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Clinical Features and Long-Term Outcomes of Living Donors of Liver Transplantation Who Developed Psychiatric Disorders

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Background: In the field of living donor liver transplantation (LDLT), it is important to ensure donor's psychological well-being. We report on clinical features and long-term outcomes of LDLT donors who developed psychiatric disorders after their donor operations. Additionally, we compare patient backgrounds, as well as surgical and perioperative aspects between LDLT donors with and without postoperative psychiatric complications.

Material/Methods: Between November 1998 and March 2018, we identified 254 LDLT donors at our hospital. Among these, we investigated those who had newly developed psychiatric complications and required psychiatric treatment after donor operation.

Results: The median duration of follow-up was 4 years. Sixty-five donors were lost to follow-up. Eight donors (3.1%) developed postoperative psychiatric complications, including major depressive disorder in 4, panic disorder in 2, conversion disorder and panic disorder in 1, and adjustment disorder in 1. The median duration from donor surgery to psychiatric diagnosis was 104.5 days (range, 12 to 657 days) and the median treatment duration was 18 months (range, 3 to 168 months). Of those, 3 donors required psychiatric treatment over 10 years, and 4 donors remained under treatment. The duration of hospital stay after donor operation was significantly longer and perioperative complications with Clavien classification greater than grade IIIa were more frequent in donors with psychiatric complications than in those without psychiatric complications ($P=0.02$ and $P=0.006$, respectively).

Conclusions: Accurate diagnosis and appropriate treatment for psychiatric disorders by psychiatrists and psychologists are important during LDLT donor follow-up. Minimization of physiological complications might be important to prevent postoperative psychiatric complications in LDLT donors.

MeSH Keywords: Liver Transplantation • Living Donors • Long-Term Care • Psychotic Disorders

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Background

Although donor safety is the critical issue in living donor liver transplantation (LDLT), most previous reports on short- and long-term outcomes of LDLT donors have focused on physical complications [1–4]. However, the postoperative psychosocial status and well-being of donors is also important. In fact, approximately 1–10% of LDLT donors have been reported to develop psychiatric complications after donor surgery [5–9]. Interestingly, in many existing studies, it is unclear whether psychiatric complications were diagnosed and treated by a psychiatrist [5,6,8]. Moreover, little is discussed about the long-term outcomes of LDLT donors who develop psychiatric complications.

We previously reported cases of LDLT donor with postoperative psychiatric complications [9]. Since then, we have performed more LDLT. In addition, LDLT donors have been followed up for a longer period of time. Here, we report on the clinical features and long-term outcomes of LDLT donors who develop psychiatric complications, which are diagnosed and treated by psychiatrists. We also compare patient backgrounds, as well as surgical and perioperative aspects between LDLT donors with and without postoperative psychiatric complications.

Material and Methods

Preoperative donor evaluation

We reviewed clinical records for LDLT donors who underwent donor surgery between November 1998 and March 2018 at Nagoya University Hospital. Family members of recipients aged from 20 to 65 years old were eligible for donor candidates at Nagoya University Hospital. Candidates who had a significant medical history or comorbidities were excluded.

Preoperative evaluation proceeded after the voluntarily to be LDLT donor was confirmed. The physiological evaluation for donor candidates has been described in full elsewhere [10]. Where initial assessment was appropriate, psychiatrists reassured that their decision is made voluntarily and evaluated the existence of psychiatric diseases. All donor candidates have been screened with the Screening Module in the Structured Clinical Interview for the Diagnostic to check the presence of psychiatric disorders [11,12]. Donor candidates were excluded where serious psychiatric problems were suspected during preoperative evaluation.

Postoperative follow-up of LDLT donors

Postoperative outpatient follow-up of LDLT donors was conducted at 1, 3, 6, and 12 months after hospital discharge.

Thereafter, it is hospital policy to employ life-long annual follow-up for the assessment of physiological and psychological status, in addition to blood tests including liver function tests.

Assessment of psychiatric complications

When attending physicians and/or transplant coordinators suspected psychiatric problems in live donors after donor surgery, the concerns were discussed at a multidisciplinary conference with psychiatrists and psychologists. If required, a subsequent appointment with psychiatrists and psychologists was arranged for patients. Independent psychiatrist expertized in the field of transplantation evaluated psychiatric diagnoses based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) or Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (SCID-5) [11–13].

Psychiatric follow-up of LDLT donors diagnosed with postoperative psychiatric disorders

Following diagnosis of psychiatric disorders, supportive psychotherapy and psychopharmacology were provided. Follow-up assessment and treatment were continued until psychiatrists decided there was no longer a need for psychiatric treatment. Following psychiatric treatment, the Global Assessment of Functioning (GAF) scale [14] was used for the evaluation of clinical course of psychiatric disorders by psychiatrist. The GAF scale measures social, occupational and psychological functioning of adults on a scale of 0 to 100, where 100 indicates superior functioning.

Statistical methods

Statistical analyses were performed using SPSS, version 24 (IBM, Armonk, NY, USA). Fisher's exact test was used to compare categorical data. Continuous variables are presented as median with range. Categorical and continuous variables was compared using a Fisher's exact test and Mann-Whitney U test, respectively. *P* values less than 0.05 were considered to be statistically significant.

Ethical approval

This study was approved by the institutional review board of Nagoya University Graduate School of Medicine (approval number: 2015-0029). Informed consent requirement was waived due to the retrospective nature of this study.

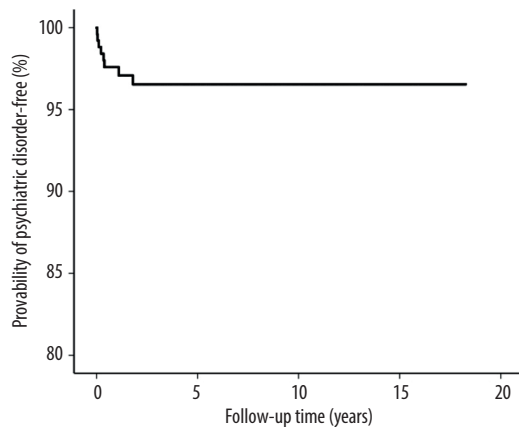


Figure 1. Kaplan-Meier curve of psychiatric disorder-free provability. Psychiatric disorder-free rate of LDLT donors was 96.5% at 5-years and 10-years after donor surgery. LDLT – living donor liver transplantation.

Results

In total, 254 LDLT donors (male, $n=119$; female, $n=135$) were reviewed. Median age at donor surgery was 35 years old (range, 20–63 years). The relationship of donors to their corresponding recipients included parents ($n=106$), child ($n=6$), spouse ($n=51$), sibling ($n=22$), grandparent ($n=3$), and other ($n=9$). At the psychiatric assessment for the transplantation, 2 donors had comorbid the psychiatric disorder (bipolar II disorder, obsessive-compulsive disorder), and 2 donors had history of psychiatric disorder (major depressive disorder, anxiety disorder). The median duration of follow-up was 4 years (6 months to 18 years). The proportion of dropouts (donors not seen for more than 5 years) was 25.6%. Four LDLT donors developed physiological disease unrelated to donor operation (diabetes mellitus in 1 case, hypertension in 2 cases, brain infarction in 1 case) during the follow-up. These donors developed no psychological disorders.

Of 254 LDLT donors, psychiatric complications following donor surgery were observed in 8 cases (3.1%) with 10-year psychiatric disorder-free rate 96.5% (Figure 1). Characteristics of LDLT donors who developed post-operative psychiatric complications are shown in Table 1. None of 8 cases had comorbid or history of the psychiatric disorder at operation except for 1 case (Case #8) who had history of major depressive disorder. Median duration from donor surgery to diagnosis of psychiatric disorder was 104.5 days (range 12 to 657 days). Psychiatric complications were as follows: major depressive disorder in 4 cases, panic disorder in 2 cases, conversion disorder and panic disorder in 1 case, and substance use disorder in 1 case. Possible psychosocial and environmental issues contributed

to the development of psychiatric complications included deteriorated relationship with the recipient or the family, recipient death, and recipient in sequelae.

Case #1 was a LDLT donor for her foster-mother with liver cirrhosis secondary to hepatitis C. After the physical and psychiatric assessment for the transplantation, she donated her right lobe to her foster-mother. She complained of gait disturbance, numbness of her legs and anxiety 17 days after transplantation. She developed conversion disorder (DSM-IV-TR) diagnosed by the attending psychiatrist. She received supportive psychotherapy and psychopharmacology (minor tranquilizer). Three years later, she developed panic disorder. Because of antidepressant side effect (nausea), she has used minor tranquilizer for a long time. She suffered from parental neglect as a child. We assume that interpersonal disability based on parental neglect can lead to prolonged psychological disorder.

Case #2 developed panic disorder (DSM-IV-TR) diagnosed by the attending psychiatrist. This donor suffered from panic attacks intermittently and received psychiatric treatment for a long time. She had a feeling of self-condemnation about subsequent complications of recipient. Furthermore, she had a mental conflict with mother-in-law who did not help her. Psychologist at our hospital figured that her self-condemnation and conflict prolonged the psychiatric symptoms. Case #4 was a LDLT donor for his brother with end-stage liver disease caused by biliary atresia. At the physical and psychiatric assessment, he wanted to be a donor and had a psychological conflict with recipient (younger brother). They were on bad terms with each other. Because the recipient didn't appreciate his donation, the donor started to use cannabis to calm his aggression. Even though a psychiatrist proposed the addiction treatment program, he reject it. He received the psychopharmacology (major and minor tranquilizer) and supportive psychotherapy.

All donors with postoperative psychiatric disorders were treated with both psychotherapy and psychopharmacology, including minor tranquilizers for all cases and antidepressants for 3 donors. Median duration of treatment for psychiatric disorders was 18 months (range 3 to 168 months). Of 8 donors with postoperative psychiatric complications, 4 continue to receive psychiatric treatment.

As for the perioperative physiological complication of donors with psychiatric disorders, 1 donor (Case #1) developed inferior vena cava (IVC) thrombus diagnosed on post-operative day (POD) 1. We immediately started intravenous continuous infusion of heparin. A computed tomography (CT) scan on POD 5 showed that the IVC thrombus was completely dissolved, thus heparin was discontinued. This patient also developed right-sided pleural effusion required therapeutic thoracentesis on

Table 1. Characteristics of living liver donors with post-operative psychiatric complications.

Case	1	2	3	4	5	6	7	8
Age at donor surgery	27	32	50	22	30	51	30	32
Sex	Female	Female	Female	Male	Female	Female	Female	Male
Relationship with recipient	Foster-daughter	Mother	Wife	Older brother	Mother	Wife	Mother	Son
Hospital stay after donor surgery (days)	41	17	33	49	18	18	33	12
Psychiatric diagnosis (DSM-IV-TR)	Conversion disorder Panic disorder	Panic disorder	Major depressive disorder	Substance use disorder	Panic disorder	Major depressive disorder	Major depressive disorder	Major depressive disorder
Duration from donor surgery to diagnosis (days)	18	40	657	143	396	12	80	129
Treatment for psychiatric disorder	Minor tranquilizer Supportive psychotherapy	Minor tranquilizer Antidepressant Supportive psychotherapy	Minor tranquilizer Antidepressant Supportive psychotherapy	Major tranquilizer Minor tranquilizer Supportive psychotherapy	Major tranquilizer Minor tranquilizer Supportive psychotherapy	Minor tranquilizer Antidepressant Supportive psychotherapy	Minor tranquilizer Supportive psychotherapy	Minor tranquilizer Supportive psychotherapy
Duration of psychiatric treatment (months)	168	156	120	12	12	3	6	24
Outcome of psychiatric disorders	Under treatment	Under treatment	Under treatment	Cure	Cure	Cure	Cure	Under treatment

POD 7. Two donors (Case #4 and #7) developed bile leakage on POD 7 and 8, respectively. The leakage resolved with percutaneous drainage after 5 days in 1 of 2 donors (Case #7). Another donor (Case #4) underwent endoscopic naso-biliary drainage because the leakage did not resolve a percutaneous placement of a peritoneal drain. The leakage eventually resolved after 7 days.

Table 2 presents a comparison of the background, and surgical and perioperative factors between donors with and those without postoperative psychiatric complications. There were no statistical differences in follow-up duration between groups. There were no statistical differences in surgical factors such as duration of operation or intraoperative blood loss between the groups. In contrast, duration of hospital stay after donor operation was significantly longer in donors with psychiatric complications than that in donors without psychiatric complications ($P=0.02$). In addition, perioperative complications with Clavien classification greater than grade IIIa were more frequent in donors with psychiatric complications than in those without psychiatric complications ($P=0.006$). There were no significant differences in perioperative complication rates or survival in recipients between the 2 groups.

Figure 2 presents GAF scale scores after initiation of treatment for psychiatric complications. GAF scale scores increased in all donors, except one (Case #8), who continues to receive treatment. Median GAF score increased from 47.5 (range 25 to 70) to 75.0 (range, 60 to 90) following psychiatric treatment with a mean follow-up of 6.1 years (range, 1 to 14 years).

Discussion

The ethical and psychosocial aspects is one of the critical issues in living organ donation [15,16]. In the current report, we investigated clinical and psychosocial factors, as well as long-term outcomes for 8 LDLT donors who developed psychiatric complications after donor surgery.

The reported incidence of psychiatric problems among donors varies from 2% to 20%, although diagnoses are ambiguous in many reports [1,4,5]. Moreover, psychiatric complications among donors are often only evaluated in the perioperative period in previous reports [1,5,17,18], and there are few reports regarding psychiatric disorders developing more than a year after donor operation. In our study, psychiatric complications

Table 2. A comparison of the background, and surgical and perioperative factors between donors with and those without post-operative psychiatric complications.

	Donors with psychiatric complication (n=8)	Donors without psychiatric complication (n=246)	P
Age at liver transplantation*	31 (22–51)	36 (20–63)	0.46
Male/Female	2/6	117/129	0.21
Duration of follow-up (year)*	8 (2–14)	4 (0.5–18)	0.72
Operation time (minute)*	468 (305–610)	415 (195–911)	0.43
Blood loss (ml)*	272 (79–2800)	364 (13–3448)	0.48
Graft type: Right/left/lateral	3/2/3	125/35/86	0.77
Hospital stay (day)*	22 (12–49)	15 (9–43)	0.02
Clavien classification of donor grade >IIIa	3 (37.5%)	11 (4.5%)	0.006
Death of relevant recipient	2 (25.0%)	45 (18.3%)	0.45
Clavien classification of recipient grade >IIIb	4 (50.0%)	59 (24.0%)	0.11

* Median with range.

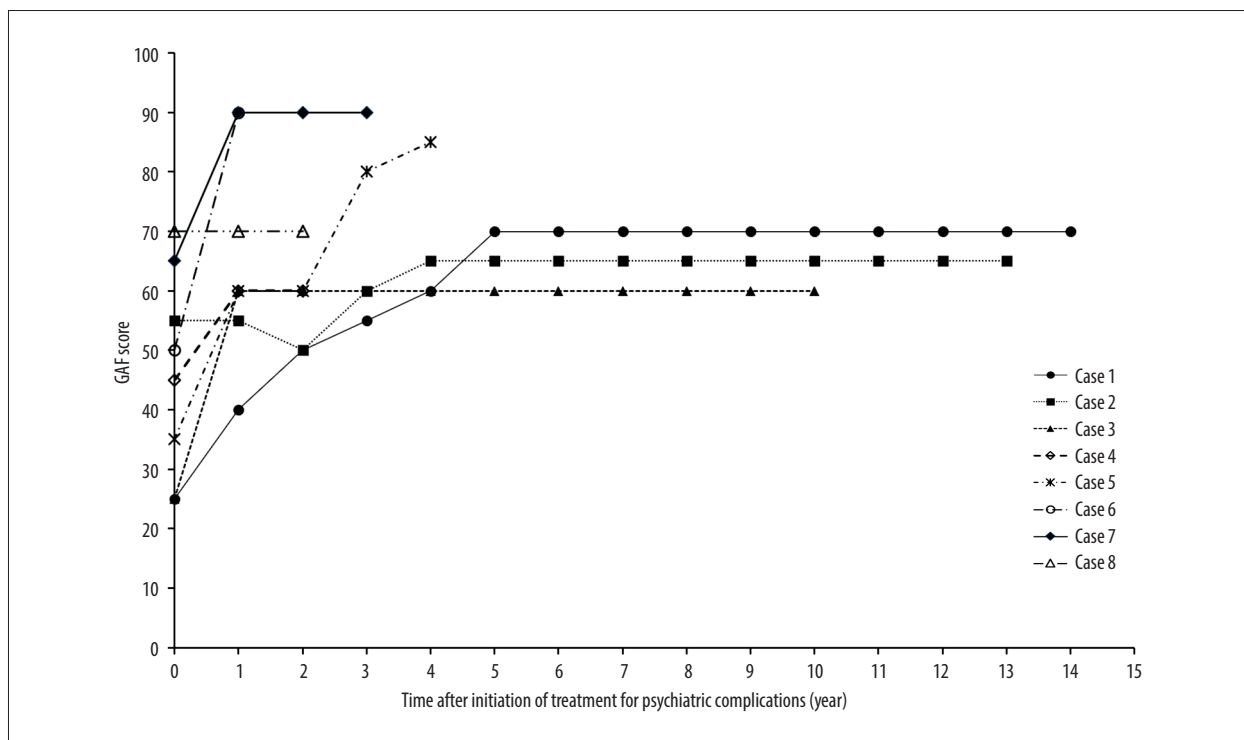


Figure 2. The course of the GAF scale after developing psychiatric complication. Median GAF score increase from 47.5 (range, 25 to 70) to 75.0 (range, 60 to 90) with psychiatric treatment. GAF – Global Assessment of Functioning.

were observed in 8 donors, which accounted for 3.1% of the total sample. Of note, 2 of these 8 LDLT donors developed psychiatric complications more than a year after donor surgery, suggesting the importance of long-term follow-up.

Although LDLT donors with psychiatric complications have been previously reported [1,8,19], little is discussed about long-term outcomes of LDLT donors who required psychiatric treatment. Additionally, there are no reports regarding the effects and outcomes of psychiatric treatment delivered by psychiatrists. In

our study, all donors with psychiatric complications were provided minor tranquilizers and supportive psychotherapy, and some donors were provided additional antidepressants and minor tranquilizers. Given our result suggesting that GAF scale scores increased in 7 of 8 donors and remained stable during a mean follow-up of 6.1 years, long-term outcomes of donors with postoperative psychiatric disorders seem to be satisfactory. However, this result is insufficient to conclude because of limitations of psychiatric evaluation using GAF score. The GAF scores often indicate the severity of symptoms rather than levels of impairment, especially when symptom severity is not congruent with level of functional impairment. In addition, the increase in GAF scale in the current report does not prove of the improvement in psychiatric status because of lack of data on GAF score after operation in those without psychiatric disorders. More quality of life questionnaires and detailed interview for psychiatric evaluation are thought to be necessary to conclude.

It is a policy at our institution that donors are offered life-long annual follow-up for a physiological health and well-being check, including psychosocial factors. Where psychiatric problems are suspected, information from follow-up assessments is shared with psychiatrists at our regular multidisciplinary conference. This strategy contributes to our ability to provide quick psychiatric support to LDLT donors with potential psychiatric disorders during long-term follow-up. A multidisciplinary approach including not only accurate diagnosis, but also prompt and appropriate treatment is thought to be important to prevent deterioration of psychiatric status in living donors. However, it is also notable that 3 of 8 donors required psychiatric treatment over 10 years, and 4 out of 8 donors remained under treatment. The definitive reasons for prolonged psychiatric disorders in these cases remain to be identified. None of 3 donors with prolonged psychiatric disorders had comorbid or history of the psychiatric disorder and pre-transplant assessment for these donors were appropriate. Further investigation on contributing factors for prolonged post-operative psychiatric disorders in LDLT donors is necessary. As previous reports mentioned [20–24], the current report suggested that the consultation-liaison psychiatry services can play the significant role in the field of LT and a long-term careful follow-up by psychiatrists is extremely important for LDLT donors who develop psychiatric disorders.

We also compared the backgrounds, and surgical and perioperative factors between LDLT donors with and without postoperative psychiatric complications. The duration of hospital stay after donor operation was significantly longer and perioperative complications with Clavien classification greater than grade IIIa were more frequent in donors with psychiatric complications than in those without psychiatric complications. In LDLT donors, age and sex, relationship with recipient,

ambivalence and motivation to be LDLT donor, feeling for donation, and hospitalization have all also been reported to be associated with psychiatric complications [8,25]. Our observations were consistent with previous reports that suggested that the development of postoperative psychiatric complications was associated with postoperative physical complications [5,6,26,27]. As such, it seems to be important to minimize physiological complications to prevent the development of psychiatric complications in LDLT donors.

A limitation of our study was that we could not follow all donors. Approximately 25% of donors did not visit the hospital over a 5-year period. Previous studies have reported a relationship between donor dropout from outpatient care and recipient outcomes [28,29]. In addition, there are also reports indicating an association between recipient's outcome and donor's mental health [19,30]. Therefore, it is possible that some donors who fail to attend follow-up outpatient appointments might also have developed psychiatric complications triggered by recipient death or serious physical complications but were not captured in this dataset. Another limitation was the small number of donors who developed psychiatric complications, which meant there was a significant difference in the number of donors between those with and without psychiatric disorders. Therefore, our results require confirmation in a larger cohort. Psychiatric disorders have not been screened systematically after operation due to the retrospective nature of this study, which can lead false negatives. Further prospective studies with appropriate screening instrument for all of LDLT donors should be addressed in future.

Conclusions

Of 254 LDLT donors, psychiatric complications following donor surgery were observed in 8 cases and 3 of 8 donors required psychiatric treatment over 10 years, and 4 of 8 donors remained under treatment. An accurate diagnosis and appropriate treatment for psychiatric disorders by psychiatrists and psychologists are important during LDLT donor follow-up and a multidisciplinary approach and vigilant long-term follow-up will likely play an important role in clinical management for LDLT donors with postoperative psychiatric disorders. Moreover, as the perioperative course might be associated with the development of psychiatric disease, decreasing physical complications could prevent development of psychiatric complications in LDLT donors.

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