Incidence and Risk Factors of Intraoperative Adverse Events During Donor Lobectomy for Living-Donor Liver Transplantation: A Retrospective Analysis

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Abstract

Objectives: **To evaluate the frequency, type, and predictors of intraoperative adverse events during donor hepatectomy for living-donor liver transplant.**

Materials and Methods: **Retrospective analyses of the data from 182 consecutive living-donor liver transplant donors between May 2002 and September 2008.**

Results: **Ninety-one patients (50%) had at least 1 intraoperative adverse event including hypothermia (39%), hypotension (26%), need for transfusions (17%), and hypertension (7%). Patients with an adverse event were older (*P* = .001), had a larger graft weight (*P* = .023), more frequently underwent a right hepatectomy (*P* = .019), and were more frequently classified as American Society of Anesthesiologists physical status class II (*P* = .027) than those who did not have these adverse events. Logistic regression analysis revealed that only age (95% confidence interval 1.018-1.099; *P* = .001) was a risk factor for intraoperative adverse events. Patients with these adverse events more frequently required admission to the intensive care unit and were hospitalized longer postoperatively. A before and after analysis showed that after introduction of in-line fluid warmers and more frequent use of acute normovolemic hemodilution, the frequency of intraoperative adverse events was significantly lower (80% vs 29%; *P* < .001).**

***Conclusions*: Intraoperative adverse events such as hypothermia and hypotension were common in living-donor liver transplant donors, and older age was associated with an increased risk of these adverse events. However, the effect of these adverse events on postoperative recovery is not clear.**

Key words: *Living-donor liver transplant, Adverse event, Anesthesia, Donor hepatectomy, Safety*

Introduction

The shortage of available deceased donors continues to limit deceased-donor liver transplant. For this reason, living-donor liver transplant (LDLT) is now accepted as an established treatment means for patients with end-stage liver disease.[1-4] Although the benefits of LDLT are obvious for the recipient, healthy donors face potential major morbidities and even mortality during this procedure for the sake of their relatives.[5-6] As a result, the major ethical and medical concern during LDLT is the safety of the donor, and every effort should be made to optimize their safety. Several investigators have reported the frequency and type of surgery-related complications in donors of LDLT. However, few studies have focused on the incidence and types of intraoperative adverse events that may occur during partial hepatectomy of healthy donors.[5, 7-8] This study sought to determine the frequency, types, and predictors of intraoperative adverse events during donor hepatectomy for LDLT.

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Patients and Methods

After obtaining approval from the Institutional Review Board and Ethics Committee, we retrospectively reviewed the medical and anesthesia records of 182 consecutive LDLT donors who underwent lobectomy from May 2002 to September 2008. All protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration, and written, informed consent was obtained from the patients or their guardians. Preoperatively, all donors underwent various medical and psychological assessments, including laboratory tests and hepatobiliary imaging studies. We assessed the arterial and venous anatomy with triphasic abdominal computed tomographic angiography, and estimated the volume of the whole liver and remnant liver. Since October 2006, we used magnetic resonance cholangiography to assess the biliary anatomy. We performed a routine preoperative liver biopsy on all donors.

Acceptance criteria for donors were that they be aged between 18 and 65 years, have identical or compatible ABO blood types, normal values for all biochemical laboratory tests, fatty liver < 20%, body mass index < 35, graft-to-recipient weight ratio > 0.8, residual liver volume always > 35% of the total liver volume (as calculated by computed tomography), and donor-recipient relationship. In our subjects, segments 2 and 3 were used for the left lateral segmental grafts; segments 2, 3, and 4 for the left lobe grafts; and segments 5 through 8 for the right lobe grafts. The same surgical techniques and equipment were used in all patients by the same surgery team.[9]

All donors received standard anesthetic management by the same anesthesia team.[10] Pressure points were padded, compression stockings were applied to lower extremities, and donors were kept warm with a convective heating blanket, forced-air warming, and warm intravenous fluids.

Acute normovolemic hemodilution (ANHD) was used in selected patients according to the decision of the attending anesthesiologist. This decision was based on the patient's consent, baseline hematocrit value, hemodynamic parameters, and arterial lactate level. Patients with no consent, a hematocrit value < 45%, mean arterial pressure < 60 mm Hg, or arterial lactate level > 2 mmol/L were not considered for acute normovolemic hemodilution. For acute normovolemic hemodilution, autologous blood donation and simultaneous colloid replacement were done at a 1:1 ratio. Acute normovolemic hemodilution was performed via an 8-French venous brachial sheet to a target hematocrit of 28% to 30%. If there was hemodynamic compromise, namely a mean arterial pressure < 60 mm Hg, autologous blood donation was stopped. All predonated autologous blood was returned to the patients at the end of the procedure, regardless of their hematocrit value. We did not use additional blood-salvage techniques, such as intraoperative cell-saver and surgical techniques, such as vascular clamping or the Pringle maneuver.

For all patients, the transfusion threshold was a hematocrit value < 27%. However, the decision to administer packed red blood cells was not always based on hematocrit level. In patients with active intraoperative bleeding and a relatively low baseline hematocrit, transfusion was begun immediately after a brief communication with the surgical team. At the end of the surgical procedure, donors were extubated in the operating suite and transferred to the surgical ward. Postoperative analgesia was provided by intravenous morphine by patient-controlled analgesia.

In December 2005, we started using in-line fluids and warm blood products to more effectively prevent hypothermia. As a departmental policy, we began to increase the use of ANHD during donor hepatectomy to decrease the need for transfusions. We decreased the hematocrit threshold from 45% to 40% for ANHD.

Intraoperative adverse events that we examined were hypotension (more than 20% decrease from the baseline mean arterial pressure), hypertension (more than 20% increase from the baseline mean arterial pressure), arrhythmia, hypoxemia (oxygen saturation < 90%), hypothermia (nasopharyngeal temperature < 35.5°C), need for transfusion, and other intraoperative adverse events. These variables were collected using anesthesia adverse events reporting sheets (that are routinely used for all anesthesia applications in our department) and patient and anesthesia records.

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 11.0, IBM Corporation, Armonk, New York, USA). Patients were divided in 2 groups based on whether they had an intraoperative adverse event or not. The 2 groups were compared with the chi-square or the Mann-Whitney *U* test. Relations between study group variables and a set of predictive variables for the

occurrence of intraoperative adverse events was estimated by means of logistic regression analysis. Variables that were significantly different, and those that were clinically relevant, were used to develop the binary logistic regression model.

We also compared donors who underwent lobectomy between 2002 and 2005 with those who underwent the same procedure during 2006 and 2008 regarding frequency and type of intraoperative adverse events to determine the effect of the aforementioned interventions on the occurrence of these adverse events. Data are expressed as mean values ± standard deviations (mean ± standard deviation). Values for *P* less than .05 were considered significant.

Results

Of 182 donors, with a mean age of 34.7 ± 9.1 years (range, 19 to 66 y), 104 were men (57%). All donors were classified as class I (n=152, 84%) or II (n=30, 16%) based on the ranking system of the American Society of Anesthesiologists. The number of patients who underwent right and left lobectomies were 85 (47%) and 97 (53%). Mean body weight of donors was 69.7 ± 10.0 kilograms (range, 44.5 to 96 kg), whereas the mean graft weight was 579.6 ± 252.5 grams (range, 210 to 1120 g).

Ninety-one patients (50%) had at least 1 intraoperative adverse event. The number of patients with 2 and 3 intraoperative adverse events were 27 (15%) and 9 (5%). The most frequently noted intraoperative adverse event was hypothermia (n=70, 39%), followed by hypotension (n=47, 26%), need for transfusion (n=30, 17%), hypertension (n=12, 7%), extravasation of intravenous fluids into the forearm (n=1, 1%), and brachial plexus injury (n=1, 1%). The number of donors who received only fresh frozen plasma, only packed red blood cells, and both fresh frozen plasmas and packed red blood cells were 7 (4%), 15 (8%), and 8 (4%). No episodes of arrhythmia and hypoxemia were recorded for these patients. Five donors (3%) required overnight admission to the intensive care unit at the end of surgery. There was no donor mortality in our series.

Compared with patients who did not develop an intraoperative adverse event, those who did had a significantly higher mean age (*P* = .001), were more frequently classified as American Society of Anesthesiologists physical status class II (*P* = .027), had a higher mean graft weight (*P* = .023), and more frequently underwent a right hepatectomy (*P* = .019) (Table 1). Using these variables, a binary logistic regression model was developed to identify possible risk factors for intraoperative adverse events. Logistic regression analyses revealed that only age

Table 1. Comparison of demographic features and preoperative, intraoperative, and postoperative variables between patients with intraoperative complications and those without intraoperative complications (mean ± standard deviation or number [%]).

	Complication (+) (n=91)	Complication (-) (n=91)	*P*
Age (y)	36.9 ± 9.4	32.6 ± 8.3	
Body mass index (kg/m^2)	24.5 ± 3.2	24.8 ± 3.4	
Women	36 (40%)	42 (46%)	
ASA I/II	70 (77%)/21 (23%)	82 (90%)/9 (10%)	
Duration of anesthesia (h)	7.1 ± 1.2	6.9 ± 1.2	
Calculated total liver volume (mL)	1501 ± 232	1496 ± 209	
Calculated graft volume/liver volume ratio	0.42 ± 0.15	0.36 ± 0.16	
Graft weight (g)	621 ± 242	534 ± 203	
Right/left hepatectomy	50 (55%)/41 (45%)	35 (39%)/56 (62%)	
Preoperative platelet count × 1000/mm^3	244.4 ± 56.5	258.5 ± 65.0	
Preoperative international normalized ratio	1.05 ± 0.09	1.05 ± 0.08	
Postoperative international normalized ratio	1.70 ± 0.36	1.57 ± 0.32	
Preoperative total bilirubin µmol/L (mg/dL)	10.43 ± 9.41 (0.61 ± 0.55)	11.12 ± 6.67 (0.65 ± 0.39)	
Postoperative total bilirubin µmol/L (mg/dL)	51.64 ± 35.40 (3.02 ± 2.07)	48.39 ± 34.20 (2.83 ± 2.00)	
Hematocrit (%)			
Preoperative	41.3 ± 4.3	41.7 ± 4.7	.634
Before hepatic dissection	38.8 ± 4.0	36.9 ± 6.0	.083
After hepatic dissection	33.9 ± 4.4	35.0 ± 4.9	.202
At the end of surgery	33.4 ± 5.6	33.7 ± 5.1	.590
Postoperative day 1	34.7 ± 5.4	36.0 ± 4.4	.025
Postoperative day 7	33.2 ± 4.8	34.5 ± 4.4	.015
Mean intraoperative arterial pH	7.38 ± 0.04	7.39 ± 0.06	.007
Mean intraoperative arterial partial oxygen pressure (mm Hg)	207.4 ± 50.1	186.1 ± 46.6	.005
Mean intraoperative arterial partial carbon dioxide pressure (mm Hg)	34.4 ± 4.9	36.2 ± 7.3	.189
Mean intraoperative arterial bicarbonate (mmol/L)	20.3 ± 2.3	22.1 ± 2.4	< .001
Mean intraoperative arterial lactate (mmol/L)	2.0 ± 0.9	2.1 ± 0.8	.254
Length of hospital stay (d)	8.7 ± 4.8	6.2 ± 3.4	
Admission to the intensive care unit	5 (6%)	0 (0%)	
Surgical complications	8 (9%)	5 (6%)	

Abbreviations: ASA, American Society of Anesthesiologists

Table 2. Binary logistic regression analysis to identify independent risk factors of intraoperative nonsurgical complications.

	P	Odds ratio	95% confidence interval
Age (y)	.004	1.057	1.018-1.099
ASA physical status class	.143	0.496	0.194-1.269
Graft weight (g)	797	1.000	0.998-1.003
Right/left hepatectomy	.462	1.669	0.426-6.545

Abbreviations: ASA, American Society of Anesthesiologists

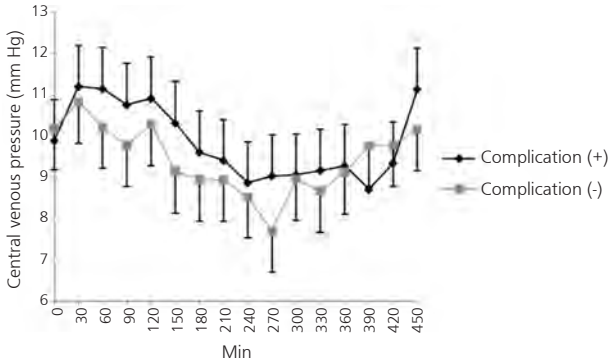

Figure 1. Intraoperative central venous pressure measurements of patients who had an intraoperative complication [Complication (+)] and those who did not have such a complication [Complication (-)]. $P > .05$ between the groups at all measurement time points.

was an independent risk factor for intraoperative adverse events (odds ratio, 1.064; 95% confidence interval: 1.025-1.105; $P = .001$) (Table 2).

Patients with an intraoperative adverse event, and those with no such adverse event, had similar intraoperative hemodynamic measurements (Figures 1 and 2). In comparison with patients who did not have an intraoperative adverse event, those who did had a significantly lower mean intraoperative arterial pH and bicarbonate levels and a higher mean intraoperative arterial partial oxygen pressure (Table 1). Mean postoperative day 1 and 7 hematocrit values were significantly lower in patients with an intraoperative adverse event than those with no adverse event (Table 1). However, these differences were not clinically relevant.

When compared with patients with no intraoperative adverse event, those with an intraoperative adverse event more frequently required admission to the intensive care unit at the end of the surgery ($P = .030$), had a longer stay in the hospital ($P = .001$), and had a higher postoperative mean international normalized ratio value ($P = .012$) (Table 1).

Overall, 13 surgical complications (7%) including biliary leak (n=5, 3%), wound infection (n=3, 2%), incisional hernia (n=2, 1%), biliary stenosis (n=1, 0.5%), portal vein thrombosis (n=1, 0.5%), and vena cava inferior thrombosis (n=1, 0.5%) occurred in 182 donors. Patients with an intraoperative adverse event, and those with no intraoperative adverse event, had similar rates of surgical complications (n=8 [9%] vs n=5 [6%]; $P = .283$).

Comparison of 2 studied times revealed that despite similar preoperative and intraoperative characteristics, patients who underwent lobectomy during the early period had a significantly higher frequency of intraoperative adverse events, hypothermia, hypotension, and transfusions ($P < .05$ for all) (Table 3). The frequency of surgical

Table 3. Before and after analysis of the perioperative management modifications, comparing patient and operative variables, and frequency of intraoperative nonsurgical complications (mean ± standard deviation or number [%]).

	2002-2005 (n=75)	2006-2008 (n=107)	*P*
Age (y)	35.4 ± 9.9	34.2 ± 8.5	.379
ASA I/II	59 (79%)/16 (21%)	93 (87%)/14 (13%)	.102
Graft weight (g)	615 ± 252	553 ± 251	.111
Right/left hepatectomy	38 (51%)/37 (49%)	47 (44%)/60 (56%)	.228
Acute normovolemic hemodilution	38 (51%)	81 (76%)	< .001
Intraoperative complication	60 (80%)	31 (29%)	< .001
Hypothermia	51 (68%)	19 (18%)	< .001
Hypotension	26 (35%)	21 (20%)	.025
Transfusions	20 (27%)	10 (9%)	.002
Hypertension	4 (5%)	8 (9%)	.272

Abbreviations: ASA, American Society of Anesthesiologists

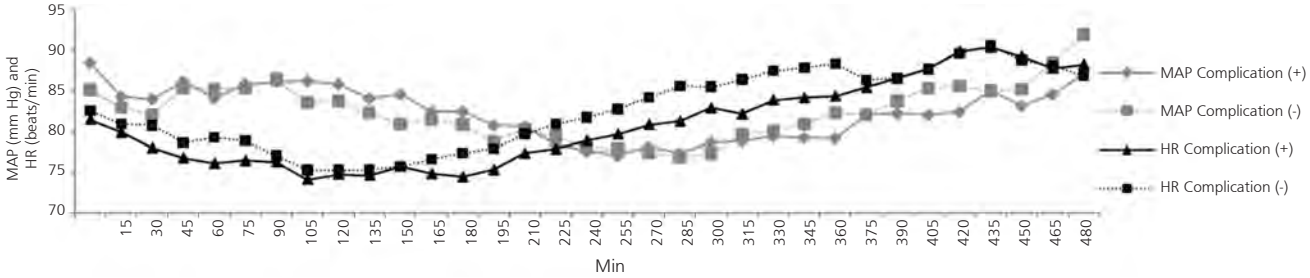

Figure 2. Intraoperative mean heart rate (HR) and mean arterial pressure (MAP) measurements of patients who had an intraoperative complication [Complication (+)] and those who did not have such a complication [Complication (-)]. $P > .05$ between the groups at all measurement time points.

complications was not significantly different between the 2 studied times (2002 to 2005, n=8 [11%] vs 2006 to 2008, n=5 [5%]; $P = .106$).

Discussion

Intraoperative adverse events such as hypothermia, hypotension, and the need for transfusion are common during donor lobectomy for LDLT. Although compared with patients with no adverse events, those with an intraoperative adverse event were significantly different in terms of mean age, mean graft weight, American Society of Anesthesiologists physical status class (I vs II), and the type of hepatectomy (right vs left).

A binary logistic regression model revealed that only age was an independent risk factor for the occurrence of intraoperative adverse events. Patients with an intraoperative adverse event also more frequently required admission to the intensive care unit and had a longer stay in the hospital than did those who did not. Finally, a before and after analysis suggested that after adoption of modifications such as use of in-line fluid warmers and ANHD, the frequency of intraoperative adverse events was significantly lower than it was before introduction of these modifications.

To best of our knowledge, no studies have focused on the frequency, type, and risk factors of intraoperative adverse events of living liver donors. Living-donor liver transplant is now an effective treatment for select patients with end-stage liver disease. Although the importance of donor safety during hepatectomy is widely recognized, donor morbidity and even mortality associated with hepatic resection may occur despite meticulous perioperative management and the best efforts of the transplant team.[2, 4-5, 11] Therefore, there remains debate concerning the ethical aspects of imposing the risk of major surgery on healthy donors for the sake of the recipient, and it is universally accepted that when considering LDLT, donor safety must be paramount.[10, 12]

Ozkardesler and associates[5] in a retrospective analysis of 113 living-liver donors, reported intraoperative complications (shoulder pain, epidural intraoperative pruritus, intraoperative transfusions, and 1 postoperative death). In another study, Akpek and associates[7] reviewed the anesthetic considerations for 30 donors who underwent lobectomy from January 1999 to May 2001 at our institution. These investigators documented massive bleeding (n=1), shoulder pain (n=1), neurapraxia (n=1), and compartment syndrome (n=1) as the intraoperative complications in this series. Different from these 2 studies, we sought to identify all the intraoperative adverse events (even the mildest ones, such as hypothermia and hypotension). The rationale for using such sensitive criteria to detect these adverse events was first, the fact that otherwise healthy donors would not face any adverse events (even the mildest ones) during their daily activity if they did not volunteer to be donors. And second, no prior studies have examined the incidence and effect of these adverse events in living-liver donors.

In our series, 50% of the patients had at least 1 adverse event. The high frequency of intraoperative hypothermia and hypotension in our series can be explained by the strict criteria that we used for reporting intraoperative adverse events. Based on these criteria (regardless of the duration and vasopressor requirement), a single mean arterial blood pressure that was less than 20% of baseline mean arterial pressure value was accepted as hypotension. Similarly, a single core body temperature that was less than 35.5°C was defined as *intraoperative hypothermia*. However, major abdominal surgery is characterized by substantial heat loss, and this level of hypothermia is not an uncommon finding during these procedures.[13] Compared with previous studies, intraoperative transfusions were more frequently used in our study.[5, 11, 14]

The discrepancy between our study and others may arise from the different definitions of intraoperative transfusion that were used. Previous studies have reported the frequency of whole blood or packed red blood cell transfusions as the intraoperative transfusion. However, because fresh frozen plasma transfusions carry a significant risk of transfusion-related adverse events, we reported intraoperative transfusions as the transfusion of any blood products. Another possible explanation for the relatively high rate of intraoperative transfusions in our series is that a lower threshold of transfusion was used in our patients. The American Society of Anesthesiologists task force on perioperative blood transfusion and adjuvant therapies recommends administration of red blood cells when the hemoglobin concentration is less than 60 g/L (6 g/dL) in young and healthy patients.[15]

This level corresponds to a lower hematocrit level than the one that we used for red blood cell transfusion (hematocrit < 27%). Nevertheless, as it has been stated by the same task force, for intermediate hemoglobin concentrations 60 to 100 g/L (6 to 10 g/dL), justification for red blood cell transfusion should be individualized based on factors such as rate and magnitude of bleeding and organ ischemia. According to this statement, the indication for red blood cell transfusion in our patients was potential or ongoing bleeding.

We also sought to identify risk factors for the occurrence of intraoperative adverse events in living-liver donors. Patients with intraoperative adverse events were significantly older, had a heavier mean graft weight, more frequently belonged to the American Society of Anesthesiologists class II and underwent right lobectomy than did patients with no intraoperative adverse events. A binary logistic regression model revealed that only age was an independent risk factor for intraoperative adverse events in our patients. Ishiko and associates[16] evaluated the effect of aging on the safety of lobectomy in 110 living-liver donors. These investigators reported that older age (age > 40 y) was a risk factor for postoperative albumin level recovery in their patients. Older patients also had a significantly higher mean intraoperative blood loss in this study, and the findings of Ishiko and associates support our results. We believe that age should be considered an important determinant of occurrence of intraoperative adverse events.

As discussed before, the intraoperative adverse events that we studied were usually mild, and therefore, the effect of these adverse events on patient outcomes and their clinical use may be questionable. However, our findings demonstrate that these adverse events may adversely affect a patient's outcome after donor lobectomy for LDLT in terms of more-frequent postoperative admission to the intensive care unit, longer stay in the hospital, and a higher mean postoperative international normalized ratio. Based on these findings, it is not possible to interpret the presence of a direct relation between the intraoperative adverse events that were sought in this study and a worse clinical outcome.

Finally, we performed a before and after analysis to investigate whether intraoperative use of ANHD and in-line fluid warmers changed the frequency of intraoperative adverse events in our living-liver donors. The efficiency of more-effective heating systems to prevent hypothermia during major abdominal surgery has been reported.[17-19] Avoidance of heterologous blood transfusion by use of blood salvage techniques may contribute to improved donor safety during LDLT.

Acute normovolemic hemodilution has several advantages over other blood salvage techniques such as minimal preoperative preparation, negligible risk of incorrect transfusion, no risk of transfusion associated viral infections, and no storage or testing costs.[20] However, there are conflicting data regarding the effectiveness of ANHD for reducing transfusion requirements during liver resection and major gastrointestinal surgery.[12, 20-25] After adopting perioperative modifications including more-frequent use of ANHD and in-line fluid warmers—rates of hypothermia, hypotension, transfusions, and overall intraoperative adverse events significantly decreased in our patients. Although it is not possible to extrapolate the presence of a causative relation between adopting perioperative modifications and a significant decrease in the rate of intraoperative adverse events, our findings point toward a beneficial effect for these changes.

Another controversial technique for minimizing blood loss during donor hepatectomy is lowering central venous pressure.[11, 26-27] In our study, the intraoperative mean central venous pressure measurements were not significantly different between patients with an intraoperative adverse event and those without such an adverse event. Ryu and associates[26] and Melendez and associates[27] have reported that a low central venous pressure may help minimize blood loss without adversely affecting organ perfusion during donor hepatectomy. In contrast to these findings, in a large series of 984 living donors, Kim and associates[11] showed no association between central venous pressure and intraoperative blood loss.

One important limitation of this study is its retrospective nature. A randomized, controlled, prospective study that focuses on the frequency, type, and risk factors of intraoperative adverse events, and the effect of perioperative management modifications on the occurrence of such adverse events will provide information that is more valuable. Another important limitation of our study is that despite the fact that outcome measures that

were used in this study strongly suggest that intraoperative adverse events adversely affect living-liver donors recovery postoperatively, it is impossible to judge these adverse events as the independent risk factor for a worse outcome, based on our results.

Intraoperative adverse events were common during donor lobectomy for LDLT, and age was the only independent risk factor for the occurrence of these adverse events. Patients with these adverse events required admission to the intensive care unit more frequently and stayed in the hospital longer than did those patients without adverse events. Perioperative management modification in terms of use of in-line fluid warmers and ANHD decreased the rate of intraoperative adverse events in our series.

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