膵島移植は組織移植として分類されており、当初、脳死ドナーは主として膵臓移植に用いられ、本邦の膵島移植ドナーのほとんどは心停止ドナーであった。しかし、改正臓器移植法施行後は、脳死下提供の増加につれ、膵臓移植に用いられない提供膵も見受けられるようになり、その中で膵島移植に用いることが可能である臓器については、膵島移植に利用できるような体制整備がなされ、2013年4月より運用されている。

膵臓・膵島移植は、治療学のみではなく、移植免疫学・分子生物学・各臓器の生理学・生化学や、近年注目される再生医学、遺伝子治療などの新しい医学/医療をも包含した分野へと発展しつつある。本研究会は、こうした専門性を越えた議論の場を設けることにより、膵・膵島移植医療の発展に大きく寄与することを目指している。

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Ⅶ.膵島移植

1．概　況

- β細胞の破壊性病変によりインスリン分泌能が廃絶した1型糖尿病では、糖尿病専門医の厳格なインスリン治療によっても、血糖変動幅が大きく、安定した血糖コントロールの維持が困難な場合があります。膵島移植はこのような1型糖尿病患者に対して、血糖変化に応じたインスリン分泌を可能にする治療として位置づけられている組織移植治療です。
- 臓器移植として実施される膵臓移植と治療疾患対象はほぼ同一となりますが、血管の脆弱性を伴う糖尿病患者に対して血管吻合を伴う侵襲の高い開腹手術を必要とする膵臓移植に比べ、ドナーより提供された膵臓から膵島組織のみを特殊な技術を用いて分離し、局所麻酔下に門脈内に輸注する膵島移植は、侵襲性が低いという利点があります。ただし、本邦では保険収載された治療法ではなく、現在、膵島移植の安全性及び有効性を確認する臨床試験が行われています。
- 膵島移植の方法の概略は、脳死または心停止ドナーからご提供いただきた膵臓から特殊な技術を用いて膵島組織のみを分離し、局所麻酔下に経皮経肝的に門脈内に留置したカテーテルから、膵島組織を点滴の要領で輸注するという流れです。侵襲性の低い治療法で、これまで本邦で臨床研究として実施されてきた膵島移植実施34回／18症例では、移植術に起因する合併症は門脈穿刺に伴う腹腔内出血が1例認められたのみで、その他の有害事象は免疫抑制剤に起因する事象に限られており、安全性の高い移植治療として期待されています。
- 膵島移植の臨床実施は海外では1970年代に始まっていましたが、1990年から1999年における膵島移植後1年の膵島生着率が41%、移植後1年以降のインスリン離脱率が11%と、その成績は、一般的な医療として確立するには不十分でした。しかし、2000年に、カナダ・エドモントンにあるアルバータ大学から報告された「エドモントン・プロトコール」では、良質な膵島を充分量分離する膵島分離法をもとに、腎機能障害のない症例で膵島単独移植が行われ、免疫抑制剤としてはsirolimusを中心にdaclizumabと低容量のtacrolimusを組み合わせ、ステロイドを使用せず、分離した膵島は直ちに移植し、移植膵島が十分な量に達するまで異時性に複数回移植するという方法をとり、膵島移植を受けた1型糖尿病患者全員がインスリンより離脱したとされました。エドモントン・プロトコールは、その後欧米の多施設が共同して第3相試験が行われ、血糖不安定性をもつ1型糖尿病患者において長期にわたる内因性インスリン産生と血糖安定性の回復に成功し、重症低血糖から解放されることが明らかにされましたが、長期的にインスリン離脱継続することは難しいとも結論づけられました。
- 我が国における膵島移植は、日本膵・膵島移植研究会・膵島移植班が中心となり、日本組織移植学会および日本移植学会とも連携しながら、臨床研究あるいは臨床試験として実施されています。膵島移植の実施施設の認定は、膵島の分離・移植が可能であることを確認するための施設基準をもとに日本膵・膵島移植研究会内の施設認定委員会で検討し認定を行っています。2014年4月現在、膵島分離・凍結・移植施設として、北から

東北大学、福島県立医科大学、国立国際医療研究センター、国立病院機構千葉東病院、信州大学、京都大学、大阪大学、徳島大学、福岡大学、長崎大学の 10 施設が認定されています。膵臓摘出から移植までの時間を短縮するために、施設認定を受けた各施設は、施設が存在する地域（都道府県）および隣接する地域を担当する形で地域を分担しブロック体制を形成しています。

- 本邦では膵島移植は組織移植として分類されています。膵グラフトのドナーとしては脳死・心停止ドナーが想定されており、ドナーの適応としては、①ドナー年齢は原則 70 歳以下とし、②温阻血時間は原則として 30 分以内、③感染症等の除外項目は日本組織移植学会の「ヒト組織を利用する医療行為に関するガイドライン」に基づき、④摘出膵保存は UW 液による単純浸漬保存あるいは二層法を用いることが望ましいとする。また、⑤糖尿病（HbA1 c 6.0%以上）を除外し、その他アルコール依存症、膵炎、膵の機能的・器質的障害を認めるものは除外する、と定められています。

2．適　応

- 膵島移植の主な適応患者の基準は、①内因性インスリン分泌が著しく低下し、インスリン治療を必要とする状態で、②糖尿病専門医の治療努力によっても血糖コントロールが困難な、③75 歳以下の患者、と定められています。重度の心・肝疾患、アルコール中毒、感染症、悪性腫瘍の既往、重症肥満、未処置の網膜症などを認める場合は禁忌となります。糖尿病性腎症に関しては、膵島単独移植の場合は糖尿病性腎症 3 期までを適応とし、腎移植後膵島移植症例では、移植後 6 ヶ月以上経過し、クレアチニン 1.8mg/dl 以下で直近 6 ヶ月の血清クレアチニンの上昇が 0.2 以下で、ステロイド内服量 10mg/dl 以下、などの基準を満たす症例を移植の対象としています。
- レシピエント候補者情報は、現時点では膵島移植班事務局（福島県立医大臓器再生外科内）で一元管理されています。糖尿病内科の主治医が「膵島移植適応判定申請書」を作成し、「膵島移植適応判定に関する承諾書」を添え膵島移植班事務局に送付します。 膵島移植班事務局は糖尿病専門医からなる膵島移植適応検討委員会に適応検討および適応判定の要請をし、適応とされた場合、候補者として登録されることとなっています。
- また、現在実施されている臨床試験への参加希望者に対してはさらに、安全性および有効性への影響を考慮した適格基準、除外基準を定めています。年齢が 20 歳から 65 歳までで、糖尿病専門医によるインスリン強化療法を行っており、12 ヶ月の間に 1 回以上の重症糖尿病発作の既往があることを主な適格基準としており、BMI25kg/m^2 以上、インスリン必要量が 0.8IU/kg/日以上あるいは 55U/日以上、過去 1 年間に複数回測定した HbA1c 値（NGSP 値)の平均値が 10.4%以上、eGFR 60ml/min/1.73m^2 以下、等といった項目を除外基準として定めています（UMIN 試験 ID：UMIN000003977)。

3．移植待機者数

- 膵島移植の適応基準に基づき 2013 年 12 月末の時点で延べ 180 名が登録され、3 回の移植を終了あるいはさらなる移植を希望しない移植完了者が 7 名、保留となったものが 5 名、辞退者 44 名、待機中死亡 10 名あり、レシピエント候補者として 114 名が待機中です。この候補者のうち、臨床試験参加希望者には、臨床試験の適格性調査を行い、適

格性が確認されれば臨床試験参加予定者として登録され、膵島移植の実施は臨床試験のプロトコールに従って行われます。臨床試験参加の希望のない候補者および臨床試験参加の適応のない候補者は、臨床試験ではなく従来通りの形式にて膵島移植が実施されます。

- 2000 年以降の新規登録者数の推移を図 1 に示し、申請から登録までに要する期間を図 2 に示します。申請から登録までの日数は 3 ヶ月以内が最も多いものの、慎重な適応判断が必要であるため半年や 1 年を越えるケースも少なくありません。膵島移植実施件数が少なく、登録患者の待機日数は年々延長しています（図 3）。

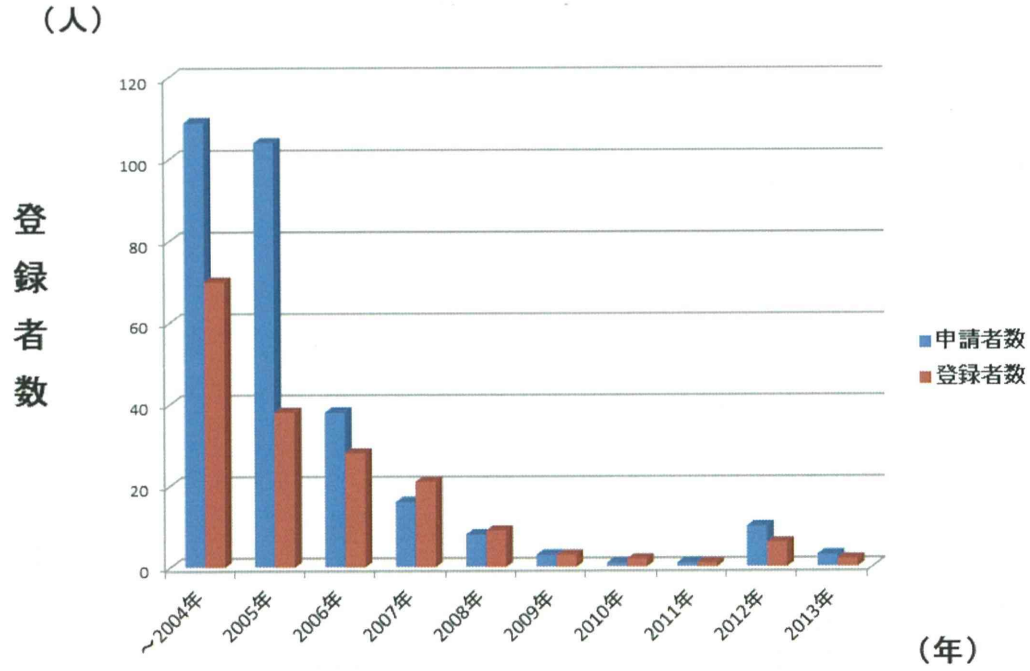

図 1. 新規登録者数の推移

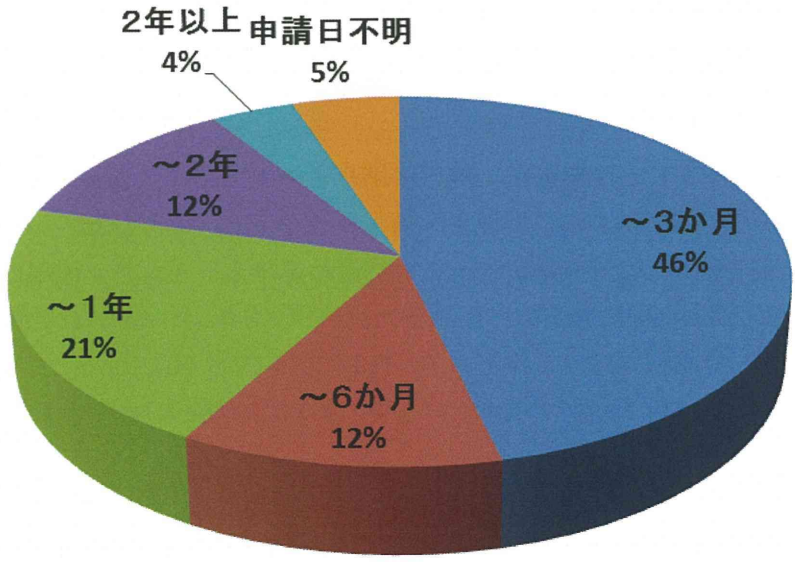

図 2. 申請から登録までの期間