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ORIGINAL ARTICLE

Safety and Feasibility of Laparoscopic Liver Resection in Antiplatelet-Burdened Patients with Arterial Thromboembolic Risks

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ABSTRACT

AIM: The aim of the study was to assess the safety and feasibility of laparoscopic liver resection (LLR) using two-surgeon technique in patients with preoperative antiplatelet therapy (APT) for arterial thromboembolic risks.

METHODS: Patients who had undergone LLR using twosurgeon technique in a tertiary care setting from 2010 to 2016 were retrospectively reviewed. Our perioperative antithrombotic management of patients with high thromboembolic risks included continuation of aspirin monotherapy for APT patients and bridging heparin substitution for patients with anticoagulation. Outcome variables, including bleeding and thromboembolic complications, were compared between the APT patients with high thromboembolic risks (APT-HR group), those with low risks (APT-LR group), and those without APT (non-APT group).

RESULTS: A total of 73 LLRs were performed, including partial resection in 54, left lateral sectionectomy in 13, S5 subsectionectomy in 4, right anterior sectionectomy in 1 and left hepatectomy in 1. APT-HR group showed significantly high frequency of history of congestive heart failure, percutaneous coronary intervention and cerebral infarction, although tumor

characteristics and the type of operation were similar between the groups. Only one patient was converted to open surgery due to massive bleeding in non-APT group but none was converted in APT-HR or APT-LR groups. In the current cohort, neither bleeding nor thromboembolic complications occurred postoperatively, but one postoperative mortality case due to unknown cause was experienced in APT-HR group.

CONCLUSION: LLR using two-surgeon technique can be performed safely and satisfactorily even under continuation of aspirin monotherapy for patients with high thromboembolic risks, although this challenging group needs to be carefully managed to prevent fatal postoperative complications.

Key words: Laparoscopic liver resection; Two surgeon technique; Antiplatelet therapy; Bleeding complication; Thromboembolic complication

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INTRODUCTION

Recently, the number of patients who have histories of cardiovascular or cerebrovascular diseases has been increasing with aging of patients, and those patients often receive antiplatelet therapy (APT) for primary and secondary prevention of thromboembolic complications. Although indications for use of APT have expanded, perioperative antithrombotic management during non-cardiac surgery is still challenging and often troublesome due to increased risks of postoperative bleeding or thromboembolic complications^[1-4]. Potential risk of vessel/stent thrombosis may increase when APT is stopped periop-

eratively, whereas surgical hemorrhage or postoperative bleeding complications may occur more often when APT is continued before or during the operation^[4-8]. We established our own risk stratification system and perioperative antithrombotic management protocol for APT-burdened patients ("Kokura Protocol"), including preoperative continuation of aspirin monotherapy in patients with high thrombo-embolic risks, and have demonstrated the safety and feasibility of both open and laparoscopic abdominal surgeries under the Kokura Protocol^[9,10].

With the advent of minimally invasive surgery and its expected benefits, many abdominal surgical procedures are now being performed or attempted laparoscopically. Concerning liver resection, several studies have shown advantages of laparoscopic liver resection (LLR) compared with conventional open liver resection, including reduced degree of body wall damage, decreased intraoperative bleeding, fewer complications, and shorter postoperative hospital stay^[11-14]. However, because a high degree of skill performance is required during LLR, the safety and feasibility of LLR in APT-burdened patients with high thromboembolic risks still remains unclear. We have adopted "twosurgeon technique"[15] during open liver resection, and also introduced and maintained this procedure even in LLR, in order to perform safe liver parenchymal transection without critical intraoperative bleeding. The aim of this study is to review consecutive 73 patients undergoing LLR and to assess the feasibility of LLR using two-surgeon technique in APT-burdened patients with thromboembolic risks.

MATERIALS AND METHODS

Patients

Between April 2010 and March 2016, a total of 232 patients underwent liver resections at our institution. Among them, 73 consecutive patients undergoing LLR were reviewed in the current study. Patients receiving laparoscopic fenestration of giant hepatic cysts were excluded from the study. Surgical procedures in this cohort included hybrid laparoscopy-assisted liver resection (n = 63) and pure laparoscopic liver resection (n = 10). All procedures were performed by or under the guidance of one of the attending surgeons at our institution.

Demographics, diagnoses, surgical treatments and postoperative outcomes were obtained through a standardized review of the electronic surgery database as well as hospital and clinic charts. The status of patients' symptoms and functions with respect to ambulatory status and need for care was described according to the ECOG Scale of Performance Status (PS)^[16]. Postoperative complications were categorized and assessed using Clavien-Dindo classification (CDC)^[17] and CDC class II and more was considered significant. Postoperative bleeding and thromboembolic complications were defined as previously described^[9,10]. Bleeding complications included luminal bleeding, abdominal bleeding, and abdominal wall hematoma; thromboembolic complication, mesenteric infarction, and pulmonary thromboembolism. Operative mortality included death within 30 days after surgery.

The primary outcome included excessive intraoperative blood loss (1,000 mL or more) and postoperative bleeding and thromboembolic complications. Background characteristics, perioperative factors, and outcome variables were compared between the APT-burdened patients with high thromboembolic risks (APT-HR group), those with low risks (APT-LR group), and those without APT (non-APT group).

Perioperative antithrombotic management

We established our perioperative antithrombotic management system including thromboembolic risk stratification and perioperative antithrombotic management protocol ("Kokura Protocol"), and have shown that both open and laparoscopic abdominal surgeries in patients with antithrombotic therapy can be performed safely under Kokura Protocol^[9,10]. Figure 1 demonstrated perioperative flowchart of patients with ATT in Kokura Protocol. The management generally consisted of interrupting ATT 5 to 7 days before surgery and early postoperative reinstitution in low thromboembolic risk patients, whereas aspirin monotherapy is continued for APT patients and ACT was substituted by bridging heparin in case of high thromboembolic risks.

High thromboembolic risk patients were defined as follows; (1) patients undergoing drug-eluting coronary stent (DES) implantation (regardless of the interval between DES implantation and surgical procedures), or drug-non-eluting coronary stent implantation within 2 months; (2) patients undergoing cerebrovascular reconstruction within 3 months, or having recent-onset cerebral stroke or transient ischemic attack; (3) patients with regular oral anticoagulation for chronic atrial fibrillation, or those with previous venous thrombosis, and (4) patients having cardiovascular or cerebrovascular diseases who were assessed as "high risk" for other reasons by cardiac/cerebral specialists. In patients using both APT and oral anticoagulation therapy, perioperative management of APT was also combined with those of anticoagulation therapy.

For prevention of venous thromboembolism, mechanical prophylaxis (intermittent pneumatic compression and/or graduated compression stockings) and enforcement of early postoperative walking are generally performed, although routine use of medical prophylaxis with heparin is not adopted, except in case of high venous thromboembolic risk patients with previous venous thrombosis or immobilization.

LLR procedure

The indications for LLR at our institution were initially limited to the lesions in S2, S3, S5, S6 and the ventral side of S4, but were later expanded to almost all areas including S1. Patients having a large tumor more than 10 cm in diameter, those requiring bile duct resection or lymph node dissection, those with tumors involving major hepatic veins or inferior vena cava were excluded. We initially conducted hybrid laparoscopy-assisted liver resection to secure direct vision from



Figure 1 Perioperative management protocol ("Kokura Protocol") for patients undergoing antithrombotic therapy (ATT) in case of elective surgery. The management generally consists of interrupting ATT 5 to 7 days before surgery and early postoperative reinstitution in low thromboembolic risk patients. In patients with high thromboembolic risks, aspirin monotherapy is continued in patients with APT, and/or ACT was substituted by bridging heparin. Abbreviations: ATT, antithrombotic therapy; APT, antiplatelet therapy; ACT, anticoagulation therapy.

mini-laparotomy and to conduct liver parenchymal transection more safely using the same devices as in conventional open liver resection. After the accumulation of experience in LLR, pure laparoscopic liver resection without mini-laparotomy was introduced and performed depending on the tumor location and patient condition. Figure 2 shows trocar placement for LLR. In case of pure LLR, 4 to 5 trocars are placed in the right subcostal margin for the lesions in the right lobe, whereas the trocars are arranged bilaterally for the lesions in the left lobe (Figure 2A and 2B). In case of hybrid laparoscopy-assisted liver resection, mini-laparotomy is performed by placing a 5 to 12 cm incision right-subcostally for the right lobe (Figure 1C) or on the upper midline for the left lobe (Figure 1D), after mobilization of the target lobe laparoscopically.

Figure 3 and 4 demonstrated typical cases of pure LLR and hybrid LLR, respectively. During pure LLR, the right lobe is fully mobilized to dissect the hepatorenal and triangular ligaments. After mobilization, the locations of the tumor and the adjacent vessels are confirmed by intraoperative ultrasound (IOUS). Liver parenchymal transection is performed under laparoscopy using two-surgeon technique with coagulating sears, ultrasonic dissecting device, and saline-linked electrocautery^[15]. Hemostasis in the difficult deep area is achieved by saline-linked electrocautery combined with wet oxidized cellrose (SLiC-WOC method).

In case of hybrid LLR, after laparoscopic mobilization of the target lobe is completed, large gauzes are placed under the diaphragm to move the left lateral section and IOUS is performed through the miniincision. Liver parenchymal transection is performed in the same fashion as conventional open liver resection through mini-laparotomy, using two-surgeon technique with coagulating sears, ultrasonic dissecting device, and saline-linked electrocautery. SLiC-WOC method for hemostasis in the difficult area and situation is also used during hybrid LLR. For left lateral sectionectomy or hemihepatectomy, hanging method was used but routine inflow occlusion was not used.

Statistical analysis

The categorized data in each group were compared by chi-square or Fisher's exact probability test. Continuous variables in the characteristics were expressed as a median with range and compared by one-way ANOVA or Kruskal-Wallis test. Non-parametric variables were also compared using Kruskal-Wallis test with Scheffe's F test. Statistical significance was set at p < 0.05. Data were analyzed using the SPSS package software.

This study was approved by our institutional review board.

RESULTS

Patient and tumor characteristics

Among patients in the current study, 41.1% (30/73) of patients undergoing LLRs were receiving APT. LLR was completed on 72 cases (98.6%), and one case (1.4%) had conversion to a large laparotomy due to the massive bleeding from injured left subphrenic vein when the lateral section was mobilized in laparoscopic procedures.



Figure 2 Trocar placement for laparoscopic liver resection (LLR). (A) and (B) show the case of pure LLR for the lesions of the right and left lobe, respectively. In case of hybrid laparoscopy-assisted liver resection (C and D), mini-laparotomy is performed by placing a 5 to 12 cm incision on the right subcostal (Figure 1C for the right lobe) or mid-line region (Figure 1D for the left lobe) over the trocar sites.

Table 1 shows background characteristics of patients in each group. The patients in the cohort were totally Asian. The median age in the APT-HR, APT-LR and non-APT groups were 78, 77 and 70 years, respectively (p = 0.002). New York Heart Association (NYHA) class II-IV (p = 0.002), history of congestive heart failure (p = 0.002), history of percutaneous coronary intervention (p < 0.001) and coronary artery bypass graft (p = 0.044), history of cerebral infarction (p = 0.006), and high ASA score (p < 0.001) were more common in APT-HR group. There was no difference between the groups in the rate of anticoagulation therapy.

Table 2 shows tumor characteristics of patients in each group. The preoperative diagnoses were hepatocellular carcinoma in 32 (43.8%), liver metastases from gastrointestinal malignancy in 35 (47.9%) and benign diseases in 6 (8.2%). There was no difference in the rate of liver diseases between the groups (p = 0.681). The median tumor sizes in APT-HR, APT-LR, and non-APT groups were 28 mm (range 13 to 50 mm), 30 mm (10 to 65 mm), and 30 mm (10 to 80 mm), respectively. There were also no differences between the groups in the number of the lesions (n = 0.322), location of the lesions (p = 0.124), and existence of bilobar lesions (0.196).

Postoperative morbidity and mortality

Perioperative characteristics and postoperative morbidity in each group were demonstrated in Table 3. Types of LLR included partial

resection in 54 (74.0%), left lateral sectionectomy in 13 (17.8%), S5 sub-sectionectomy in 4 (5.5%), right anterior sectionectomy in 1 (1.4%) and left hepatectomy in 1 (1.4%). The types of operation or LLR modes (pure vs hybrid) were similar between the groups. The median length of maximal incisions in each group were 9 cm (range 2 to 12 cm), 8 cm (2 to 10 cm), 8 cm (2 to 12 cm), respectively (p = 0.456). One patient (1.4%) was converted to open surgery due to massive bleeding in non-APT group, but none was converted in APT-HR or APT-LR groups.

No case suffering uncontrollable excessive intraoperative bleeding due to the continuation of APT was experienced in APT-HR group. Although the estimated operative blood loss was identical between the groups (p = 0.730), there was a significant tendency of higher rate of intraoperative RBC transfusion in APT-HR group (3/13, 23.1%), mainly because early adjustment of preoperative mild anemia was performed in order to reduce cardiac stress by anemia. The duration of operation was also identical between the groups (p = 0.653).

Postoperative complications developed in 8.2% (6/73) of overall patients. The most common complication was superficial surgical site infection (4.1%). In the current cohort, neither bleeding nor thromboembolic complications occurred in any group postoperatively, but one postoperative mortality case due to unknown cause was experienced in APT-HR group. The patient with long-term maintenance of hemodialysis for severe chronic kidney disease, who proceeded to hybrid



Figure 3 Pure laparoscopic partial liver resection in S8 resion. (A) The right lobe was fully mobilized to dissect the hepatorenal and triangular ligaments. (B) After mobilization, the locations of the tumor and the adjacent vessels were confirmed by intraoperative ultrasound (IOUS). (C) Liver parenchymal transection was performed under laparoscopy using two-surgeon technique with coagulating sears, ultrasonic dissecting device, and saline-linked electrocautery. (D) Hemostasis in the difficult deep area was achieved by saline-linked electrocautery combined with wet oxidized cellrose (SLiC-WOC method).

laparoscopic partial liver resection for hepatocellular carcinoma with continuation of aspirin due to history of multiple DES implantation, had an excellent early postoperative course but developed sudden cardiopulmonary arrest with unknown cause (coronary stent thrombosis or pulmonary embolism were denied by urgent cardiac catheterization), probably unrelated to surgical procedures, and expired 10 days after surgery.

DISCUSSION

Our study demonstrates that 41.1% of patients undergoing LLRs in our institution are receiving APT. The cohort comprised 73 LLRs including both pure and hybrid LLRs, and we used our perioperative management protocol ("Kokura Protocol") to maintain aspirin monotherapy in case of high thromboembolic risks. No case suffering excessive bleeding due to continuation of APT was encountered, and neither hemorrhagic nor thromboembolic complications in any group.

Reduction of intraoperative blood loss is one of the main goals during liver surgery, and various technical development has been introduced, including the Pringle maneuver, hanging maneuver, and two-surgeon technique^[15,18,19]. Two-surgeon technique during liver resection, introduced by Aleoia *et al*, is a simple technique for reducing surgical blood loss and bile leakage while maintaining

the hepatic viability^[15]. The primary surgeon directs the dissection using ultrasonic dissection device; the secondary surgeon operates the saline-linked electrocautery device to perform strict hemostasis. We adopted this technique during not only conventional open liver resection, but also both hybrid and pure LLRs. In our institution, the rate of APT-burdened patients requiring major hepatobiliary and pancreatic surgery is almost 30-40%, and the number is expected to be increasing. For this reason, a simple but strong hemostatic devices and technique should be adopted and utilized especially in this critical patient population.

In patients undergoing major hepatobiliary and pancreatic surgery, perioperative surgical stress, as well as the insufficient APT management, is thought to affect surgical outcome. The stress of surgery has been shown to generate an inflammatory response predisposing to plaque fissure and subsequent acute arterial thrombosis^[20,21]. Thus, we should consider an indication of minimally invasive laparoscopic surgery including LLRs to even more troublesome APT-burdened patients. Our current data demonstrated that no patient suffering excessive bleeding due to continuation of APT use was encountered during LLRs using two-surgeon technique, and neither bleeding nor thromboembolic complications were encountered postoperatively. Our policy in managing APT patients using Kokura Protocol is valid and feasible even when LLRs are performed.



Figure 4 Hybrid laparoscopy-assisted left lateral sectionectomy. (A, B) Under the laparoscopy, the falciform ligament was transected and the left lobe was fully mobilized by using coagulating sears or electrocautery. (C) Large gauzes were placed under the diaphragm to move the left lateral section under the mini-incision. (D) Liver parenchymal transection was performed through mini-laparotomy using two-surgeon technique with coagulating sears, ultrasonic dissecting device, and saline-linked electrocautery.

Fujikawa T et al. Laparoscopic liver resection in thromboembolic risk patients

Table 1 Background characteristics of patients in the cohort.								
Variables	APT-HR (<i>n</i> = 13)	APT-LR (<i>n</i> = 17)	non-APT (<i>n</i> = 43)	<i>p</i> value				
Age, y, median (range)	78 (69-86)	77 (59-90)	70 (45-89)	0.002				
Gender, n (%)				0.094				
Female	1 (7.7)	5 (29.4)	17 (39.5)					
Male	12 (92.3)	12 (70.6)	26 (60.5)					
BMI				0.599				
$< 30 \text{kg/m}^2$	13 (100.0)	16 (94.1)	42 (97.7)					
$\geq 30 \text{kg/m}^2$	0 (0.0)	1 (5.9)	1 (2.3)					
Performance status, n (%)				0.133				
0,1	10 (76.9)	15 (88.2)	41 (95.3)					
2,3	3 (23.1)	2 (11.8)	2 (4.7)					
NYHA class II-IV, n (%)				0.002				
No	9 (69.2)	14 (82.4)	43 (100.0)					
Yes	4 (30.8)	3 (17.6)	0 (0.0)					
Concurrent diseases, n (%)								
Diabetes mellitus	4 (30.8)	6 (35.3)	6 (14.0)	0.138				
Hx of congestive heart failure	5 (38.5)	3 (17.6)	1 (2.3)	0.002				
Coronary artery disease								
Hx of PCI	9 (69.2)	8 (47.1)	0 (0.0)	< 0.001				
Hx of CABG	2 (15.4)	2 (11.8)	0 (0.0)	0.044				
Hx of cerebral infarction	3 (23.1)	1 (5.9)	0 (0.0)	0.006				
Current hemodialysis/PD	1 (7.7)	0 (0.0)	0 (0.0)	0.096				
Liver cirrhosis (Child-Pugh B)	3 (23.1)	3 (17.6)	7 (16.3)	0.854				
ASA score, n (%)				< 0.001				
1,2	2 (15.4)	5 (29.4)	39 (90.7)					
3,4	11 (84.6)	12 (70.6)	4 (9.3)					
Antithrombotic therapy, <i>n</i> (%)								
Antiplatelet therapy	13 (100.0)	17 (100.0)	-	< 0.001				
Anticoagulation therapy	1 (7.7)	2 (11.8)	4 (9.3)	0.927				

APT: antiplatelet therapy; HR: high risk, LR: low risk, BMI; body mass index, NYHA; New York Heart Association, PCI; percutaneous coronary intervention, CABG: coronary artery bypass graft, PD; peritoneal dialysis, ASA: American Society of Anesthesiologists.

Table 2 Tumor characteristics of patients in the cohort.								
	APT-HR	APT-LR	non-APT					
Variables	(n = 13)	(n = 17)	(n = 43)	<i>p</i> value				
Liver diseases, n (%)				0.681				
HCC	8 (61.5)	7 (41.2)	17 (39.5)					
Liver metastases from GI malignancy	4 (30.8)	9 (52.9)	22 (51.2)					
Others	1 (7.7)	1 (5.9)	4 (9.3)					
Number of the lesions, n (%)				0.322				
Single	12 (92.3)	12 (70.6)	35 (81.4)					
Multiple	1 (7.7)	5 (29.4)	8 (18.6)					
Location of the lesions, n (%)				0.124				
S1	1 (7.7)	0 (0.0)	2 (4.7)					
S2-S4	6 (46.2)	12 (70.6)	22 (51.2)					
S5,S6	0 (0.0)	4 (23.5)	17 (39.5)					
S7,S8	6 (46.2)	5 (29.4)	10 (23.3)					
Bilobar lesions existed, n (%)				0.196				
Yes	0 (0.0)	3 (17.6)	3 (7.0)					
No	13 (100.0)	14 (82.4)	40 (93.0)					
Size, mm, median (range)	28 (13-50)	30 (10-65)	30 (10-80)	0.982				

APT: antiplatelet therapy; HR: high risk; LR: low risk; HCC: hepatocellular carcinoma; GI: gastrointestinal; SD: standard deviation.

With the widespread use of antiplatelets for secondary prevention of cardiovascular or cerebrovascular diseases^[22-24], it is quite common that patients with APT receive surgical procedures. Approximately 5 to 15 % of patients undergoing implantation of coronary stent are estimated to undergo non-cardiac surgery within 2 years^[25]. In patients with APT, bleeding and thromboembolic complications are major perioperative concerns; continuation of APT is associated with an increased risk of bleeding, whereas discontinuation of APT might cause thromboembolic complications^[1,26]. If the thromboembolic risk is low, interruption of antiplatelets is possible. However, if the risk of thromboembolism is high, continuation of single antiplatelet, such as aspirin monotherapy seen in the management in Kokura Protocol, should be adequate.

Premature discontinuation of antiplatelet agents is one of the risk

Table 3 Factors concerning operative procedures and postoperative morbidity.								
¥7 · 11	APT-HR	APT-LR	non-APT	<i>p</i> valu				
Variables	(n = 13)	(n = 17)	(n = 43)					
Type of operation, n (%)				0.196				
Partial resection	9 (69.2)	11 (64.7)	34 (79.1)					
S5 sub-sectionectomy	0 (0.0)	0 (0.0)	4 (9.3)					
Mono-/bi-sectionectomy	4 (30.8)	6 (35.3)	5 (11.6)					
Mode of laparoscopic surgery, n (%)				0.732				
Pure laparoscopic surgery	1 (7.7)	3 (17.6)	6 (14.0)					
Hybrid laparoscopic surgery	12 (92.3)	14 (82.4)	37 (86.0)					
Conversion to open surgery, n (%)	0 (0.0)	0 (0.0)	1 (2.3)	0.702				
Duration of ope., min, median (range)	174 (98-359)	180 (101-331)	208 (104-353)	0.653				
Surgical blood loss, mL, median (range)	185 (1-850)	103 (1-570)	159 (1-2230)	0.730				
Intraoperative RBC transfusion, n (%)	3 (23.1)	1 (5.9)	4 (9.3)	0.283				
Length of incision, cm, median (range)	9 (2-12)	8 (2-10)	8 (2-12)	0.456				
Postop. complication, n (%)								
None	11 (84.6)	16 (94.1)	40 (93.0)	0.578				
superficial SSI	0 (0.0)	1 (5.9)	2 (4.7)	0.696				
deep SSI	1 (7.7)	0 (0.0)	1 (2.3)	0.427				
Bleeding complication	0 (0.0)	0 (0.0)	0 (0.0)	-				
Thromboembolic complication	0 (0.0)	0 (0.0)	0 (0.0)	-				
Cardiopulmonary arrest	1 (7.7)	0 (0.0)	0 (0.0)	0.096				
Length of postop. stay, d, median (range)	12 (7-22)	14 (7-23)	11 (6-19)	0.074				

APT: antiplatelet therapy; HR: high risk; LR: low risk; RBC: red blood cell; ope.: operation; postop.: postoperative; SSI: surgical site infection.

factors of late coronary stent thrombosis, which is uncommon but life-threatening complication with the rate of mortality between 9 and 45%^[23,25,27]. Current guidelines also specify that in the perioperative period, the continuation of APT, but not using heparin bridging, should be considered, particularly in high thromboembolic risk patients^[28-31]. Considering those circumstances, we have established our own perioperative antithrombotic management protocol ("Kokura Protocol"), and shown that either open or laparoscopic abdominal surgery can be performed safely in APT-burdened patients under the Kokura Protocol^[9,10]. In addition, the current study also demonstrated that the Kokura Protocol is valid and feasible even in the setting of laparoscopic liver resection, resulting in no occurrence of either bleeding or thromboembolic complications in the present cohort.

The current study has some limitations. It is a retrospective review from a single center, which lessens the efficacy of the statistical analysis and conclusion. This limitation will be mitigated in a later follow-up study or in a multi-institutional prospective study. In addition, as we continue to manage APT patients undergoing LLRs using the same perioperative antiplatelet management protocol and operative policy, we will accumulate more patients to help us understand the feasibility and safety of our approach on this challenging patient population.

CONCLUSION

We demonstrated that LLRs using two-surgeon technique can be performed safely and satisfactorily even under continuation of aspirin monotherapy for patients with high thromboembolic risks, although this challenging group needs to be carefully managed to prevent fatal postoperative complications.

CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

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