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Donor Selection and Prophylactic Strategy for Venous Thromboembolic Events in Living Donors of Liver Transplantation Based on Results of Thrombophilia Screening Tests

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Background: We reported a strategy of thrombophilia testing-guided venous thromboembolic events (VTE) prophylaxis for living donors of liver transplantation in 2011. The aim of the present study was to evaluate the safety and efficacy of this protocol for VTE prophylaxis.

Material/Methods: Thrombophilia testing, including protein S (PS), protein C (PC), antithrombin (AT) III, and anti-phospholipid antibody (APLA), was performed in 306 living donor candidates between July 2005 and June 2016. Donors who met any of the criteria of PS <60%, PC <64%, AT-III <70%, and positive APLA were classified into the borderline group and received continuous venous infusion of heparin immediately after surgery, in addition to use of elastic stockings and intermittent pneumatic compression (IPC) until patients were ambulatory. Other donors who were classified into the normal group used elastic stockings and IPC with no anticoagulants. The efficacy and safety endpoints were VTE occurrence and bleeding events, respectively.

Results: PS was considerably decreased in 3 candidates and PC was considerably reduced in 1 candidate, and they were excluded for high risk of VTE. Seventeen candidates in the borderline group and 137 in the normal group underwent donor surgery. One donor in the borderline group developed a wound hematoma. Postoperative complications were similar between the 2 groups. None of the donors in either group developed VTE.

Conclusions: Thrombophilia testing-guided VTE prophylaxis is safe and may contribute to reduced VTE risk in donors, although further investigations are warranted to assess the necessity of thrombophilia testing prior to surgery among living donors.

MeSH Keywords: **Donor Selection • Liver • Living Donors • Postoperative Complications • Safety Management • Venous Thrombosis**

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Background

Donor safety is the highest priority in living donor liver transplantation (LDLT). We experienced a donor who developed pulmonary embolism (PE) in the early postoperative period, despite no risk factors of thrombosis by usual preoperative donor evaluation in 2005. The activity of protein S (PS) in this donor, which was tested after surgery, was low. Since then, we have routinely performed thrombophilia screening tests in addition to conventional coagulation test for evaluation of donors and established these screening criteria for donor selection and venous thromboembolic events (VTE) prophylaxis [1]. As additional parameters, we determined the activity of PS, protein C (PC), and antithrombin III (AT-III) for inherited thrombophilia. We also measured anti-phospholipid antibody (APLA), including levels of lupus anticoagulant, IgG anti-cardiolipin (CL) antibodies, and anti-beta-2-glycoprotein I (β2GPI) antibodies, for anti-phospholipid syndrome.

This study aimed to evaluate the safety and efficacy of thrombophilia testing-guided VTE prophylaxis for living donors of liver transplantation. This study was approved by the Ethics Committee of Nagoya University School of Medicine (approval number: 2016-0271). Signed informed consent was obtained from all participants in this study.

Material and Methods

Patients

All donor candidates who were evaluated for LDLT between July 2005 and June 2016 were enrolled. Family members of recipients, including those aged between 20 and 65 years old, were eligible to be donor candidates. Candidates with a medical history or comorbidities were excluded before evaluation. When the donor candidates expressed their will to donate their partial liver, evaluation proceeded in a stepwise fashion as follows. We interviewed the candidates regarding their medical history, comorbidities, family history of the disease, and smoking and alcohol consumption. Potential donors then underwent a blood test, including a complete blood count, biochemical tests, and infection analysis, measurement of tumor markers, and coagulation tests, as well as thrombophilia screening tests. Chest and abdominal X-rays, an electrocardiogram, and a pulmonary function test were also undertaken simultaneously.

The results of thrombophilia screening tests were obtained in approximately 1 week. Therefore, donor candidates proceeded with a computed tomography scan unless the complete blood count, biochemical tests, the conventional coagulation test, chest and abdominal X-rays, electrocardiogram, and pulmonary function test were contraindicative of donor surgery before the results of thrombophilia testing were obtained.

Criteria of thrombophilia screening tests and the algorithm for donor selection

The activity of PS, PC, and AT-III, and levels of lupus anticoagulant, IgG anti-CL antibodies, and anti-β2GPI antibodies levels were examined. We also examined information from the interview on the history of thrombosis in addition to conventional coagulation tests, including prothrombin time, activated partial prothrombin time, fibrinogen levels, and D-dimer levels. A flow diagram of donor candidates in the study is shown in Figure 1. Based on the results of thrombophilia screening tests, the candidates were classified into 2 groups as follows. Candidates who satisfied all of the criteria for PS, PC, and

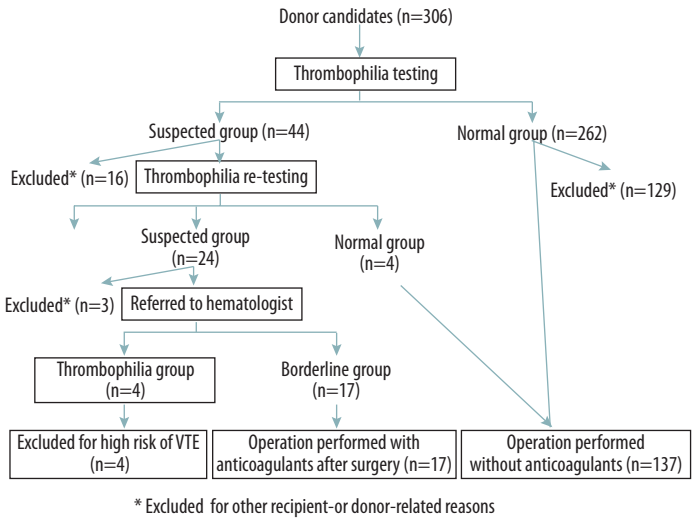

Figure 1. Flow diagram of donor candidates in study. There were 306 living donor candidates who underwent thrombophilia screening tests. Of these, 262 donor candidates were classified in the normal group and 44 in the suspected group after the first thrombophilia screening tests. Four donor candidates were excluded for high risk of VTE. There were 137 donor candidates in the normal group and 17 donor candidates in the borderline group who underwent living donor surgery. VTE – venous thromboembolic events.

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Table 1. Thrombophilia screening tests scoring.

Variables	Scores			
	0	1	2	3
Protein S* (%)	>60	50–60	40–50	<40
Protein C* (%)	>64	54–64	44–54	<44
AT III (%)	>70	60–70	50–60	<50
LAC**	<1.3	>1.3		
IgG anti-CL antibodies (U/mL)	<10	>10		
Anti-β2GPI antibodies (U/mL)	<3.5	>3.5		
Medical history of thrombosis	No	Yes		

* Activity; ** measured with dRVVT method. AT – Antithrombin; LAC – lupus anticoagulant; CL – Cardiolipin; β2GPI – beta-2-glycoprotein I.

normal AT-III (PS >60%, PC >64%, AT-III >70%) and APLA negative (lupus anticoagulant <1.3 U/ml, IgG anti-CL antibodies <10 U/mL, anti-β2GPI <3.5 U/mL) were classified in the normal group. All candidates other than those in the normal group were classified in the suspected group.

For candidates classified in the suspected group by the initial tests, we repeated thrombophilia screening tests to avoid misdiagnosis caused by spurious results [2,3]. Potential donors who were classified in the suspected group after the initial and second tests were referred to hematologists. Potential donors in the suspected group were eventually divided into the thrombophilia group and the borderline group according to thrombophilia screening tests scoring (Table 1) after discussion with hematologists. PS and PC activity are good indicators for detection of inherited thrombophilia [4]. Therefore, we determined the cut-off as the mean -3 standard deviation (SD) and mean -2SD for this scoring [4]. According to Caprini score [5], medical history of thrombosis represents the same score as positive APLA for this scoring. Donor candidates with total score ≥3 were classified in the thrombophilia group and excluded from the potential donors. Donor candidates with total score of 1 to 2 were classified in the borderline group and underwent a Doppler ultrasound examination of the lower limbs to exclude the preexistence of deep vein thrombosis prior to donor surgery.

Strategy of prophylaxis against thrombosis

As prophylaxis for VTE for donors in the normal group, we followed the instruction of an original computer-linked check scoring and decision-making system for the screening of thromboembolism types developed by Nagoya University Hospital [6] on the basis of the sixth American College of Chest Physicians (ACCP)-recommended prophylaxis guideline [7], which was modified recently on the basis of the 8th ACCP guideline [8]. We routinely used elastic stockings and intermittent pneumatic compression (IPC) in addition to the advocated early ambulation for all donors postoperatively. There was a previous report of high incidence of PE in living liver donors with thrombophilia despite using subcutaneous low-molecular weight heparin (LMWH) [9]. A transient hypercoagulable state has been also described after hepatectomy in living liver donors despite usual prophylaxis with LMWH [10]. Therefore, for donors in the borderline group, anticoagulant therapy using continuous venous infusion of heparin was given in addition to elastic stockings and IPC postoperatively. Continuous intravenous heparin was administered at the rate of 500 units per hour starting immediately after surgery until patients were fully ambulatory, according to guidelines from the Japanese Circulation Society [11]. The dose of heparin was adjusted for targeting the range of the APTT ratio (patient/control) of 1.5 to 2.0. When APTT was less than 1.5, the dose of heparin was increased by 250 units per hour. When APTT was greater than 2.0, the dose was reduced by 250 units per hour. APTT was checked every 6 h after starting infusion. After 2 consecutive APTT ratios were within target range, it was monitored daily.

Postoperative monitoring for thrombosis

We carefully monitored the presence of symptoms related to thrombosis, including swelling, pain, redness of the leg, acute shortness of breath, chest pain, or hemoptysis, and vital signs, and oxygen saturation by pulse oximetry for postoperative course. When thrombosis was suspected, we performed further examinations, including chest radiography, a Doppler ultrasound examination of the lower limbs, arterial blood gas analysis, contrast-enhanced chest CT scan, and ventilation/perfusion lung scanning, as needed.

Statistical analysis

Data were analyzed with IBM SPSS Statistics software version 20 (IBM Corp, Armonk, NY). All values are shown as the

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Table 2. Characteristics and conventional measurement findings of the donor candidates in normal and suspected group*.

	Normal group (n=262)	Suspected group (n=44)	*P*
Age at evaluated (years)	36.9±11.6	35.7±11.7	0.58
Sex (female/male)	135/127	29/15	0.08
PLT (×1000/μL)	237.9±48.5	240.6±58.2	0.94
PT (%)	101.4±9.2	97.7±8.9	0.14
APTT (%)	94.8±19.6	95.7±22.9	0.90
Fibrinogen (mg/dL)	267.8±58.5	286.4±72.8	0.95
D-dimer (μg/dL)	0.54±0.14	0.58±0.27	0.40

Values are shown as the mean ±SD. PLT – platelet count; PT – prothrombin time; APTT – activated partial prothrombin time.
* Classified with first thrombophilia test.

mean ±SD. Results were compared using χ^2 tests for categorical variables and a *t*-tests for continuous variables. A value of $p<0.05$ was considered to be statistically significant. Patient and graft survival curve estimates were calculated according to the Kaplan-Meier method and compared using the log-rank test.

Results

Between July 2005 and June 2016, we evaluated 306 living donor candidates, consisting of 164 female and 142 male candidates, with a median age of 36 years (range, 20–64 years) for LDLT. All donor candidates were Asian. Of these, 262 and 44 donor candidates were classified in the normal and the suspected groups, respectively, after the first thrombophilia screening tests. Table 2 shows characteristics and conventional measurements of donor candidates in the normal (n=262) and the suspected groups (n=44) who were classified at the first thrombophilia screening tests. There were no significant differences in characteristics and conventional measurements between the 2 groups. Of 44 potential donors in the suspected group, 16 were excluded due to either donor- or recipient-related reasons. Therefore, 28 donor candidates underwent a second thrombophilia screening test. Thrombophilia screening re-testing showed normal results in 4 patients, who were then re-assigned to the normal group. Further evaluation was discontinued in 3 candidates in the suspected group after the second test because of recipient death. Therefore, we consulted hematologists for another 21 donor candidates for further discussion. Eventually, 4 donor candidates were classified in the thrombophilia group and excluded due to a high risk of VTE. There were 137 donor candidates in the normal group and 17 donor candidates in the borderline group who underwent living donor surgery. All donors in the normal group were classified as low risk for VTE according to ACCP guidelines. Therefore, we used mechanical prophylaxis, including IPC, but no pharmacologic prophylaxis for donors in the normal group. Vascular-related complications after transplantation, including portal vein thrombosis and hepatic artery thrombosis, were comparable with those in recipients with transplantation from donors in the normal group. No recipients developed VTE after transplantation.

Candidates excluded due to high risk of VTE

Four donor candidates who were classified in the thrombophilia group were excluded due to high risk of VTE (Table 3). The first excluded candidate (case #1) was a 35-year-old female. Thrombophilia screening tests showed that PC activity was considerably decreased to 43% and 41% on first and second test, respectively. Additionally, IgG anti-CL and anti-β2GPI antibodies were present (19 U/mL and 4.8 U/mL, respectively). The second donor candidate (case #2) was a 21-year-old male in whom initial screening showed that PS activity was considerably decreased to 37% and a second test also indicated that PS activity was low (38%). This candidate mentioned that he had a history of thrombosis after the screening tests. The third donor candidate (case #3) was a 27-year-old female in whom the first screening showed that PS activity was considerably decreased (35%) and a reexamination also indicated that PS activity was low (32%). The fourth donor candidate (case #4) was a 38-year-old female in whom the initial screening showed that PS activity was significantly decreased to 31% and a repeated test also showed that PS activity was low (33%). A missense mutation in the PC and PS genes was later found in #1 and #3 donor candidates, respectively, who are currently being followed up periodically by a hematologist. However, the remaining donor candidates (#2 and #4) did not consent to genetic analysis and further follow-up.

Perioperative and postoperative courses in living donors

Seventeen donors in the borderline group underwent donor surgery with postoperative anticoagulants using continuous

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Table 3. Donor candidates in thrombophilia group (excluded for high risk of VTE).

#	Age (year)/ Sex	Protein S (% activity)	Protein C (% activity)	LAC	IgG anti-CL antibodies (U/mL)	Anti-β2GPI antibodies (U/mL)	Medical history of thrombosis
1	35/Female	71.9	43	1.12	19	4.8	No
2	21/Male	38	120	0.99	<8.0	<1.2	Yes
3	27/Female	35	122	0.99	<8.0	<1.2	No
4	38/Female	31	97	0.99	<8.0	<1.2	No

VTE – venous thromboembolic events; LAC – lupus anticoagulant; CL – Cardiolipin; β2GPI – beta-2-glycoprotein 1.

Table 4. Surgical aspect and post-operative variables of donors in Normal and Borderline group.

	Normal group (n=137)	Borderline group (n=17)	*p*
Graft type (Right/Left/Lateral)	65/21/51*	10/3/4*	0.70
Operative time (min)	438±104	423±112	0.93
Blood loss (ml)	411±331	449±213	0.75
Hospital stay (day)	15.6±8.2	14.0±3.4	0.58
Postoperative complications			
Clavien-Dindo Grade (II/III≤)	16/4	3/1	0.09
Bleeding complication	1**	1**	
Thromboembolism complication	0	0	

* Reduced graft was included; * * wound hematoma.

venous infusion of heparin in addition to elastic stockings and IPC postoperatively. Of these, a low level of PS activity was observed in 13 donors, a low level of PC activity was observed in 1 donor, and IgG anti-CL antibodies were positive in 4 donors. One patient had a low level of PS activity and IgG anti-CL antibodies were positive. We performed right hepatectomy in 10, left in 3, and left lateral segmentectomy in 4 donors, and all operations were carried out without any complications.

Surgical aspects and postoperative variables in donors in the normal and borderline group are shown in Table 4. Of those in the normal group, 4 (2.9%) donors developed Clavien's grade IIIa complications and 1 developed wound hematoma, which were resolved without surgical intervention. Surgical and postoperative characteristics in donors in the borderline group were similar to those in the normal group. No donors in the borderline group were complicated by postoperative bleeding, except for 1 donor who developed a wound hematoma on postoperative day 1. We discontinued heparin when the wound hematoma was found. Fortunately, this donor ambulated well on postoperative day 2; therefore, we did not resume heparin treatment. Median duration of heparin administration for donors in the borderline group was 5 days (range, 1–7days) and no donors developed heparin-induced thrombocytopenia. No donors in the borderline or the normal groups developed thromboembolism complications postoperatively. Currently, all donors in the borderline group are doing well without any episodes of thromboembolism at the median follow-up of 7.5 years (7 months to 11 years).

Discussion

We performed a prospective, observational study analyzing the safety and validity of our algorithm for donor selection and strategy of prophylaxis of postoperative VTE according to the results of thrombophilia screening tests. We excluded 4 donor candidates because of the likelihood of developing VTE according to our evaluation. Moreover, 17 living donors with marginal results of thrombophilia screening tests were administered continuous venous infusion of heparin postoperatively to prevent VTE. As a result, importantly, no living donors have been complicated by VTE over the last decade since this strategy was applied. To the best of our knowledge, this is the first report to determine the necessity and usefulness for risk stratification approaches for VTE prophylaxis based on the results of thrombophilia tests for LDLT donors in a large cohort.

We examined antigen activity because patients with inherited thrombophilia can show normal antigen levels [2,12,13]

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The use of PS and PC activity is accepted as the initial test for identifying patients with deficiency [2,12,13]. We repeatedly examined PS and PC activity and consulted a hematologist because abnormal assay values should be re-evaluated after at least 4–6 weeks to confirm the persistence of deficiency before the final diagnosis of hereditary PS and PC deficiency is assigned [2].

From a cost-effectiveness perspective, there is no evidence supporting universal thrombophilia screening in patients undergoing major surgery [14]. However, evaluation and management in living donors require extraordinary caution because donor safety is the highest priority in LDLT. Risk factors for VTE include advanced age, obesity, medical history of VTE, malignancy, heart failure, recent myocardial infarction, and hormonal therapy [15]. While most of these factors are usually excluded in the process of donor selection, thrombophilia, such as deficiency of PC, PS, AT-III factor, and lupus anticoagulant, which are also risk factors of VTE [15], can be comorbidities in the healthy population. A medical history of thrombosis is one of the most significant risk factors for thrombosis. However, most thrombophilia cases are latent, and thrombosis is likely to be triggered by surgery or pregnancy [16]. Therefore, although interviewing donor candidates about a medical history of thrombosis is still important, it is not adequate to exclude donor candidate with thrombophilia and prevent thrombosis. In fact, 44 of 306 (14.4%) donor candidates did not pass the first thrombophilia screening in our center. In the current study, the results of conventional coagulation tests, including platelet count, PT, APTT, fibrinogen levels, and D-dimer levels, were not different between donor candidates in the normal and suspected groups. These findings show that conventional screening parameters are not sufficient for accurate evaluation of thrombophilia. Therefore, we agree with the necessity of screening for thrombophilia in donor candidates, as suggested in previous reports [9,17].

We eventually excluded 4 candidates by systematic screening for thrombophilia. We considered that their results of thrombophilia screening tests were serious enough to exclude them from being from donor candidates, because it was reported that patients with thrombophilia can develop VTE after surgery, even with anticoagulants [9]. Although these donor candidates would not have developed VTE after surgery, we believe that excluding these donor candidates was reasonable to ensure donor safety.

There is controversy about whether mildly decreased levels of PS or PC are associated with an increased risk of VTE [4,18–21]. Levels of PS and PC activity are usually 35–60% and 35–65%, respectively, in heterozygous deficiency, whereas the majority of healthy individuals have levels of 70–130% [3,22]. Kinoshita et al. reported that PS activity of patients with deep vein thrombosis with a gene mutation varied from 10% to 60%, and PC activity of patients with deep vein thrombosis with a gene mutation varied from 18% to 63% [4].

The outcome of living donors with marginal results in PS, PC activity, and/or APLA-positive result has not been previously investigated. Liver resection is associated with a postoperative hypercoagulable state which can contribute to the occurrence of VTE. This hypercoagulability after liver resection can be explained by the fact that PC and AT-III levels were reported to decrease significantly more after liver resection compared to other abdominal major surgeries [23]. Therefore, it is important to clarify whether candidates with marginal results of thrombophilia screening tests are suitable as living donors. In the context of the current donor shortage, especially in areas in which deceased donor liver grafts are in short supply, achieving an increase in the living donor pool without compromising recipient and donor safety is important. The risk of bleeding complications in patients undergoing hepatectomy is perceived by some surgeons to outweigh the risk of postoperative VTE, especially with higher volume resection [24–28]. We followed the ACCP guidelines for VTE prevention for donors in the normal group. However, routine use of pharmacological prophylaxis, including subcutaneous LMWH or low-dose unfractionated heparin (LDUH) or enoxaparin for donors in the normal group, can be considered because VTE can be lethal complication. We identified 17 donors at moderate risk for thrombosis with our screening system, although it was not considered significant enough to cancel the operation. We understand that the use of continuous venous infusion of heparin, instead of LMWH or LDUH, for donors in the borderline group is arguable. The occurrence of hypercoagulability after hepatectomy in the majority of living liver donors are reported despite using LMWH [10]. The usual doses of anticoagulants and subcutaneous LMWH are also reported to be insufficient to prevent perioperative VTE in donors who have thrombophilia [9]. Dondero et al. [9] speculated that VTE after liver resection may be more frequent in living donors because the liver of healthy persons has a normal synthesis capacity and can synthetize more procoagulable factors than a pathological liver. Therefore, these donors underwent the operation with intravenous anticoagulants, although ACCP guidelines recommend use of LWMH or LDUH with mechanical compression. As a result, surgical and postoperative characteristics in donors in the borderline group were similar to those in the normal group who underwent surgery in the same period. Additionally, no donors were complicated by VTE postoperatively. This finding indicates anticoagulant therapy with continuous intravenous heparin for living donors with marginal results of thrombophilia testing can be safe and useful for donors and recipients. We consider that the benefit of this strategy outweighs the risks because of the contribution to increase the donor pool. Although the donors might not have developed VTE without anticoagulant

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therapy, we chose prevention of VTE prevention over the adverse effects of anticoagulants because VTE can be a lethal complication and a high incidence of PE in living liver donors with thrombophilia despite of using subcutaneous LMWH was previously reported [9].

In the current report, the median duration of heparin administration for donors in the borderline group was 5 days (range, 1–7 days). Because hypercoagulability can last at least several days after hepatectomy, a longer period of prophylaxis might be desirable unless the donor develops a serious complication related to anticoagulation.

Fortunately, no donors developed VTE at the median follow-up of 7.5 years (7 months to 11 years). However, for the long-term follow-up of donors in the borderline group, we recommend continuation of careful monitoring, including periodical thrombophilia tests and Doppler ultrasound examination of the lower limbs.

A limitation of this study is that all donor candidates who were investigated were Asian. There is a significant difference in the type of thrombophilia test required for screening between Asian and Western populations. A previous study showed a lack of distinctive inherited thrombophilia-related factor V Leiden and the prothrombin G20210A polymorphism in Asian subjects [29]. In non-Asian candidates, factor V Leiden and the prothrombin G20210A polymorphism need to be examined [30]. Another limitation is lack of data on postoperative PC, PS, and AT-III levels in donors in the normal or borderline group. Bezeaud et al. [31] studied the coagulation changes after partial liver resection in 12 living donors. This report showed an AT-III decrease of less than 50% of baseline, which persisted to day 5 and coincided with similarly sized reductions in levels of PC [31]. In this report, PS also showed transient decrease but returned to normal within 24 h [31]. Because hypercoagulability can develop after hepatectomy, results of thrombophilia testing after hepatectomy in living liver donors is important and this should be investigated in future.

There is no consensus on the cut-off level of PS or PC because of large standard deviations [32]. Therefore, the range of normal values for determination of risk cannot be clearly defined. We set the cut-off level of PS and PC between groups according to previous reports [4,21,33,34] Although further studies are needed to define the lowest level of PS and PC without compromising donor safety, caution is necessary in accepting living donors with lower PS or with PC levels lower than our cut-off value.

Conclusions

We reviewed the outcomes of the protocol established at our institution for preventing VTE in donors in LDLT. Our strategy for donor selection and indication of chemoprophylaxis for VTE using risk stratification according to the results of thrombophilia screenings appears to be safe. Thrombophilia testing-guided VTE prophylaxis may contribute to reduced VTE risk in donors, although further investigations are necessary to assess the necessity for thrombophilia testing prior to surgery among living donors.

Conflicts of interest

The authors declare no conflict of interest.

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