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Original Article General Surgery

Factor 5 and Factor 2 heterozygous positivity and complications in living donor liver transplant donors

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ABSTRACT

OBJECTIVE: Factor 2 and Factor 5 mutations are among the most common procoagulant genetic disorders and are routinely evaluated in donor preparation. Homozygous mutations are contraindicated for surgery, but heterozygous mutations cannot be said to be an impediment. We aimed to investigate the effect of heterozygous gene mutation of F2 and/or F5 on complications.

METHODS: In our study, 210 living liver donors were examined. The available data of Factor 2 and 5 heterozygous positive donors were evaluated in terms of 21 donor patients and 30 liver recipients. The heterozygous positive group and the control group were statistically compared in terms of age, gender, length of hospital stay, post-operative deep vein thrombosis, pulmonary embolism, portal vein thrombosis, bile duct stenosis and bile leakage complications, lung infection and atelectasis, and wound infection. In addition, these patients were statistically compared in terms of laboratory tests. In addition, complications in recipients implanted with mutant grafts were evaluated statistically and numerically.

RESULTS: Hospital staying was longer statistically in the donor group with heterozygous mutations than in the control group. Hemoglobin and albumin blood levels were lower (p=0.031, p=0.016); INR and ALT levels were higher (p=0.005, p=0.047) statistically in the control group than in the donor group with heterozygous mutations. There was no statistically significant difference between heterozygous mutant groups in terms of biliary tract complications and hepatic vessel thrombosis in recipients.

CONCLUSION: Considering the longer hospital stay in the presence of these mutations, the increased need for treatment in this process and the close follow-up of liver functions should be considered.

Keywords: Factor 2; Factor 5; heterozygous; liver; mutation; transplant.

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Minimizing the rates of complications related to surgery and ensuring post-operative quality of life in people undergoing donor hepatectomy are crucial for the safety and social incentive dimension of this surgery [1,2]. Therefore, thorough donor preparation is vital to reduce complications. When we consider thrombotic events among the complications related to donor hepatectomy, it is important to detect the presence of procoagulant factors during the preparation process and to predict post-operative bleeding, thrombosis, and other complications that may occur. It is recognized that Factor 2 and Factor 5 mutations are among the most common procoagulant genetic disorders and are routinely evaluated in donor preparation. While homozygous mutations

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constitute an obstacle to surgery, there is no data or acceptance that heterozygous mutations are contraindicated [3–5]. Likewise, the effect of prothrombotic genetic disorders on complications in liver recipients is also significant for graft survival, although it varies in different populations [6]. In our study, we aimed to investigate the effect of heterozygous gene mutation of F2 and/or F5 on both thrombotic and other complications in the light of post-operative laboratory and clinical parameters.

MATERIALS AND METHODS

There were 21 living donors with Factor II and V heterozygous positivity identified among 210 consecutive liver donors in the study period (June 2017 to November 2019). These patients were compared with 125 matched control donor groups in the same period.

The heterozygous positive group and the control group were statistically compared in terms of age, gender, duration of hospital stay, post-operative complications of deep vein thrombosis (DVT), pulmonary embolism, portal vein thrombosis (PVT), biliary stricture and bile leakage, pulmonary infection and atelectasis, and wound infection. In addition, hemoglobin, platelet, INR, ALT, AST, total bilirubin, and albumin values on post-operative days 1 and 5 were compared statistically. The changes in these laboratory values between days 1 and 5 were compared statistically between both groups.

Mean age, etiology, G.R.W.R. rates, and MELD, and child scores were determined in liver recipients of Factor 2 and/or Factor 5 heterozygous positive donors. In addition, Factor 2 and/or Factor 5 heterozygous positive donors were numerically compared and statistically evaluated in terms of hepatic artery, portal vein, and hepatic vein thrombosis, biliary complications, and graft loss rates.

Post-operative courses including complications and laboratory values were compared across both groups. Routine clexane was prophylactically administered to the test group.

RESULTS

Of the 21 patients positive for procoagulant mutations, Factor 2 and 5 mutation was found in 8 and 13, respectively. The mean age of these donors was 34.9 years. The mean duration of hospitalization was 6.8 days in those with the mutation. Post-operative PVT, pulmonary embolism, and DVT were not observed in donors with heterozygous mutation positivity. However, the pulmonary infection rate was 13.3%, the wound infection rate was 3.3%, and the post-operative biliary complication rate was 6.7%. The hospital stay was statistically longer in the heterozygous mutant donor group than in the control group ($p<0.001$) (Fig. 1). Post-operative laboratory values revealed that hemoglobin (hb) and albumin blood levels were statistically lower ($p=0.031$, $p=0.016$), INR and ALT levels were higher ($p=0.005$, $p=0.047$) in the control group than in the donor group with heterozygous mutation. There was no statistically significant difference in platelet, AST, and total bilirubin levels ($p=0.843$, $p=0.954$, and $p=0.199$) (Table 1). When the change in the same laboratory values between post-operative days 1 and 5 was analyzed, no statistically significant difference was observed between the two groups (Table 2). Baseline and demographic characteristics were comparable in the two groups. There was no difference in overall complications (Clavien–Dindo classification I-V; 9.5% vs

Highlight key points

- Longer hospital stay in heterozygous donors may indicate an increased need for treatment.
- It is significant that thrombosis rates do not change according to greft mutation in liver recipients.
- The presence of heterozygous mutations does not change the complication rates in donors.
- Hb and albumin blood levels were higher, INR and ALT levels were lower statistically in the donor group with heterozygous mutations than in the control group.

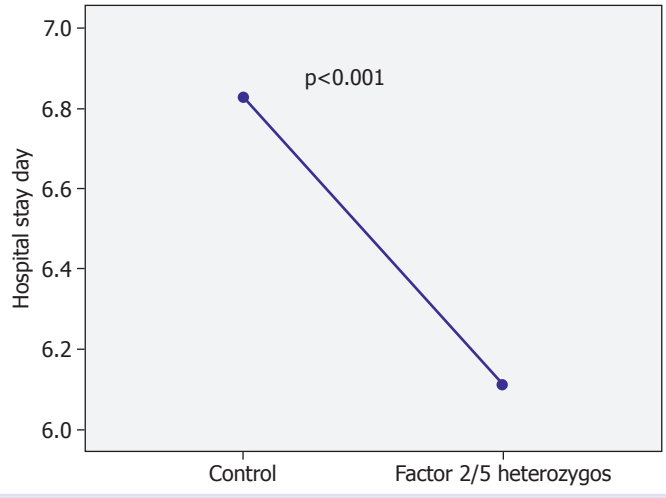

FIGURE 1. Evaluation of hospital staying in heterozygous and control group statistically.

Table 1. Demographic data rates, length of hospital stay; statistical results of complication rates, and laboratory findings in heterozygous and control groups

	Factor 2/5 heterozygous positive group	Control group	p
Age	34.90±9.08	34.82±9.19	0.947
Gender female (%)	30	33.6	0.846
Hospital stay, day	6.83±1.41	6.11±0.96	**0.000**
Post-o-perative DVT, n (%)	0 (0.0)	0 (0.0)	–
Pulmonary embolism, n (%)	0 (0.0)	0 (0.0)	–
Pulmonary infection/atelectasis, n (%)	4 (13.3)	8 (6.3)	0.283
Wound infection, n (%)	1 (3.3)	4 (3.1)	0.953
Portal vein thrombosis, n (%)	0 (0.0)	1 (0.8)	0.627
Post-operative bile complication, n (%)	2 (6.7)	4 (3.1)	0.427
Hemoglobin (g/dl)			
Pre-operative	14.61±1.37	13.88±1.58	**0.031**
Post-operative day 1	13.61±1.48	12.83±1.59	**0.037**
Post-operative day 5	12.26±1.25	11.52±1.54	**0.024**
International normalization ratio pre-operative	1.00±0.06	1.04±0.06	**0.005**
Post-operative day 1	1.33±0.20	1.35±0.24	0.713
Post-operative day 5	1.11±0.09	1.13±0.08	0.354
Platelet (10^3/μL)			
Pre-operative	235.53±49.60	236.94±56.04	0.843
Post-operative day 1	206.80±35.44	197.76±45.73	0.182
Post-operative day 5	236.86±73.59	227.10±79.54	0.199
Alanine aminotransferase (IU/L)			
Pre-operative	24.87±14.00	19.97±10.93	**0.047**
Post-operative day 1	244.17±154.76	242.38±144.51	0.632
Post-operative day 5	122.90±57.80	110.79±51.56	0.263
Aspartate aminotransferase (IU/L)			
Pre-operative	21.79±6.45	21.51±6.03	0.954
Post-operative day 1	210.38±126.58	199.62±91.44	0.622
Post-operative day 5	122.90±52.80	110.79±51.56	0.572
Total bilirubin (mg/dL)			
Pre-operative	0.70±0.46	0.58±0.33	0.199
Post-operative day 1	2.57±1.43	2.65±1.11	0.585
Post-operative day 5	2.00±1.65	1.84±1.08	0.485
Albumin (g/dl)			
Pre-operative	4.69±0.33	4.52±0.29	**0.016**
Post-operative day 1	3.92±0.36	3.70±0.29	**0.007**
Post-operative day 5	3.55±0.28	3.48±0.31	0.321

DVT: Deep vein thrombosis.

7.1% p=0.772) and major complications (Clavien–Dindo classification ≥IIIa, 0% vs. 1.4%, p=0.892) between the test and the control groups. There was no difference in peak Bilirubin (2.49 vs. 2.69 mg/dL, p=0.561), peak INR (1.38 vs. 1.33, p=0.418), or peak platelet count (203×10^3 vs. 193×10^3) in the post-operative period.

When the recipients in whom livers from donors with Factor 2 and/or 5 heterozygous mutations were implanted were evaluated, the rate of biliary tract complications was 18% in Factor 2 heterozygous mutant donors and 47% in Factor 5 donors, while the rate of hepatic artery complications was 9% in Factor 2 mutants and 5% in

TABLE 2. Statistical analysis of the difference between the post-operative 1st and 5th-day laboratory results in heterozygous and control groups

	Factor 2/5 heterozygous positive group	Control group	p
Change hemoglobin (g/dL)			
Pre-operative–post-operative day 1	1.00±0.83	1.05±0.99	0.726
Post-operative day 1–5	1.33±1.21	1.31±1.01	0.789
International normalization ratio			
Pre-operative–post-operative day 1	-0.33±0.16	-0.30±0.23	0.266
Post-operative day 1–5	0.23±0.16	0.21±0.24	0.462
Platelet (10^3/μL)			
Pre-operative–post-operative day 1	28.73±23.46	38.19±29.18	0.070
Post-operative day 1–5	-33.31±64.66	-29.34±61.60	0.945
Alanine aminotransferase (IU/L)			
Pre-operative–post-operative day 1	-220.24±150.84	-222.41±141.00	0.505
Post-operative day 1–5	123.86±164.20	131.58±131.15	0.097
Aspartate aminotransferase (IU/L)			
Pre-operative–post-operative day 1	-190.42±126.51	178.11±90.06	0.639
Post-operative Day 1–5	144.28±134.59	130.74±96.14	0.351
Total Bilirubin (mg/dL)			
Pre-operative–post-operative day 1	-1.89±1.09	-2.00±1.23	0.659
Post-operative day 1–5	0.59±2.17	0.83±1.76	0.640
Albumin (g/dL)			
Pre-operative–post-operative day 1	0.79±0.28	0.81±0.31	0.851
Post-operative day 1–5	0.37±0.36	0.22±0.32	0.057

Factor 5 mutants. However, there was no statistically significant difference between different heterozygous mutant groups in terms of biliary tract complications and hepatic artery thrombosis (HAT) ($p>0.05$). PVT and hepatic vein thrombosis were not observed in any group of patients. While graft loss was not observed in Factor 2 heterozygous group, graft loss rate was 16% in Factor 5 heterozygotes (Table 3).

DISCUSSION

Factor 5 heterozygous mutation increases the risk of venous thromboembolism 5–10-fold with an incidence of 5% in the population [3], whereas in Factor 2, this rate is 2.3% for the whole population and the increased risk of thromboembolism is 2–3-fold [4–7]. It can be stated that these mutations are significant risk factors for venous thromboembolism [8,9]. Although cases of thrombosis after different abdominal surgeries have been reported in the presence of Factor 2 heterozygous mutation [10,11], Factor 5 heterozygous mutation has been reported in 6% of liver donors, and this condition carries a small risk of thrombosis after liver transplantation, the relative risk for the development of hepatic vein thrombosis has been reported to be low [12–14]. In terms of hepatic artery and vein thrombosis, which occurs with a rate of 5–15% after liver transplantation, it may be necessary to consider technical reasons in addition to prothrombotic factors [12]. While post-transplant thrombotic events are an essential morbidity factor, there are studies demonstrating that graft loss increases as a result of hepatic vein thrombosis due to microthrombi in the presence of Factor 2 and 5 heterozygous mutations in organ transplant recipients [6,15,16]. In our study, although PVT, DVT, and pulmonary embolism were not observed in heterozygous mutant donors, no statistically significant difference was detected in terms of these thromboembolisms compared to non-mutant donors. However, PVT and hepatic vein thrombosis were not observed in recipients of mutated grafts, while the rate of HAT was 7%.

Considering that factor mutations lead to a general microcirculatory disorder in the vessels, it is necessary to examine the problems that the decrease in tissue nutrition may occur during tissue healing and may be a

Table 3. Rates of recipients of Factor 2 and Factor 5 positive grafts in terms of age, gender, etiology, meld, child score, g.r.w.r., biliary and vascular complications, and graft loss

	Factor 2 (n=11) (%)	Factor 5 (n=19) (%)	Factor 2 and 5 (n=30) (%)
Age (average)	59.1 (43–72)	50.8 (21–64)	53.9 (21–72)
Gender			
Male	82	79	80
Female	18	21	20
Etiology			
HBV	9	5	7
HCV	–	10	7
Ethanol	9	10	10
NASH	18	16.5	17
Cryptogenic	9	21	17
HCC	37	16.5	22
Others	18	21	20
MELD score (average)	14.1	15.1	14.8
Child score (A, B, and C)			
Child A	18	16	17
Child B	73	79	76
Child C	9	5	7
G.R.W.R. (average)	1.17 (0.7–1.6)	1.2 (0.7–2.4)	1.2 (0.7–2.4)
Bile anastomosis complication	2 (18)	9 (47)	11 (37)
Hepatic artery complication	1 (9)	1 (5)	2 (7)
Portal vein complication	–	–	–
Hepatic vein complication	–	–	–
Graft loss	–	3 (16)	3 (10)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholicsteatohepatitis; HCC: Hepatocellular carcinoma; MELD: The model for end-stage liver disease; G.R.W.R.: The Graft-to-Recipient Weight Ratio.

predisposing factor for infections that may progress to sepsis [10,15,17,18]. An increased rate of biliary tract complications may be encountered especially in HAT [19]. From this point of view, although the hospitalization period was longer in donors in this study compared to those without mutations, no statistically significant difference was observed in terms of wound infection, pulmonary infection, and biliary complications. However, it was observed that F5 mutation caused more biliary complications in recipients of mutated grafts.

In addition, when studies indicating that Factor 2 and Factor 5 mutations increase liver damage and fibrosis [20–22] are examined, no statistically abnormal change was observed in mutant donors compared to the control group in terms of ALT, AST, total bilirubin, INR, albumin, and platelet values, which may indicate liver damage and loss of function and portal hypertension. Likewise, in terms of post-operative hemorrhage, there was no significant decrease in hemoglobin in mutant donors compared to the control group.

Conclusion

In donors with Factor 2 and 5 heterozygous mutations, pre-operative anticoagulant therapy should be scheduled and post-operative thromboembolism and complications should be carefully considered. Given that hospital stay is longer in the presence of these mutations, the need for increased treatment during this period and close monitoring of liver function tests should be taken into consideration.

Ethics Committee Approval: The Haseki Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 09.12.2020, number: 2020-224).

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Authorship Contributions: Concept – YT, YY; Design – EA; Supervision – EA; Materials – TS, AO; Data collection and/or processing – FT, EA; Analysis and/or interpretation – AO; Literature review – EA, TS; Writing – EA; Critical review – YT, YY.

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