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# Predictors of intra-abdominal coagulopathic hemorrhage after living donor liver transplantation

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A R T I C L E I N F O

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A B S T R A C T

*Background:* Results of preoperative conventional coagulation assays are a poor predictor of hemorrhage after liver transplantation. In this study, we evaluated the factors that are predictive of intra-abdominal coagulopathic hemorrhage after living donor liver transplantation surgery.
*Methods:* During the period from January 2009 to December 2012, 118 adults underwent living donor liver transplantation (LDLT) in our institution. Of those patients, 18 (15.3%) developed intra-abdominal coagulopathic hemorrhage ($n = 7$) or hemorrhage due to non-coagulopathic causes ($n = 11$) that required emergency medical, radiological, or surgical intervention within the first month after LDLT. Possible predictors of postoperative coagulopathic hemorrhage included donor-related factors, age, body mass index, MELD score, INR value, intra-operative blood transfusion, graft/recipient weight ratio, anhepatic phase, cold ischemia time, operative time, APACHE II score, onset of re-bleeding, and hemoglobin levels during rebleeding episodes.
*Results:* There were no differences in any of the variables between the two groups (coagulopathic and noncoagulopathic hemorrhage) except for cold ischemia time. We found that cold ischemia time was significantly longer in patients with postoperative coagulopathic hemorrhage (160.50 ± 45.02 min) than in patients with hemorrhage due to non-coagulopathic causes (113.55 ± 29.31 min; $P = 0.027$).
*Conclusion:* Prolonged cold ischemia time is associated with postoperative intra-abdominal coagulopathic hemorrhage in patients after LDLT. It is, therefore, necessary to shorten the cold ischemia time in order to reduce the risk of postoperative intra-abdominal hemorrhage due to coagulopathic causes.


## 1. Introduction

Liver transplantation is the only treatment available for patients with end-stage liver disease (ESLD).[1] Although liver transplantation is a curative treatment for most patients with ESLD, the shortage of deceased donor organs continues to be the main obstacle in the treatment of these patients.[2] Fortunately, with improvements in medical knowledge, surgical skills, and radiological techniques, living donor liver transplantation (LDLT) is now an option for many patients with ESLD. However, LDLT is associated with a number of post surgical complications that contribute to hospital mortality such as portal hypertension with various degrees of coagulopathy.[3] Hemorrhage due to coagulopathy often manifests as diffuse oozing at the operative site. Postoperative intra-abdominal bleeding, due to vascular complications or disseminated intravascular coagulopathy due to underlying diseases may result in catastrophic consequences. It has been reported that 7% of patients who undergo LDLT experience an intra-abdominal bleed and that 24% of those patients require re-exploration soon after transplant.[4] Although the mechanism of bleeding is multifactorial, non-surgical etiologies such as abnormalities of the hemostatic system can contribute to bleeding after liver surgery. Failure to surgically control bleeding vessels at the operative site is the most frequent cause of postoperative bleeding, which can manifest as hemorrhage at the operative site with expanding hematoma or excessive blood in surgical drains or wound dressings. Thus, patients should undergo studies for the

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identification and correction of deficiencies in circulating clotting factors, in platelet number and function, in hematocrit, blood volume, and body temperature, and should undergo proper treatment for any underlying infection.[5] Several investigators have shown that the results of preoperative conventional coagulation assays are a poor predictor of hemorrhage after liver transplantation. In addition, correction of prolonged prothrombin time with recombinant factor VIIa has not been shown to lead to a reduction in blood loss or transfusion in patients undergoing liver surgery.[6]

Sudden drainage of fresh blood from the drainage tube or an acute decrease in hemoglobin level with or without systemic hypotension suggests the presence of intra-abdominal bleeding and requires emergency exploratory laparotomy. However, the clinical presentation of hemorrhage is usually nonspecific, consisting mainly of localized pain and a falling serum hematocrit.[7] Although Doppler sonography combined with computed tomography (CT) is crucial for establishing a diagnosis of complications in hepatic vessels,[8–10] the correct diagnosis cannot be made with imaging examination alone. Thus, it is essential to understand the clinical and hematologic parameters relevant to postoperative intra-abdominal hemorrhage. In this study, we evaluated the predictors of postoperative intra-abdominal coagulopathic hemorrhage in patients after LDLT.

## 2. Materials and methods

### 2.1. Patients

This was a cross-sectional retrospective study. During the period January 2009 to December 2012, 118 adult patients with ESLD underwent right lobe LDLT at the Changhua Christian Hospital. Of those patients, 18 developed postoperative intra-abdominal hemorrhage within the first month after surgery and were enrolled in the present study (Fig. 1). Surgical bleeding after liver transplantation was defined as bleeding at the vascular anatomotic site, bleeding in the splenic hilum or stump of the hepatoduodenal ligament, bleeding in the para inferior vena cava space or right subsplenic area, bleeding in the abdominal wound, or bleeding at the surgical site requiring reoperation. Non-surgical bleeding was defined as oozing or bleeding at an extrasurgical site (hemoglobin drop $\geq$2 g/dL).

The study protocol was approved by the hospital's institutional review board.

### 2.2. Clinical data

All clinical data were obtained through chart review. Donor-related factors such as age and steatosis grades were evaluated. Before surgery, patients were evaluated for liver disease severity (Model for End-Stage Liver Disease, MELD score), coagulation function (International Normalized Ratio, INR), and the presence of hepatitis B virus (HBV), hepatitis C virus (HCV), and alcoholic hepatitis. The intra-operative variables included graft/recipient weight ratio (GRWR; %), operative time, intra-operative blood transfusion (units of packed red blood cells; PRBC), units of fresh frozen plasma (FFP), units of platelets and units of cryoprecipitate transfused, warm and cold ischemia time, and anhepatic phase. Postoperative variables included acute physiologic and health evaluation (APACHE) II score, onset of re-bleeding, re-bleeding blood loss, international normalized ratio (INR) value, hemoglobin level, blood pressure at onset of re-bleeding, and the presence of abdominal compartment syndrome.

### 2.3. Measurements

Clinical criteria were used in addition to imaging studies to determine the presence of hemorrhage. For example, patients who showed signs of overt bleeding combined with a hemoglobin drop $\geq$2 g/dL requiring transfusion and patients with drainage of $\geq$150 mL per hour of fresh blood through a Jackson-Pratt drain for at least 2 h, or intra-abdominal pressure (IAP) > 20 mm Hg combined with a drop in systolic blood pressure <90 mm Hg, and tachycardia

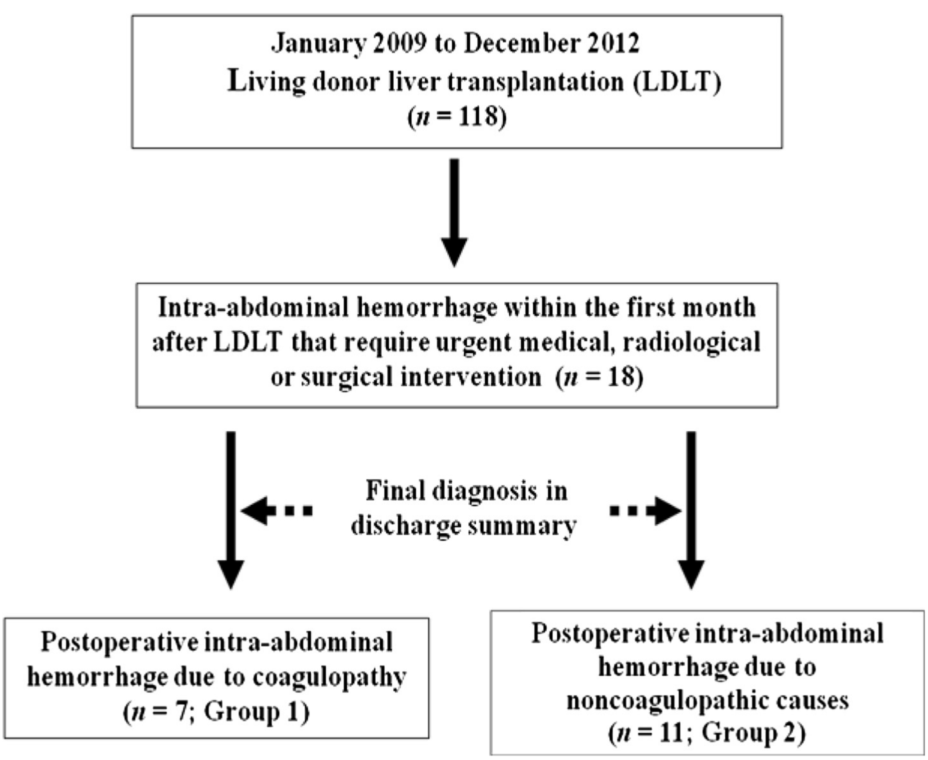


**Fig. 1.** The study population.

(>120 beats per minute) were evaluated by Doppler sonography combined with CT. Hemorrhage was then defined as coagulopathic or noncoagulopathic after an exploratory laparotomy was performed. Doppler sonography and abdominal CT scans were obtained within 24 h after the development of signs of intra-abdominal bleeding. Doppler sonographic examinations were performed by an experienced gastroenterologist at the patient's bedside. CT images of the liver were obtained with a 16-slice multi-detector CT scanner (Lightspeed Ultra 16, GE Medical Systems, Milwaukee, WI, USA) using the following parameters: a gantry rotation time of 0.8 s for each phase; a 5-mm section thickness; 27.5-mm/s table speed; 120 kVp; and 160–440 mA. Patients were imaged in a craniocaudal direction. Nonionic contrast medium (Omnipaque 350, General Electric Healthcare, Princeton, NJ, USA) was administered at a total dose of 100 mL–120 mL with an injection rate of 3 mL/s through a 20-gauge venous cannula placed in the antecubital vein. Scanning was started with a 10-s scan delay (about 25–30 s after injection of the contrast agent) for the hepatic arterial phase after the attenuation value of the aorta reached 120 HU. Equilibrium-phase images were acquired approximately 180–200 s after injection of the contrast agent. The abdominal CT scans were reviewed by two radiologists who specialize in abdominal imaging.

### 2.4. Statistical analysis

Data were recorded in a computer database. Possible predictors of postoperative coagulopathic hemorrhage included age, donor-related factors, body mass index, MELD score, INR value, intra-operative blood transfusion (PRBC), GRWR, units of FFP, units of platelets, units of cryoprecipitate transfused, anhepatic phase, cold ischemia time, operative time, APACHE II score, onset of re-bleeding, and hemoglobin levels at re-bleeding. We used the chi-square test or Fisher's exact test for categorical comparisons of data and the Mann–Whitney $U$-test to determine differences in the means of continuous variables. A $P$-value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the statistical package SPSS for Windows (Version 16.0, SPSS Inc; Chicago, IL, USA).

## 3. Results

During the study period, 18 patients (mean age, 53.5 years; range, 43–70 years) developed intra-abdominal hemorrhage within one month after LDLT. In the majority of patients (14 of 18; 78.8%), abdominal bleeding occurred within 10 days after transplantation. In two patients, bleeding occurred within 14 days, in one patient bleeding occurred 15 days after surgery, and in one patient bleeding was noted 22 days after the operation. Of the 18 patients who developed hemorrhage, 13 (72.2%) were men. Most of the donors in this study were young and had healthy liver function. Approximately one-third (6 of 18; 33.3%) of the donors had fatty liver with liver steatosis grades ranging from 1 to 3. The distribution of high-density fluid accumulation in these patients is shown in Fig. 2. Patients were stratified into one of two groups depending on whether they developed hemorrhage due to coagulopathy (group 1, $n = 7$) or hemorrhage due to non-coagulopathic causes (group 2, $n = 11$). Sites of intra-abdominal hemorrhage are shown in Table 1. Bleeding sites in patients in group 1 included the retrohepatic region ($n = 1$), the subphrenic region ($n = 2$), the retroperitoneal region ($n = 2$), splenic artery ($n = 1$), and the abdominal wall ($n = 1$). In group 2, bleeding sites comprised the hepatic artery ($n = 6$), the inferior vena cava ($n = 2$), the portal vein ($n = 1$), the splenic artery ($n = 1$), and the adrenal gland ($n = 1$). The clinical features of the two groups of patients are shown in Table 2. There were no significant differences between the two groups in donor related factors, age, body mass index (BMI), MELD score, preoperative INR value, intra-operative blood transfusion, units of fresh frozen plasma, units of platelets, units of cryoprecipitate transfused, GRWR, anhepatic phase, operative time, APACHE II score, onset of re-bleeding, or hemoglobin levels at the time of re-bleeding. However, cold ischemia time was significantly longer in patients with post-operative coagulopathic hemorrhage ($160.50 \pm 45.02$ min) than in patients with hemorrhage due to non-coagulopathic causes ($113.55 \pm 29.31$ min; $P = 0.027$). Our results show that prolonged cold ischemia time is associated

**Table 1**
Sites of intra-abdominal hemorrhage after LDLT due to coagulopathy (group 1) and due to non-coagulopathic causes (group 2).

| Location | Group 1 ($n = 7$) | Group 2 ($n = 11$) |
|---|---|---|
| Retrohepatic region | 1 | – |
| Subphrenic region | 2 | – |
| Retroperitoneal region | 2 | – |
| Splenic artery | 1 | – |
| Abdominal wall | 1 | – |
| Hepatic artery | – | 6 |
| Inferior vena cava | – | 2 |
| Portal vein | – | 1 |
| Splenic artery | – | 1 |
| Adrenal gland | – | 1 |

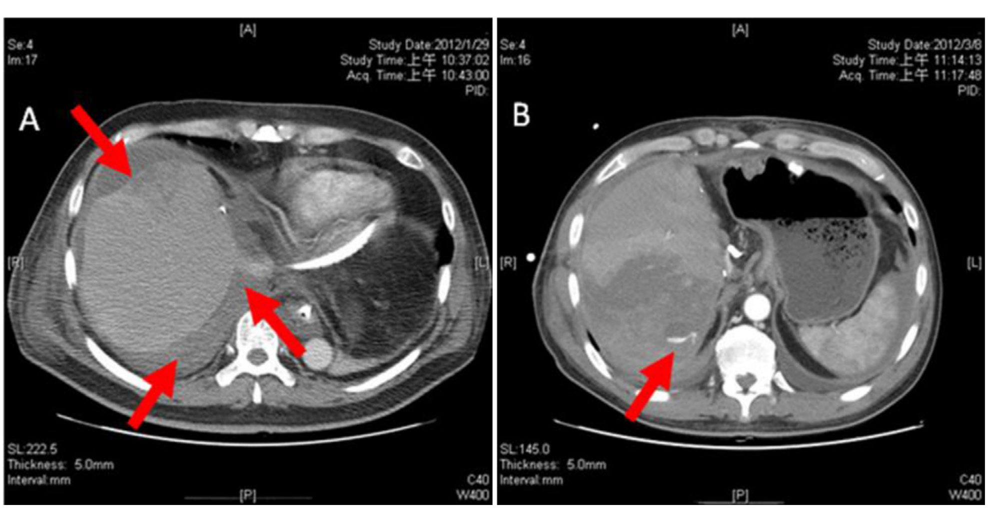


**Fig. 2.** (A) Postoperative intra-abdominal hemorrhage attributed to coagulopathy; (B) Postoperative intra-abdominal hemorrhage attributed to non-coagulopathic causes.

**Table 2**
Comparisons of demographic and clinical features of patients with intra-abdominal hemorrhage after LDLT.

| Variables | | Group 1 $n = 7$ | Group 2 $n = 11$ | $P$ | Total $N = 18$ |
|---|---|---|---|---|---|
| Age; yr | (SD) | 51.29 (9.16) | 55.00 (6.34) | 0.256 | 53.56 (7.53) |
| Gender (%) | Female | 2 (28.6) | 3 (27.3) | 1 | 5 (27.8) |
| | Male | 5 (71.4) | 8 (71.4) | | 13 (72.2) |
| BMI | (SD) | 25.71 (4.46) | 24.18 (4.49) | 0.439 | 24.78 (4.41) |
| Age of donor; yr | (SD) | 32.57 (14.27) | 28.00 (6.16) | 0.820 | 29.78 (9.97) |
| Donor steatosis grades | 0 | 4 (57.1) | 8 (72.7) | 0.463 | 12 (66.7) |
| | 1 | 2 (28.6) | 2 (18.2) | | 4 (22.2) |
| | 2 | 0 (0) | 1 (9.1) | | 1 (5.6) |
| | 3 | 1 (14.3) | 0 (0) | | 1 (5.6) |
| GRWR; % | (SD) | 0.994 (0.201) | 0.967 (0.112) | 0.364 | 0.978 (0.148) |
| MELD score | (SD) | 19.14 (9.49) | 18.09 (12.54) | 0.586 | 18.50 (11.16) |
| INR | (SD) | 1.94 (0.91) | 1.84 (1.24) | 0.341 | 1.88 (1.09) |
| Intra-operative blood transfusion; Packed RBC; units | (SD) | 15.71 (11.22) | 12.73 (10.93) | 0.716 | 13.89 (10.81) |
| FFP; units | (SD) | 14 (7.75) | 10.18 (8.36) | 0.386 | 11.67 (8.12) |
| Platelet; units | (SD) | 12 (12) | 8.18 (12.08) | 0.495 | 9.67 (11.85) |
| Cryoprecipitate; units | (SD) | 0 (0) | 2.18 (7.24) | 0.425 | 1.33 (5.66) |
| Anhepatic phase | (SD) | 67.86 (45.62) | 44.09 (22.56) | 0.113 | 53.33 (34.29) |
| Cold ischemia time; min | (SD) | 160.50 (45.02) | 113.55 (29.31) | 0.027 | 130.12 (41.29) |
| Operative time; min | (SD) | 484.29 (86.19) | 457.73 (95.30) | 0.586 | 468.06 (90.23) |
| APCHE II score | (SD) | 22.86 (7.24) | 18.09 (8.67) | 0.339 | 19.94 (8.27) |
| Re-bleeding time; days | (SD) | 10.00 (6.98) | 5.45 (4.08) | 0.145 | 7.22 (5.67) |
| Hb at re-bleeding; gm/dl | (SD) | 8.71 (2.22) | 7.67 (1.07) | 0.317 | 8.08 (1.64) |

Abbreviations: BMI: body mass index; GRWR: graft/recipient weight ratio; MELD score: model of end liver disease; INR: international normalized ratio; Fresh Frozen Plasma: FFP; Hb: hemoglobin.

with postoperative intra-abdominal coagulopathic hemorrhage in patients after LDLT.

## 4. Discussion

Although the overall outcomes of patients after liver transplantation have improved, early graft failure remains a serious concern because it is associated with high rates of morbidity and mortality.[11] A number of studies have reported that donor-related factors such as age and steatosis grades can affect post-transplant outcomes.[12,13] Most of the donors in this study were young and had healthy liver function; thus, there were no significant differences between patients with hemorrhage due to coagulopathy and patients with hemorrhage due to non-coagulopathic causes. The risk of intra-abdominal coagulopathic hemorrhage and hemorrhage due to iatrogenic causes is high during the early post-transplantation period. The incidence of postoperative vascular complications among recipients ranges from 11.8% to 13.0% after LDLT,[14,15] and the incidence of arterial complications has been reported to range from 6.5% to 9.1%.[16,17] Arterial complications, especially those occurring during the early postoperative period, frequently require laparotomy, re-transplantation, or surgical reconstruction. Jung et al. reported that the hepatic artery was the most frequent site of bleeding requiring laparotomy among 94 patients with evidence of abdominal hemorrhage after orthotopic liver transplantation.[18] Although CT is crucial for establishing a diagnosis of complications in hepatic vessels, it is important to understand the predictors of postoperative intra-abdominal coagulopathic hemorrhage.[7] In the present study, we found that prolonged cold ischemia time was associated with postoperative intra-abdominal coagulopathic hemorrhage.

After liver resection, grafts are stored on ice at 0 °C–4 °C. The length of time that grafts are stored on ice varies depending on the amount of time it takes to perform the recipient hepatectomy. It has been reported that 10% of early transplant failures are due to liver ischemia–reperfusion injury.[19] Prolonged hepatic allograft cold ischemia time (i.e. >12 h) has been shown to significantly increase the rate of graft loss and the rate of primary nonfunction.[20] According to the results of a recent meta-analysis, maximum patient and graft survival rates were associated with a cold ischemia time ranging from 7.5 to 12.5 h.[21] Therefore, additional efforts should be made to minimize cold ischemia time.[22]

In conclusion, prolonged cold ischemia time is associated with postoperative intra-abdominal coagulopathic hemorrhage in patients after LDLT. It is, therefore, necessary to shorten the cold ischemia time in order to reduce the risk of postoperative intra-abdominal hemorrhage due to coagulopathic causes.

*Ethical approval*

This was an observational study and data was collected using retrospective chart reviews. Thus, ethical approval was not required.

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*Author contribution*

Man-Ling Kao, Chia-En Heish, Kuo-Hua Lin and Yao-Li Chen designed and performed the research. Chen-Te Chou and Chih-Jan Ko collected data. Ping-Yi Lin contributed mainly to the data analysis and revised the manuscript. Man-Ling Kao, Ping-Yi Lin and Yao-Li Chen wrote the manuscript.

*Conflict of interest*

There are no conflicts of interest, either financial or otherwise, regarding this paper.

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