Clinical Significance of Plasma Tenascin-C Levels in Recipients With Prolonged Jaundice After Living Donor Liver Transplantation

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ABSTRACT

Background. Focusing on tenascin-C (TNC), whose expression is enhanced during the tissue remodeling process, the present study aimed to clarify whether plasma TNC levels after living donor liver transplantation (LDLT) could be a predictor of irreversible liver damage in the recipients with prolonged jaundice (PJ).

Methods. Among 123 adult recipients who underwent LDLT between March 2002 and December 2016, the subjects were 79 recipients in whom we could measure plasma TNC levels preoperatively (pre-) and on postoperative days 1 to 14 (POD1 to POD14). Prolonged jaundice was defined as serum total bilirubin level >10 mg/dL on POD14, and 79 recipients were divided into 2 groups: 56 in the non-PJ (NJ) group and 23 in the PJ group.

Results. The PJ group had significantly increased pre-TNC; smaller grafts; decreased platelet counts POD14; increased TB-POD1, -POD7, and -POD14; increased prothrombin time−international normalized ratio on POD7 and POD14; and higher 90-day mortality than the NJ group. As for the risk factors for 90-day mortality, multivariate analysis identified TNC-POD14 as a single significant independent prognostic factor ($P = .015$). The best cut-off value of TNC-POD14 for 90-day survival was determined to be 193.7 ng/mL. In the PJ group, the patients with low TNC-POD14 (<193.7 ng/mL) had satisfactory survival, with 100.0 % at 90 days, while the patients with high TNC-POD14 (≥193.7 ng/mL) had significantly poor survival, with 38.5 % at 90 days ($P = .004$).

Conclusions. In PJ after LDLT, plasma TNC-POD14 is very useful for diagnosing postoperative irreversible liver damage early.

THE cholestasis type after liver transplantation (LT) is extrahepatic, involving a mechanical obstruction of the main bile ducts, or intrahepatic, involving impairment of bile duct secretion because of a defect in the hepatocytes or microscopic bile ducts within the liver [1]. Several etiologic factors have been suggested for intrahepatic cholestasis, such as inflammation or destruction of bile ducts [2], bacterial or viral infection [3], acute cellular or antibody-mediated rejection, hepatotoxic drugs including immunosuppressives, hepatic ischemia-reperfusion injury (IRI), or a combination of these factors [4−6]. The pathogenesis of early intrahepatic cholestasis after LT, especially within a month, is still unclear, and its

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incidence, natural history, and consequences have not been defined [7]. There is a group of patients who develop severe cholestasis, that is, prolonged jaundice, which is sometimes associated with irreversible liver damage requiring retransplantation. Liver biopsy is the most used method for the early diagnosis of irreversible liver damage after LT, although it alone is insufficient to diagnose it. The background of irreversible liver damage is thought to be related to the impairment of various tissue remodeling processes, such as inflammation, tissue repair and/or regeneration, and fibrosis in the liver tissue.

Tenascin-C (TNC), an extracellular matrix glycoprotein, usually presents as a hexamer consisting of subunits −190 to 300 kDa in length. Tenascin-C production is rare in normal adult tissues. Its expression is transiently enhanced in embryonic organ formation, wound healing, cancer invasion, and regeneration at locations where the tissue structure is dynamically remodeled [8−11]. Because TNC overexpressed in organs is released into the blood, the TNC value in the blood reflects organ damage and regeneration [12]. A previous study showed that TNC is a relevant mediator of pathogenic events underlying hepatic IRI [13]. Since hepatic IRI and liver regeneration are involved in living donor liver transplantation (LDLT), it is suggested that TNC may be associated with tissue repair and remodeling. Although several reports have examined the association of hepatitis and cirrhosis with TNC, to the best of our knowledge, no studies have investigated the association between TNC and liver damage after LT.

We focused on TNC, whose expression is enhanced during the tissue remodeling process. The present study aimed to clarify whether serum TNC levels after LDLT could predict irreversible liver damage in recipients with prolonged jaundice.

MATERIALS AND METHODS

Patients Characteristics

Among 123 adult recipients who underwent LDLT at Mie University Hospital between March 2002 and December 2016, 79 recipients were able to measure plasma TNC levels perioperatively. The patient characteristics are shown in Table 1.

Prolonged jaundice was defined as total bilirubin (TB) level >10 mg/dL on postoperative day 14 (POD14), according to a previous report [14]. The patients were divided into 2 groups: the non-prolonged jaundice (NJ) group (n = 56) and the prolonged jaundice (PJ) group (n = 23). In all cases in the PJ group, an abdominal ultrasound scan was routinely performed to exclude biliary obstruction.

The study protocol was approved by the Medical Ethics Committee of Mie University (No.H2021-159), and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Immunosuppression

According to our previous study, the immunosuppression protocol consisted of tacrolimus and low-dose steroids [15]. The target whole-blood trough level for tacrolimus was 10 to 15 ng/mL during the first 2 weeks, approximately 10 ng/mL after that, and 5 to 10 ng/mL from the second month after LDLT. Methylprednisolone (10 mg/kg of body weight) was administered intravenously immediately before perfusion of the graft portal vein and then 1 mg/kg on postoperative days (POD) 1 to 3, followed by 0.5 mg/kg on POD 4 to 6. Steroid administration was then switched to oral prednisolone (0.3 mg/kg/d) on POD 7, and the dose was reduced to 0.1 mg/kg/d at 1 month after LDLT. If their liver function was stable, the recipients were weaned off steroids 3 to 6 months after LDLT.

Table 1. Characteristics of 79 LDLT Patients

Demographics	(n = 79)
Preoperative factors	
Sex (male/female)	45/34
Age	54 (20-70)
Child-Pugh score	10 (5-14)
MELD score	15 (2-44)
ABO compatibility (identical/compatible/incompatible)	64/9/6
Diseases	
HCV (HCC)	34 (16)
HBV (HCC)	14 (8)
Alcohol (HCC)	8 (2)
PBC	7
Cryptogenic (HCC)	6 (1)
PSC	3
BA	2
Others	5
Operative factors	
CIT (min)	118 (25-323)
WIT (min)	45 (21-82)
Blood loss (mL)	11,608 (514-80,000)
GRWR	0.966 (0.504-1.571)

BA, biliary atresia; CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; WIT, warm ischemia time.

Measurement of Portal Venous Pressure

To monitor portal venous pressure, a 16-gauge antithrombotic catheter was inserted via the inferior mesenteric vein before the recipient's liver was removed, as described in our previous report [16].

CT Volumetry of Recipient's Graft Liver

Volumetric studies of the recipient's graft liver (GV) were conducted according to our previous report [17]. Standard liver volume (SLV) was calculated using the formula proposed by Urata et al [18]. Liver regeneration was assessed using the GV/SLV.

Measurement of Plasma TNC Levels and Immunohistochemistry for TNC Expression

Plasma levels of TNC were measured as described in our previous report [19] using an ELISA kit (Immuno-Biological Laboratories, Co, Gunma, Japan).

A liver biopsy was performed on 10 patients suspected of having acute cellular rejection around 14 days after LDLT. Immunohistochemical analysis of TNCs was performed as described in our previous report [20]. Tenascin-C expression in liver biopsy tissue was evaluated at 3 levels: high, intermediate, and low. High was defined as diffusely

expressed, intermediate was locally or diffusely low expression, and low was scarcely expressed.

Statistical Analysis

The results for continuous variables are expressed as median values with ranges. Numerical data were compared using paired and unpaired Student's *t* tests. Cumulative survival rates for TB and TNC were analyzed using the Kaplan-Meier method. Factors affecting 90-day mortality were analyzed using a multivariate Cox proportional hazards model. Individual variables with a significance of $P < .05$ in the univariate Cox proportional hazards model were selected for inclusion in the multivariate analysis. Variables with a significance of $P < .05$ were selected for multivariate analysis. All statistical calculations were conducted using SPSS (version 24.0; IBM SPSS, Inc, Armonk, NY, United States). When significant factors contributed to 90-day mortality after LDLT, the best cutoff value for 90-day mortality was determined by the receiver operating characteristic (ROC) curve. Statistical significance was set at $P < .05$.

RESULTS

Patient Characteristics and Survival in NJ and PJ Groups

Patient backgrounds, perioperative data, and outcomes in the NJ and PJ groups are shown in Table 2. The graft-to-recipient weight ratio (GRWR) and graft types were significantly different between the 2 groups, indicating that the graft size in the PJ group was significantly smaller than in the NJ group. Regarding perioperative data, PLT on POD14 (PLT-POD14) was significantly lower in the PJ group, and TB and prothrombin time −international normalized ratio (PT-INR) were significantly higher in the PJ group than in the NJ group: PLT-POD14, TB on POD1 (TB-POD1), TB-POD7, TB-POD14, PT-INR on

Table 2. Backgrounds, Perioperative Data, and Patient Outcomes Between NJ and PJ Groups

Variables	NJ group TB 14 <10 mg/dL (n = 56)	PJ group TB 14 ≥10 mg/dL (n = 23)	*P* value
Sex (male/female)	34/22	11/12	.310
Age	55 (20-69)	54 (30-70)	.645
Child-Pugh score	9 (5-14)	10 (6-14)	.161
MELD	14 (2-33)	15 (5-44)	.233
Non-Virus/Virus	23/33	9/14	.876
GRWR	1.017 (0.641-1.571)	0.831 (0.504-1.176)	< .001
Donor age	37.5 (18-62)	39 (18-59)	.934
Graft type (left/right)	11/45	14/9	.001
ABO incompatibility	5/51	1/22	.433
CIT	118 (25-323)	116 (35-323)	.688
WIT	45 (21-82)	44 (22-60)	.091
Blood loss	11,270 (514-80,000)	12,706 (1.600-75,180)	.654
Postoperative examination			
Pre-PLT	57 (24-308)	52 (18-200)	.589
PLT-POD1	69 (11-211)	77 (42-153)	.289
PLT-POD7	81 (3-387)	54 (27-218)	.050
PLT-POD14	160 (25-598)	60 (12-155)	< .001
Pre-TB	3.6 (0.6-22.3)	4.0 (0.5-26.1)	.136
TB-POD1	4.7 (0.9-12.8)	6.9 (1.7-13.6)	.041
TB-POD7	3.4 (0.9-9.8)	9.8 (0.9-33.6)	< .001
TB-POD14	2.2 (0.4-9.3)	17.1 (10.3-59.4)	< .001
Pre-ALB	2.8 (1.5-4.4)	2.8 (1.9-3.9)	.912
ALB-POD1	3.6 (2.9-4.9)	3.5 (2.5-4.8)	.132
ALB-POD7	3.3 (2.2-4.9)	3.5 (2.5-4.8)	.415
ALB-POD14	3.0 (2.2-4.1)	3.2 (1.9-4.5)	.070
Pre-PT-INR	1.37 (0.98-3.18)	1.56 (1.04-3.75)	.297
PT-INR-POD1	1.75 (1.19-3.21)	1.70 (1.06-2.15)	.015
PT-INR-POD7	1.09 (0.89-1.78)	1.31 (1.07-2.65)	< .001
PT-INR-POD14	1.09 (0.86-2.46)	1.34 (1.14-2.18)	< .001
Pre-TNC	73.0 (10.6-282.7)	104.4 (30.8-384.9)	.020
TNC-POD1	117.2 (20.6-484.0)	132.4 (25.0-289.2)	.669
TNC-POD7	133.1 (12.3-441.5)	127.6 (43.7-498.1)	.208
TNC-POD14	144.3 (22.7-554.6)	194.5 (29.6-482.9)	.137
WBC-POD14	12,470 (4.840-29,500)	13,280 (3.630-34,760)	.155
CRP-POD14	2.2 (0.2-20.9)	3.3 (0.5-10.2)	.752
90 d (alive/death)	53/3	15/8	.010

ALB, albumin level; CIT, cold ischemia time; CRP, C-reactive protein; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; NJ, non-prolonged jaundice; PJ, prolonged jaundice; PLT, platelet count; POD, postoperative day; PT-INR, prothrombin time−international normalized ratio; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

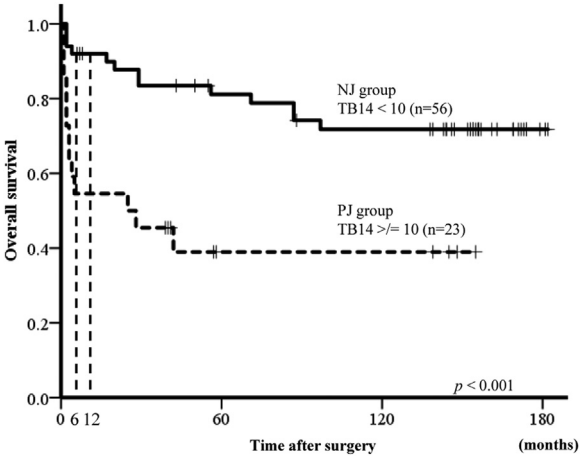

Fig 1. Overall survival between non-prolonged jaundice and prolonged jaundice groups. The overall survival rate in the non-prolonged jaundice group was significantly higher than that in the prolonged jaundice group (3-month survival 94.0% vs 63.6%, 6-month survival 92.0% vs 54.5%, 12-month survival 92.0% vs 54.5%, 60-month survival 81.1% vs 39.0%, 120-month survival 71.8% vs 39.0%, $P < .001$). NJ, non-prolonged jaundice; PJ, prolonged jaundice; POD, postoperative day; TB, total bilirubin level.

POD7 (PT-INR-D7), and PT-INR-POD14. The PT-INR-POD1, however, was significantly lower in the PJ group than in the NJ group: 1.70 vs 1.75 ($P = .015$), showing that median values were similar between the 2 groups. Tenascin-C on the day before LDLT (pre-TNC) was significantly higher in the PJ group than in the NJ group: 104.4 vs 73.0 ($P = .020$); however, TNC levels after LDLT did not differ between the 2 groups. The incidence of 90-day mortality after LDLT was significantly higher in the PJ group than in the NJ group (34.8% vs 5.4%, $P = .010$).

The overall survival curves of the NJ and PJ groups are shown in Fig 1. The overall survival rate in the NJ group was significantly higher than that in the PJ group (3-month: 94.0 % vs 63.6 %; 6-month: 92.0 % vs 54.5 %; 12-month: 92.0 % vs 54.5 %; 60-month: 81.1% vs 39.0%, and 120-month: 71.8 % vs 39.0 %, $P < .001$, respectively).

Prognostic Factors Affecting 90-day Mortality

Uni- and multivariate analyses for 90-day mortality after LDLT are shown in Table 3, by comparing 90-day survivors (n = 68) and 90-day non-survivors (n = 11). The TB-POD7, TB-POD14, PT-INR-POD7, PT-INR-POD14, pre-TNC, TNC-POD7, TNC-POD14, and WBC-POD14 were significantly higher in 90-day non-survivors than in 90-day survivors. The PLT-POD14 was significantly lower in non-survivors than in survivors. Multivariate analysis identified TNC-POD14 as a significant independent prognostic factor ($P = .015$).

Examining the cut-off value of TNC-POD14 by ROC curve, the best cut-off value for 90-day survival after LDLT was determined to be 193.731 ng/mL: area under the concentration-time curve, 0.876; sensitivity, 0.909; and specificity, 0.765 (Fig 2A). According to this cut-off value of TNC-POD14 as 193.7 ng/mL, the patients were divided into low TNC-POD14 (<193.7 ng/mL, n = 53) and high TNC-POD14 (>/=193.7 ng/mL, n = 26). The overall survival curves for low and high TNC-POD14 levels are shown in Fig 2B. The overall survival rate in the low TNC-POD14 group was significantly higher than that in the high TNC-POD14 (3-month: 97.9 % vs 58.3 %, 6-month: 93.8 % vs 54.2 %, 12-month: 93.8 % vs 54.2 %, 60-month: 82.3 % vs 41.7 %, 120-month: 79.5 % vs 26.0 %, $P < .001$, respectively).

Patient Characteristics in Low and High TNC-POD14

Between the 2 patients with low and high TNC-POD14, GRWR in the high TNC-POD14 group was significantly lower than that in the low TNC-POD14 group (0.909 vs 0.987, $P = .028$). After the operation, the following data for TB-POD7, TB-POD14, PT-INR-POD7, PT-INR-POD14, TNC-POD1, TNC-POD7, TNC-POD14, and WBC-POD14 in the high TNC-POD14 group were significantly higher than those in the low TNC-POD14 group, as shown in Table 4. Ninety-day mortality was significantly higher in the high TNC-POD14 group than in the low TNC-POD14 group (38.5 % [10/26] vs 1.9% [1/53]).

We compared survival curves between the low TNC-POD14 and high TNC-POD14 groups according to the NJ and PJ groups (Fig 3). In the NJ group, 90-day mortality was not significantly different between the high TNC-POD14 and low TNC-POD14 groups (15.4% [2/13] vs 2.3% [1/43], $P = .242$). However, the long-term survival was significantly poorer in the high TNC-POD14 group than in the low TNC-POD14 group (83.5% vs 72.7% at 60 months, and 80.4% vs 41.6% at 120 months). In the PJ group, the patients with low TNC-POD14 had satisfactory survival, with 100% at 90 days, 88.9% at 6 and 12 months, and 77.8% at 60 and 120 months, respectively, similar to those with low TNC-POD14 in the NJ group. In contrast, the patients with high TNC-POD14 in the PJ group showed significantly poor survival, with 38.5% at 90 days, 30.8% at 6 and 12 months, and 15.4% at 60 and 120 months.

Background and perioperative data between the low and high TNC-POD14 patients in the NJ and PJ groups are shown in Tables 5 and 6, respectively.

The changes in portal venous pressure and hepatic regeneration rate (GV/SLV) after LDLT were compared between the low and high TNC-POD14 groups in the NJ and PJ groups, respectively (Figs 4 and 5).

The characteristics of the 11 patients who died within 90 days are shown in Table 7. Three patients in the NJ group died of sepsis and 2 and died of graft liver failure due to uncontrollable acute cell rejection from ABO-incompatible LDLT. Of the 8 patients in the PJ group, 2 had a small graft of GRWR <0.7%, 6 died of graft liver failure, and 2 died of gastrointestinal bleeding due to graft liver failure.

Table 3. Uni- and Multivariate Analysis for 90-day Mortality After LDLT

Variables	Univariate 90-day survivor (n = 68)	90-day death (n = 11)	*P* value	Multivariate Odds ratio (95% CI)	*P* value
Sex (male/female)	39/29	6/5	.870		
Age	54 (20-70)	54 (30-70)	.974		
Child-Pugh score	10 (5-14)	10 (7-14)	.245		
MELD	14.5 (2-38)	18 (6-44)	.182		
Non-Virus/Virus	29/39	3/8	.333		
GRWR	0.967 (0.504-1.571)	0.839 (0.612-1.120)	.168		
Donor age	38 (18-62)	36 (18-59)	.727		
Graft type (left/right)	21/47	4/7	.741		
ABO incompatibility	2/66	4/7	.054		
CIT	118 (25-323)	118 (35-218)	.770		
WIT	45 (21-82)	45 (28-59)	.723		
Blood loss	12,157 (514-80,000)	11,086 (1600-75180)	.649		
Postoperative examination					
Pre-PLT	54 (18-308)	61 (31-130)	.438		
PLT-POD1	72 (11-211)	62 (19-171)	.849		
PLT-POD7	74 (27-387)	54 (3-137)	.172		
PLT-POD14	131 (15-598)	56 (12-166)	< .001	.999 (.991-1.006)	.753
Pre-TB	3.6 (0.5-22.3)	4.0 (0.6-26.1)	.138		
TB-POD1	5.0 (1.7-12.8)	8.2 (0.9-13.6)	.194		
TB-POD7	4.5 (0.9-19.6)	11.5 (2.8-33.6)	.011	1.132 (.788-1.628)	.502
TB-POD14	3.8 (0.4-41.9)	22.0 (1.2-59.4)	.011	1.031 (.862-1.233)	.738
Pre-ALB	2.8 (1.5-4.4)	3.0 (2.2-3.7)	.299		
ALB-POD1	3.6 (2.6-4.9)	3.4 (2.5-4.8)	.486		
ALB-POD7	3.3 (2.2-4.9)	3.7 (2.6-4.3)	.089		
ALB-POD14	3.1 (1.9-4.4)	3.1 (2.4-4.5)	.429		
Pre-PT-INR	1.40 (0.98-2.90)	1.78 (1.05-3.75)	.124		
PT-INR-POD1	1.69 (1.15-3.03)	1.75 (1.06-3.21)	.760		
PT-INR-POD7	1.10 (0.89-1.78)	1.32 (1.07-2.65)	.034	2.509 (.021-305.423)	.707
PT-INR-POD14	1.14 (0.86-2.46)	1.58 (1.19-2.18)	.002	11.476 (.595-221.470)	.106
Pre-TNC	75.0 (10.6-282.7)	132.6 (53.2-384.9)	.031	1.000 (.989-1.009)	.965
TNC-POD1	117.2 (20.6-484.0)	117.2 (25.0-423.7)	.513		
TNC-POD7	112.6 (12.3-327.8)	244.3 (116.2-498.1)	.006	.999 (.989-1.009)	.860
TNC-POD14	144.7 (22.7-554.6)	302.6 (148.3-507.0)	.002	1.010 (1.002-1.019)	.015
WBC-POD14	12,470 (3.630-29,280)	19,370 (6.370-34,760)	.048	1.000 (1.000-1.000)	.626
CRP-POD14	2.7 (0.2-20.9)	1.8 (0.8-8.0)	.385		

ALB, albumin level; CIT, cold ischemia time; CRP, C-reactive protein; GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PLT, platelet count; POD, postoperative day; PT-INR, prothrombin time–international normalized ratio; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

Immunohistochemical staining for TNC in liver biopsy specimens from the 2 typical cases is shown in Fig 6; one is a low expression of TNC in the patient with low plasma levels of TNC (58.3 ng/mL) on POD14 who underwent a liver biopsy on POD12 (Case No. 2 in Table 8), and the other is a high expression of TNC in the patient with high plasma levels of TNC (302.6 ng/mL) on POD14 who underwent a liver biopsy on POD19 (Case No. 9 in Table 8). Table 8 shows the relationship between plasma TNC levels and immunostaining of TNC in liver tissue obtained by liver biopsy around 14 days after LDLT in the 10 patients. All 6 patients with low TNC-POD14 had low TNC expression in liver tissue obtained by liver biopsy on POD7 to 12. None of the 4 patients with high TNC-POD14 showed low expression of TNC in the liver tissue: one had an intermediate expression on POD12, and 3 had a high expression on POD15 to 19. These results indicated that low plasma levels of TNC-POD14 (low TNC-POD14) were significantly associated with low expression of TNC in the liver tissue around POPOD14 ($P = .012$).

DISCUSSION

The characteristic examination of prolonged jaundice after LDLT in the present study revealed that the PJ group had significantly increased pre-TNC; smaller grafts; decreased PLT-POD14; increased TB-POD1, -POD7, and -POD14; increased PT-INR-POD7 and -POD14; and higher 90-day mortality, resulting in poor prognosis compared with the NJ group. As for risk factors for 90-day mortality, multivariate analysis identified TNC-POD14 as a single significant independent prognostic factor. The best cut-off value of TNC-POD14 for 90-day survival was determined to be 193.7 ng/mL. Between the 2 patient

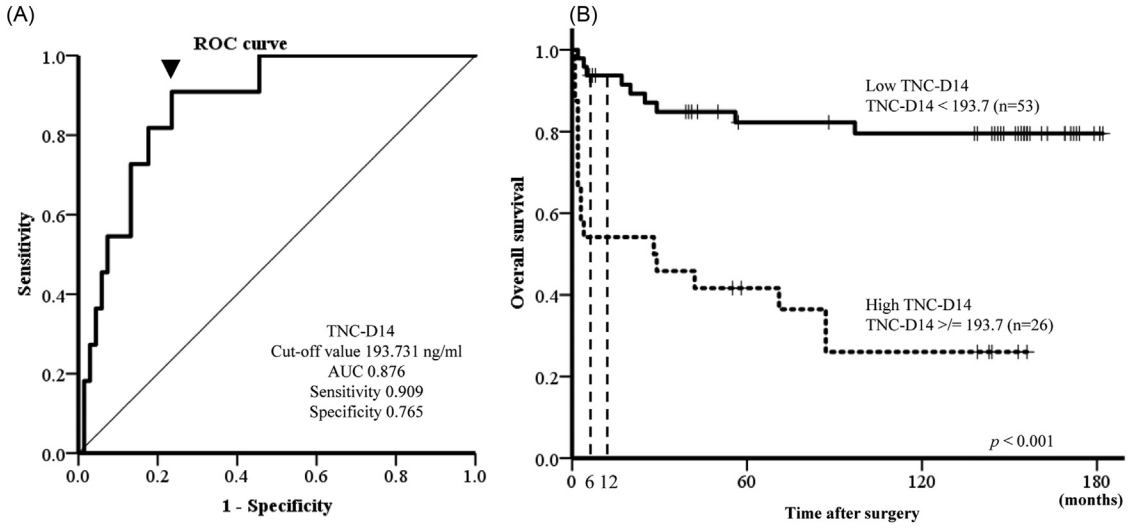

Fig 2. Receiver operating characteristic (ROC) curves of tenascin-C level on postoperative day 14 (TNC-POD14) for 90-day mortality after living donor liver transplantation and overall survival in low and high TNC-POD14 groups. **(A)** ROC curves of TNC-POD14 for 90-day mortality after living donor liver transplantation. According to ROC analysis, the optimum cut-off value of TNC-POD14 was set as193.7 ng/mL (area under the curve 0.876, sensitivity 90.9%, specificity 76.5%). **(B)** Overall survival in low and high TNC-POD14 groups. The overall survival rate in patients with low TNC-POD14 levels (<193.7 ng/mL) was significantly higher than that in patients with high TNC-POD14 levels (≥193.7 ng/mL) (survival rate in low TNC-POD14 vs high TNC-POD14: 3-month survival 97.9% vs 58.3%, 6-month survival 93.8% vs 54.2%, 12-month survival 93.8% vs 54.2%, 60-month survival 82.3% vs 41.7%, 120-month survival 79.5% vs 26.0%, $P < .001$). AUC, area under the curve; TNC-POD14, tenascin-C level on postoperative day 14; ROC, receiver operating characteristic.

groups with low and high TNC-POD14, there were no significant differences in patients' backgrounds and preoperative laboratory data, including Pre-TNC, and operative factors, including blood loss; however, GRWR in the high TNC-POD14 group was significantly lower than that in the low TNC-POD14 group, and postoperative liver function in the high TNC-POD14 group was significantly impaired in comparison with the low TNC-POD14 group. In the PJ group, the patients with low TNC-POD14 had satisfactory survival, showing 100% at 90 days, while the patients with high TNC-POD14 had significantly poor survival, showing 38.5% at 90 days. By examining the relationship between plasma TNC levels and immunostaining of TNC in liver tissue obtained by liver biopsy around 14 days after LDLT, low plasma levels of TNC-POD14 were significantly associated with low expression of TNC in the liver tissue.

Prolonged jaundice following LDLT can be a risk factor for early graft loss and mortality. However, some recipients with prolonged jaundice recover and maintain good liver function. Regarding hyperbilirubinemia after LDLT, Marubashi et al reported that when the peak bilirubin level (p-Bil) exceeded 27 mg/dL by 28 days after surgery, death or graft loss was likely to occur within one year [21]. In their report, among 67 adult LDLT patients, 9 of 10 patients (90.0%) with p-Bil >27 mg/dL died within 1 year, while none of 57 (0.0%) with p-Bil <27 mg/dL developed graft loss or death. In our study, however, among 79 adult LDLT patients, 5 of 8 patients (62.5%) with p-Bil >27 mg/dL died, while 9 of 71 (12.7%) with p-Bil <27 mg/dL died within one year. Therefore, it should be noted that there were deaths even with a p-Bil level <27 mg/dL. As in Marubashi et al, Matsushima et al focused on postoperative p-Bil and investigated the survival rate and risk factors that caused hyperbilirubinemia [22]. Among 107 adult LDLT patients, they compared prognoses in 17 patients with p-Bil >30 mg/dL and 90 patients with p-Bil <30 mg/dL. Nine of 17 patients (53.0%) with p-Bil >30 mg/dL died within 1 year, while 20 of 90 (22.2%) with p-Bil <30 mg/dL died within 1 year. Risk factors for p-Bil >30 mg/dL were reported to be donor age and preoperative total bilirubin level, and donor age was the most significant. Applying our case to their study, p-Bil >30 mg/dL was present in 6 of the 79 patients (7.6%), and donor age was not recognized as a risk factor for hyperbilirubinemia ($P = .948$). Hyperbilirubinemia after LDLT is certainly important as a prognostic factor, and the peak value of bilirubin level can be one index that is reported; however, what is more clinically important is the duration of hyperbilirubinemia (the state of prolonged jaundice). Until now, prolonged jaundice has no fixed definition, although there have been various reports [21−24].

In 2004, Ben-Ari et al examined whether early cholestasis after LT could predict early patient outcomes and graft function. They revealed that the strongest correlation was found between serum bilirubin levels >10 mg/dL on POD 10 and early death, sepsis, and poor graft function [25]. In 2010, Goralczyk et al defined TB

Table 4. Background and Perioperative Course Between Low and High TNC-POD14 Patients

Variables	Low TNC-POD14 <193.7 ng/mL (n = 53)	High TNC-POD14 ≥193.7 ng/mL (n = 26)	*P* value
Sex (male/female)	28/25	17/9	.291
Age	54 (20-70)	54 (25-70)	.939
Child-Pugh score	10 (5-14)	9 (5-14)	.497
MELD	15 (2-38)	14 (6-44)	.689
Non-Virus/Virus	22/31	10/16	.799
GRWR	0.987 (0.694-1.571)	0.909 (0.504-1.213)	.028
Donor age	37 (18-62)	39 (18-59)	.731
Graft type (left/right)	13/40	12/14	.069
ABO incompatibility	2/51	4/22	.141
CIT	118 (25-323)	118 (35-161)	.191
WIT	45 (21-82)	45 (22-82)	.643
Blood loss	11,608 (514-80,000)	12,745 (1.600-75,180)	.331
Postoperative examination			
Pre-PLT	51 (18-308)	65 (26-156)	.886
PLT-POD1	69 (19-211)	74 (11-171)	.374
PLT-POD7	72 (31-196)	74 (3-387)	.334
PLT-POD14	119 (15-454)	69 (12-598)	.572
Pre-TB	4.5 (0.6-22.3)	2.3 (0.5-26.1)	.914
TB-POD1	5.1 (0.9-12.8)	4.7 (1.7-13.6)	.857
TB-POD7	4.5 (0.9-14.7)	7.3 (0.9-33.6)	.023
TB-POD14	2.9 (0.6-28.5)	8.2 (0.4-59.4)	.007
Pre-ALB	2.8 (1.5-4.4)	2.8 (1.9-3.9)	.541
ALB-POD1	3.7 (2.6-4.9)	3.6 (2.5-4.8)	.844
ALB-POD7	3.3 (2.2-4.9)	3.4 (2.4-4.8)	.354
ALB-POD14	3.1 (2.2-4.4)	3.0 (1.9-4.5)	.804
Pre-PT-INR	1.41 (0.99-2.90)	1.35 (0.98-3.75)	.552
PT-INR-POD1	1.70 (1.17-3.21)	1.71 (1.06-2.23)	.136
PT-INR-POD7	1.09 (0.89-1.78)	1.28 (0.98-2.65)	.005
PT-INR-POD14	1.12 (0.86-2.46)	1.31 (0.94-2.18)	.003
Pre-TNC	76.8 (10.6-282.7)	85.4 (25.9-384.9)	.175
TNC-POD1	116.9 (20.6-289.2)	159.8 (25.0-484.0)	.028
TNC-POD7	110 (12.3-321.5)	195.1 (65.1-498.1)	< .001
TNC-POD14	126.9 (22.7-193.5)	255.2 (194.0-554.6)	< .001
WBC-POD14	11,090 (3.630-29,280)	16,480 (5.860-34,760)	.005
CRP-POD14	2.2 (0.2-20.9)	4.0 (0.8-11.3)	.352
90 days (alive/death)	52/1	16/10	.001

ALB, albumin level; CIT, cold ischemia time; CRP, C-reactive protein; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; PLT, platelet count; POD, postoperative day; PT-INR, prothrombin time–international normalized ratio; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

>10 mg/dL on POD14 as prolonged jaundice as one of the criteria for small-for-size syndrome after LDLT; this was employed in our present study because the data obtained in the present study were on POD 1, 7, and 14 [14]. The results showed that the comparison of prognoses between the PJ group (23 patients) and the NJ group (53 patients) was 3 months: 94.0% vs 63.6%; 6 months: 92.0% vs 54.5%; and 12 months: 92.0% vs 54.5%, respectively, which were significantly poorer in the PJ group. Comparing the preoperative characteristics of the PJ and NJ groups, there were no differences in donor age and preoperative TB levels, but significant differences were observed in GRWR and Pre-TNC: GRWR was significantly smaller, and pre-TNC was significantly higher in the PJ group. GRWR was identified as a preoperative risk factor for the PJ group because postoperative liver regeneration was delayed due to shear stress after reperfusion [17]. On the other hand, the preoperative value of TNC in the PJ group was significantly higher than that in the NJ group, possibly because high TNC levels in the blood reflect inflammation and fibrosis in the liver [26–28].

However, looking at the survival curves between the PJ and NJ groups, a large difference was observed in 90-day mortality, whereas no significant difference was observed in subsequent long-term prognosis between the 2 groups. Therefore, we investigated further to clarify the factors contributing to 90-day mortality, paying special attention to the pre- and postoperative changes in TNC. In examining risk factors contributing to 90-day mortality, TB-POD7 and TB-POD14 were significantly different in the univariate analysis but not in the multivariate analysis. In other words, despite a large difference in 90-day mortality between the PJ and NJ groups, TB levels were not a risk factor for 90-day mortality. In comparing preoperative factors between the PJ and NJ groups, there was a significant difference in GRWR and Pre-TNC, but multivariate analysis

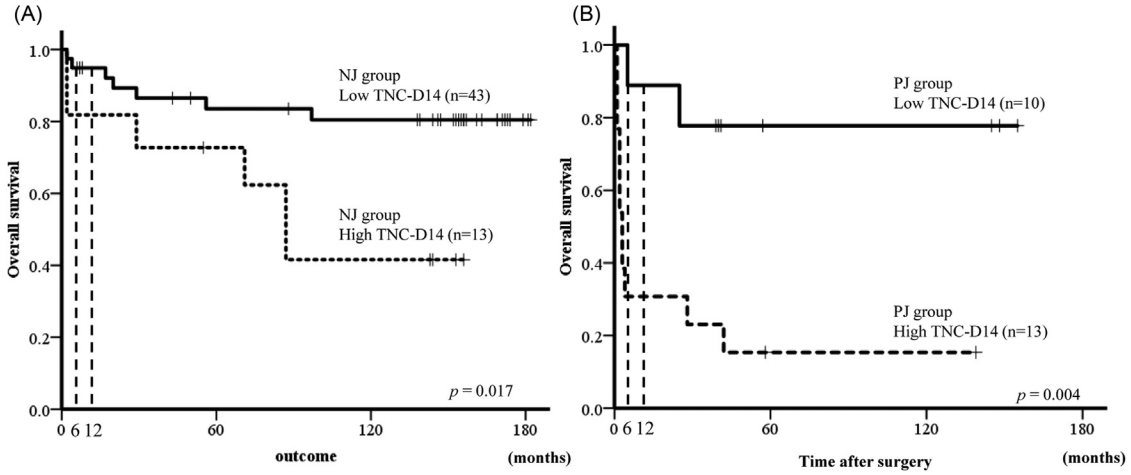

Fig 3. Overall survival between low and high tenascin-C level on postoperative day 14 (TNC-POD14) according to non-prolonged jaundice and prolonged jaundice groups. **(A)** Overall survival between low and high TNC-POD14 levels in the non-prolonged jaundice group. Patients with low TNC-POD14 had a better prognosis than those with high TNC-POD14 (3-month survival 97.4% vs 81.8%, 6-month survival 94.9% vs 81.8%, 12-month survival 94.9% vs 81.8%, 60-month survival 83.5% vs 72.7%, 120-month survival 80.4% vs 41.6%, *P* = .017). **(B)** Overall survival between the low and high TNC-POD14 groups in the prolonged jaundice group. Patients with low TNC-POD14 had a better prognosis than those with high TNC-POD14 (3-month survival 100% vs 38.5%, 6-month survival 88.9% vs 30.8%, 12-month survival 88.9% vs 30.8%, 60-month survival 77.8% vs 15.4%, 120-month survival 77.8% vs 15.4%, *P* = .004). NJ, non-prolonged jaundice; PJ, prolonged jaundice; TNC-POD14, tenascin-C level on postoperative day 14.

Table 5. Background and Perioperative Course Between Low and High TNC-POD14 Patients in NJ Group

Variables	NJ group: Low TNC 14 <193.7 ng/mL (n = 43)	NJ group: High TNC 14 ≥193.7 ng/mL (n = 13)	*P* value
Sex (male/female)	24/19	10/3	.156
Age	54 (20-69)	57 (25-69)	.497
Child-Pugh score	10 (5-14)	9 (5-14)	.127
MELD	15 (2-33)	11 (6-31)	.075
Non-Virus/Virus	19/24	4/9	.393
GRWR	1.016 (0.753-1.571)	1.043 (0.641-1.213)	.256
Donor age	37 (18-62)	38 (25-57)	.712
Graft type (left/right)	6/37	5/8	.123
ABO incompatibility	2/41	3/10	.166
CIT	118 (25-323)	118 (38-118)	.162
WIT	45 (21-82)	45 (27-82)	.780
Blood loss	11,100 (514-80,000)	14,404 (1.660-74,480)	.814
Postoperative examination			
Pre-PLT	51 (24-308)	70 (26-156)	.776
PLT-POD1	62 (19-211)	76 (11-171)	.273
PLT-POD7	76 (31-196)	91 (3-387)	.249
PLT-POD14	148 (25-454)	169 (33-598)	.323
Pre-TB	4.2 (0.6-22.3)	1.7 (0.9-10.1)	.031
TB-POD1	5.0 (0.9-12.8)	4.1 (1.7-9.4)	.079
TB-POD7	3.3 (0.9-9.8)	3.5 (1.0-8.8)	.893
TB-POD14	2.0 (0.6-9.3)	4.4 (0.4-6.0)	.449
Pre-ALB	2.7 (1.5-4.4)	2.9 (2.2-3.9)	.220
ALB-POD1	3.6 (3.1-4.9)	3.8 (2.9-4.7)	.404
ALB-POD7	3.3 (2.2-4.9)	3.2 (2.8-4.3)	.702
ALB-POD14	3.1 (2.2-4.1)	2.7 (2.4-3.8)	.102
Pre-PT-INR	1.47 (0.99-2.90)	1.25 (0.98-3.18)	.183
PT-INR-POD1	1.75 (1.19-3.21)	1.75 (1.34-2.23)	.411
PT-INR-POD7	1.07 (0.89-1.78)	1.13 (0.98-1.41)	.055
PT-INR-POD14	1.06 (0.86-2.46)	1.15 (0.94-1.68)	.436
Pre-TNC	72.9 (10.6-282.7)	73.1 (25.9-112.6)	.289
TNC-POD1	116.6 (20.6-201.3)	177.8 (70.6-441.5)	.043
TNC-POD7	110.0 (12.3-321.5)	178.8 (70.6-441.5)	.013
TNC-POD14	123.2 (22.7-193.5)	249.6 (194.6-554.6)	< .001
WBC-POD14	10,860 (4.840-29,280)	16,035 (5.860-29,500)	.074
CRP-POD14	1.7 (0.2-20.9)	4.6 (1.1-11.3)	.315
90 days (alive/dead)	42/1	11/2	.242

ALB, albumin level; CIT, cold ischemia time; CRP, C-reactive protein; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; NJ, non-prolonged jaundice; PLT, platelet counts; POD, postoperative day; PT-INR, prothrombin time−international normalized ratio; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

revealed that TNC-POD14 was the single independent risk factor for 90-day mortality.

There have been various studies on TNC in the heart, especially acute myocardial infarction (AMI). During the healing process after AMI, TNC is synthesized in interstitial fibroblasts provoked by various cytokines, growth factors, hypoxia, acidosis, and mechanical stress [26,29,30]. Sato et al evaluated the predictive value of serum TNC level as a prognostic biomarker in 239 patients with AMI and revealed that serum TNC level on day 5 after admission was useful for early risk stratification after AMI [28]. According to multivariate analyses of clinical variables related to cardiac death, serum TNC level on day 5 was selected as a significant independent predictor, revealing a cut-off value of 122 ng/mL with a sensitivity of 82% and a specificity of 70%. Their previous study also demonstrated that serum TNC levels peaked at day 5 and then gradually decreased after AMI, reflecting the local expression of TNC in the myocardium [26]. These results reported by Sato et al are very similar to ours, although the organs differ. In our study, TNC-POD14 was selected as a single significant independent predictor of 90-day mortality after LDLT, showing a cut-off value of 193.7 ng/mL with a sensitivity of 90.9% and a specificity of 76.5%. When we studied TNC expression in the liver tissue obtained from 10 patients, serum TNC levels were confirmed to reflect local TNC expression in liver tissue.

There are several reports of TNC studies of hepatitis and cirrhosis in the liver. To test the plasma level of TNC as a simple biomarker to identify cirrhotic patients with active hepatitis C virus (HCV) infection from those with HCV eradication, Benbow et al conducted a prospective study of 82 patients with HCV cirrhosis, including 38 with active HCV infection and 44 with virologic cure [31]. As a result, plasma TNC levels in active HCV infection patients were significantly higher than those in the virologic cure group. Furthermore, based on their ROC analyses and a cut-off TNC value of 170 ng/mL, TNC discriminated active HCV infection from virologic cure with 68% accuracy. They concluded that TNC provided the best model for discriminating HCV cirrhosis with active infection from virologic cure cohorts, suggesting that TNC is a potential indicator of ongoing hepatic injury and inflammation. Tanaka et al

Table 6. Background and Perioperative Course Between Low and High TNC-POD14 Patients in PJ Group

Variables	PJ group: Low TNC 14 <193.7 ng/mL (n = 10)	PJ group: High TNC 14 ≥193.7 ng/mL (n = 13)	*P* value
Sex (male/female)	4/6	7/6	.532
Age	60 (45-70)	53 (30-70)	.163
Child-Pugh score	11 (6-12)	10 (7-14)	.764
MELD	15 (5-38)	16 (6-44)	.724
Non-Virus/Virus	3/7	6/7	.450
GRWR	0.836 (0.694-1.176)	0.831 (0.504-1.120)	.400
Donor age	37 (19-57)	40 (18-59)	.921
Graft type (left/right)	7/3	6/7	.450
ABO incompatibility	0/10	1/12	.337
CIT	106 (50-323)	115 (35-161)	.746
WIT	44 (28-60)	44 (22-59)	.620
Blood loss	13,278 (1873-31,300)	11,086 (1.600-75,180)	.191
Postoperative examination			
Pre-PLT	52 (18-200)	61 (31-153)	.856
PLT-POD1	85 (49-133)	73 (42-153)	.423
PLT-POD7	61 (34-76)	54 (27-218)	.394
PLT-POD14	76 (15-155)	52 (12-132)	.103
Pre-TB	4.9 (1.2-21.0)	3.5 (0.5-26.1)	.497
TB-POD1	6.6 (1.9-9.9)	6.9 (1.7-13.6)	.485
TB-POD7	9.8 (4.7-14.7)	11.5 (0.9-33.6)	.120
TB-POD14	15.1 (11.9-28.5)	22.0 (10.3-59.4)	.068
Pre-ALB	3.0 (2.1-3.9)	2.7 (1.9-3.7)	.484
ALB-POD1	3.8 (2.6-4.3)	3.3 (2.5-4.8)	.680
ALB-POD7	3.4 (2.4-3.8)	3.6 (2.4-4.8)	.489
ALB-POD14	3.2 (2.5-4.4)	3.2 (1.9-4.5)	.756
Pre-PT-INR	1.38 (1.04-2.11)	1.79 (1.10-3.75)	.040
PT-INR-POD1	1.59 (1.17-2.15)	1.70 (1.06-2.10)	.739
PT-INR-POD7	1.25 (1.07-1.45)	1.38 (1.12-2.65)	.068
PT-INR-POD14	1.24 (1.14-1.47)	1.56 (1.18-2.18)	.004
Pre-TNC	87.3 (37.1-176.5)	119.9 (30.8-384.9)	.106
TNC-POD1	126.9 (42.0-289.2)	155.0 (25.0-277.9)	.914
TNC-POD7	115.4 (43.7-234.6)	222.7 (65.1-498.1)	.021
TNC-POD14	139.2 (29.6-149.6)	258.0 (194.0-482.9)	< .001
WBC-POD14	12,220 (3.630-25,220)	16,480 (6.370-34,760)	.095
CRP-POD14	3.4 (0.5-10.2)	2.8 (0.8-8.8)	.931
90 days (alive/dead)	10/0	5/8	< .001

ALB, albumin level; CIT, cold ischemia time; CRP, C-reactive protein; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; PJ, prolonged jaundice; PLT, platelet counts; POD, postoperative day; PT-INR, prothrombin time−international normalized ratio; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

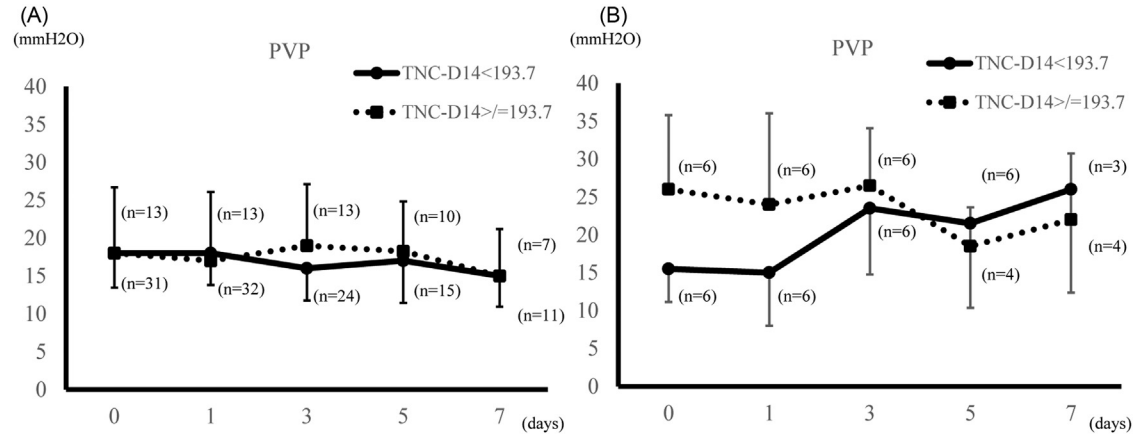

Fig 4. Portal venous pressure (PVP) between low and high tenascin-C level on postoperative day 14 (TNC-POD14) in non-prolonged jaundice (NJ) and prolonged jaundice (PJ) groups after living donor liver transplantation (LDLT). **(A)** PVP between low and high TNC-POD14 in NJ group after LDLT. Comparison between low and high TNC-POD14 in NJ group; there was no significant difference in PVP between patients with low TNC-POD14 and those with high TNC-POD14, though PVP on POD 3 of high TNC-POD14 was higher than low TNC-POD14 without any significance (P = .081). **(B)** PVP between low and high TNC-POD14 in PJ group after LDLT. Comparison between low and high TNC-POD14 in PJ group; PVP on POD 0, 1, and 3 was higher in patients with high TNC-POD14 compared with low TNC-POD14, though there were no significant differences (P = .079, P = .102, and P = .476, respectively). PVP, portal venous pressure; TNC-POD14, tenascin-C level on postoperative day 14.

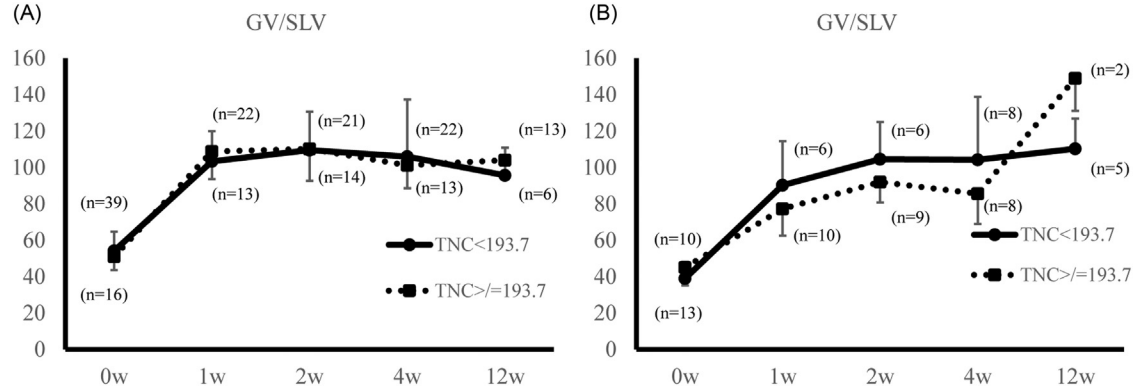

Fig 5. Hepatic regeneration rate (graft volume/standard liver volume [GV/SLV]) after living donor liver transplantation (LDLT) between low and high tenascin-C level on postoperative day 14 (TNC-POD14) groups in non-prolonged jaundice and prolonged jaundice groups after LDLT. **(A)** Hepatic regeneration rate between low and high TNC-POD14 groups in non-prolonged jaundice group after LDLT. There was no significant difference in GV/SLV between patients with low TNC and those with high TNC (0 weeks; P = .064, 1 week; P = .662, 2 weeks; P = .312, 4 weeks; P = .224, 12 weeks; P = .174). **(B)** Hepatic regeneration rate between low and high TNC-POD14 groups in prolonged jaundice group after LDLT. The GV/SLV 1, 2, and 4 weeks after LDLT was lower in patients with high TNC in comparison with those with low TNC, though there were no significant differences (1 week; P = .327, 2 weeks; P = .053, 4 weeks; P = .166). GV/SLV: graft volume/standard liver volume, LDLT: living donor liver transplantation; TNC, tenascin-C level.

measured serum TNC levels in 150 patients with chronic hepatitis C and examined their correlation with the degree of inflammatory activity and fibrosis as evaluated in liver biopsy specimens [19]. Serum TNC levels were significantly correlated with the severity of piecemeal necrosis, an important necroinflammatory activity parameter. They concluded that the measurement of serum TNC levels is a useful marker of chronic hepatitis C activity.

Applying these results to our present study, it was suggested that the patients with high TNC-POD14 had been in a persistent inflammatory state of the liver tissue, which in turn caused severe hepatocyte damage and finally led to liver failure. On the other hand, in patients with low TNC-POD14, there was no persistent inflammation in the liver tissue; they, in turn, developed satisfactory liver regeneration and showed a favorable prognosis. In our study, we

Table 7. Characteristics and Cause of Death in NJ and PJ Patients who Died Within 90 Days

No.	Age	Sex	MELD	GRWR	CIT	WIT	Blood loss (mL)	TB-POD14	TNC-POD14	WBC-POD14	PT-INR-POD14	Survival days after operation	Cause of death
NJ-1	66	Female	11	1.000	218	50	33,392	5.0	148.3	20,650	1.29	53 d	Liver failure*
NJ-2	62	Female	31	1.017	118	45	7.511	6.0	500.6	12,800	1.66	63 d	Sepsis
NJ-3	58	Male	6	0.790	38	54	1.660	1.2	507.0	29,500	1.19	66 d	Sepsis
PJ-1	54	Male	44	1.120	90	59	11,086	30.5	194.0	6.370	1.41	77 d	GI bleeding
PJ-2	49	Male	40	0.831	35	35	35,954	22.0	200.4	24,910	1.80	56 d	Liver failure*
PJ-3	30	Male	29	0.612	161	49	75,180	23.5	229.7	11,160	1.47	84 d	Liver failure*
PJ-4	35	Male	10	0.920	-	-	32,340	22.8	249.5	23,030	1.56	29 d	GI bleeding
PJ-5	54	Male	9	0.600	83	44	1.600	14.0	302.6	13,140	1.60	58 d	Liver failure*
PJ-6	70	Female	15	0.804	54	28	4.078	59.4	318.8	19,370	2.18	19 d	Liver failure*
PJ-7	43	Female	30	0.839	159	30	10,620	27.9	395.0	34,760	2.06	61 d	Liver failure*
PJ-8	64	Female	18	1.078	118	45	15,815	20.7	482.9	10,700	1.61	27 d	Liver failure*

* Graft failure due to uncontrolled acute rejection.

CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; NJ, non-prolonged jaundice; PJ, prolonged jaundice; POD, postoperative day; PT-INR, prothrombin time−international normalized ratio. TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count; WIT, warm ischemia time.

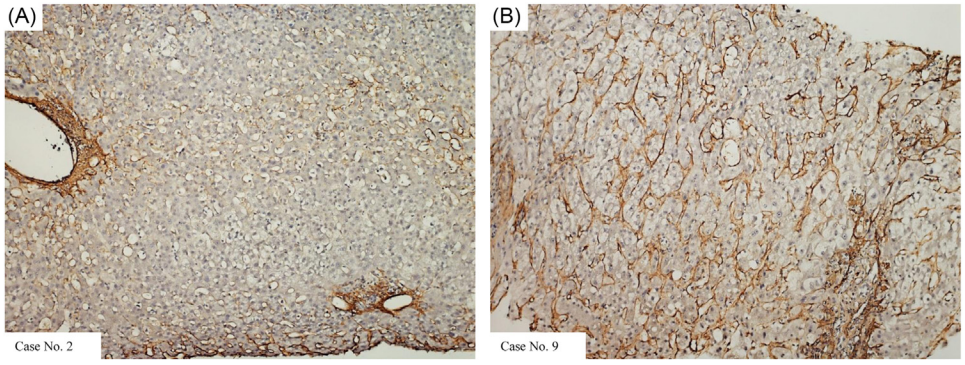

Fig 6. Immunohistochemical staining for tenascin-C level (TNC) in liver biopsy specimens in the 2 typical cases (100× magnification). **(A)** Low expression of TNC in the patient with low plasma levels of TNC (58.3 ng/mL) on postoperative day (POD) 14 who underwent liver biopsy on POD 12 (Case No. 2 in Table 8). **(B)** High expression of TNC in the patient with high plasma levels of TNC (302.6 ng/mL) on POD 14 who underwent liver biopsy on POD 19 (Case No. 9 in Table 8).

Table 8. Relationship Between Serum TNC Level and Immunostaining of TNC in the Liver Tissue Obtained by Liver Biopsy Around 14 Days After LDLT

No.	NJ/PJ	Age/Sex (F/M)	Child-Pugh score	MELD	GRWR	WBC-POD14	PT-INR-POD14	TB-POD14	Plasma TNC-POD14	TNC expression in liver tissue (day of biopsy)	RAI score	Prognosis
1	NJ	58/F	7	2	0.950	10,570	1.18	6.9	Low (32.6)	Low (POD13)	8	7 mo (alive)
2	NJ	50/F	10	26	1.000	17,110	1.40	9.3	Low (58.3)	Low (POD12)	3	4 mo (alive)
3	PJ	64/M	7	11	0.702	9.100	1.28	12.5	Low (85.5)	Low (POD7)	6	5 mo (alive)
4	NJ	23/F	5	2	1.065	6.780	0.97	2.2	Low (104.8)	Low (POD12)	2	8 mo (alive)
5	NJ	37/F	12	19	0.987	15,470	0.91	6.4	Low (135.3)	Low (POD11)	3	6 mo (alive)
6	PJ	61/M	6	5	0.694	12,140	1.18	12.4	Low (145.6)	Low (POD12)	2	41 mo (alive)
7	PJ	42/M	8	16	0.724	13,090	1.18	41.9	High (194.5)	High (POD18)	6	42 mo (death)
8	NJ	69/F	10	11	0.800	12,820	1.43	4.6	High (210.7)	Intermediate (POD12)	5	55 mo (alive)
9	PJ	54/M	7	9	0.600	13,140	1.60	14.0	High (302.6)	High (POD19)	5	2 mo (death)
10	PJ	70/F	10	15	0.804	19,370	2.18	59.4	High (318.8)	High (POD15)	3	1 mo (death)

GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; NJ, non-prolonged jaundice; PJ, prolonged jaundice; POD, postoperative day; PT-INR, prothrombin time−international normalized ratio; RAI, rejection activity index; TB, total bilirubin level; TNC, tenascin-C level; WBC, white blood cell count.

investigated the relationship between TNC expression in liver tissue and plasma TNC levels approximately 14 days after LDLT. Patients with low plasma TNC levels showed low TNC expression in liver tissue. Therefore, the measurement of plasma TNC levels could estimate the amount of TNC expression and evaluate the status of persistent inflammation in the liver.

In conclusion, plasma TNC-POD14 can be used as a predictive marker of prognosis in patients after LDLT. Especially in cases of prolonged jaundice after LDLT, plasma TNC-POD14 is very useful in the early diagnosis of postoperative liver regeneration disorders.

DISCLOSURES

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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