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Preoperative Thrombophilia Profile in Living Liver Transplant Donors from Pakistan

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ABSTRACT

Objective: To determine the frequency of thrombophilia disorders among healthy Pakistani liver transplant donors through extended thrombophilia screening.

Methodology: Descriptive, cross- sectional study was conducted at department of hematology, Shifa International Hospital, Islamabad from January 2020 to July 2024. A total of 362 living liver donors were selected who met the inclusion criteria. Blood samples were collected in sodium citrate tubes for extended thrombophilia screening which includes quantitative measurements of Protein C, Protein S, Antithrombin and Lupus anticoagulant.

Results: A total of 362 study participants were included. Majority of the study participants were males (222, 61.3%). Mean age was 27.24.±7.71 years. The frequency of thrombophilia markers was as follow: Protein C deficiency 5.2%, AT deficiency 13.8%, Protein S deficiency 18.8%. Lupus anticoagulant was positive in 1.4% of donors

Conclusion: Pre-operative thrombophilia profile in living liver donors from Pakistan revealed significant prevalence of hereditary thrombophilia markers within the donor population. Extended thrombophilia screening protocol for LLDs is essential for identifying at risk individuals guiding appropriate perioperative thromboprophylaxis and ultimately improving the safety of both donors and recipients undergoing LLDT

Key words: Antithrombin; Living Liver Donors; Living Liver Donor Transplantation; Protein C; Protein S.

Authors' Contribution:

[1,2]Conception; Literature research; manuscript design and drafting; [3,4]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

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Introduction

Thrombophilia refers to a hypercoagulable (high risk for blood clotting) state characterized by an increased predisposition to form thrombi. Thrombosis is a result of environmental risk factors and genetic risk factors. The thrombophilia is influenced by environmental risk factors, some of which have a provocative role, such as malignancies, metabolic stress due to surgical intervention, bone injury/fracture leading to secondary immobilization, and prolonged travel. Some of the factors are non-provocative, like demographic features, exercise and physical activity, and genetics.[1] The liver makes clotting factors and other important proteins involved in the regulation of the coagulation cascade. Liver transplantation (LT) has been extensively performed worldwide as a curative therapy for end-stage liver disease.[2] Hepatic surgery is a difficult surgical intervention linked with guarded outcome as it has very high mortality and morbidity. It is challenging as liver performs many vital metabolic and anabolic functions and has very complex anatomic structure.[3] Donor assessment

must reveal any condition that would place the healthy donor at risk for any intra/or post-operative complications[4]. Donor safety is paramount as it may influence the willingness of the community to donate their organs. Undiagnosed and untreated hypercoagulability may pose a risk to both donors and recipients in particular the postoperative period.[6] Thrombophilia does not appear in standard laboratory testing (PT/APTT, Fibrinogen levels, D-dimers) testing but can lead to post-operative thrombotic complications. Extended thrombophilia screening should be performed. Kamel et al. conducted a study in Japan on 306 potential liver transplant donors, and of the 306 donors, 17 donors with borderline low thrombophilia profiles went on to undergo donor surgeries and were managed by intravenous Heparin infusions, further supported by elastic stockings and intermittent pneumatic compression (IPC). No donors in this study developed VTE.[7] In another study conducted in Japan by Hayato O, Yasuhiro F, Koji Y, et al, 4 of 44 potential liver donors had thrombosis risk based on the results of thrombophilia screening.[8] It has been observed that living donor LT improves overall survivability for recipients and is associated with decreased mortality risk for patients, as well as decreased wait list times.[9] For this reason, this study aims to evaluate the preoperative thrombophilia profile in living liver transplant donors.

Methodology

This descriptive cross-sectional study was conducted in the hematology laboratory of Shifa International Hospital (SIH), Pakistan from January 2020 to July 2024. The non-probability purposive sampling technique was applied.

Inclusion criteria:

- Adult healthy liver transplant donors related to the patient (legally or by blood) presenting to Shifa International Hospital, Islamabad
- Age 18 to 60 years

Exclusion criteria:

- Age less than 18 years or greater than 60 years
- Donors with pre-existing coagulopathy
- Donors on any anticoagulant therapy (warfarin, heparin, direct oral anticoagulants)

After history and examination, the blood samples were collected in sodium citrate tube for quantitative measurements of Protein C, Protein S, Antithrombin and Lupus anticoagulant. Antithrombin was determined using Siemens Innovance Antithrombin Kit which utilizes a chromogenic measuring principle. Protein S was determined by clotting time method using Siemens Protein S Kit. Protein-C determined using Siemens Berrichon Protein C Kit which utilizes chromogenic measuring principle. Lupus anticoagulant was determined using Siemens Kit which utilizes Direct Russell Viper Venom Time (DRVVT) method.

Data were analyzed using IBM® Statistical Package for Social Sciences version 25.0. the descriptive statistics like mean and SD was used for quantitative data (protein S, age, levels of protein C, and Antithrombin) whereas frequencies and percentages were reported for qualitative data (gender and lupus anticoagulant).

Ethical approval was granted by the Institutional Review Board of the Shifa International Hospital. (Ref No. 031-851-2020) dated. 08 February, 2020.

Results

A total of 362 study participants were included during the study period. Majority of the study participants were males (222, 61.3%). Mean age was 27.24.±7.71 years. Number of donors whose thrombophilia profile was normal are 308 (85.08%)

Details are shown in Table-I and Table-II. Protein C was low in 19 donors (5.2%) and high in 4 (1.1%), Protein S was low in 68 donors (18.8%) and anti-thrombin was low in 50 donors (13.8%) as shown in Table-II.

Table-I: Basic Demographic and Clinical Characteristics (n=362)	
Variable	**Descriptive Statistics**
Age, years, mean ± SD	27.24.±7.71 years
Gender, n (%) Male Female	 222 (61.3%) 140 (38.70%)
Protein C Levels, mean ± SD	99.19±18.66
Protein S Levels, mean ± SD	73.72±23.79
Antithrombin Levels, mean ± SD	96.60±16.99.

Table-II: Frequencies of thrombophilia abnormalities in apparently healthy donors (n=362)	
Variable	**Number of donors (%)**
Protein C Low Normal High	 19 (5.2) 339 (93.6) 4 (1.1)
Protein S Low Normal High	 68 (18.8) 288 (79.6) 6 (1.7)
Antithrombin Low Normal High	 50 (13.8) 297 (82.0) 15 (4.1)
Lupus Anticoagulant Negative Positive	 357 (98.6) 5 (1.4)

Discussion

Annual data report of liver transplantation in United States published in 2020 revealed the fraction of living donor liver transplants has increased in the past decade, from 3.1% in 2008 to 4.4% in 2018.[10] VTE episodes happen frequently in patients undergoing hepatectomy. A meta-analysis and meta-regression comparing adult living donor liver transplantation to deceased donor transplantation revealed similar risk of post- operative hepatic complications, including hepatic artery thrombosis.[11] In the absence of specific post- liver transplant thrombosis management guidelines, vigilant monitoring and the use of rapid diagnostic tools to detect vascular complications are essential to reduce the risk of graft failure and death.[12] In the general healthy population, the prevalence of this condition varies among different types of thrombophilia. Specifically, the occurrence of protein C deficiency is estimated to be between 0.15% and 0.33%. For protein S deficiency, the prevalence is somewhat lower, ranging from 0.03% to 0.13%. Additionally, Antithrombin deficiency is found in approximately 0.17% of healthy individuals.[13,14] Additionally, antiphospholipid antibodies are present in about 1% of healthy controls.[15] The rate of VTE after hepatectomy was reported at 2.9 percent in the National Surgical Quality Improvement Program (NSQIP) database and can be minimized by undergoing minimally invasive liver section.[16] In a study from Japan, 44 donors were evaluated and two candidates were found to be deficient one had low protein S, and the other had lower protein C levels and additionally, anti-2GPI came positive. Keeping these findings in view, they were removed from the donation pool. Two borderline deficient donors were also found; they underwent hepatectomy and received anticoagulants before surgery, completing the process without issues. Without additional screening, the two deficient and two borderline donors would not have been identified.[8] In our study, we aimed to assess the frequency of thrombophilia disorders in healthy liver donors. Among 362 donors, we found protein C deficiency in 19 donors, protein S deficiency in 68 donors, and anti-thrombin deficiency in 50 donors. Only five donors tested positive for lupus anticoagulant. In another 2005 study, 32 donors were excluded from LDLT due to various factors, including factor V Leiden mutation in two donors, factor II mutation in four donors, protein C deficiency in three, protein S deficiency in seven, factor VIII levels below 65% in one and above 150% in four, positive lupus anticoagulant tests in five, and high homocysteine levels in nine donors. This study concluded that thrombophilia tests should be a part of the laboratory workup for donors before LDLT to

identify any disorders linked to increased risk of thrombotic or bleeding issues.[17] In another study from Spain, 188 potential donors were evaluated, 38 (20.2%) participants had abnormality in their coagulation pathways. Donors with serious and complex disease patterns and abnormalities were removed from the list, in an attempt to avoid unforeseen complications and events.[18] The transplant specialists at Hospital Beaujon recommended testing donor candidates for thrombophilia as well.[19] In a study from Pakistan aimed at determining thrombophilia disorders, especially hereditary, and assessing their severity among living donors for liver transplantation, 567 donors were reviewed. Out of these, protein IgM and IgG anti-phospholipid antibodies (0.4%), Protein C deficiency 21 (3.7%), and 14 (2.5%) antithrombin-III was seen.[20] In the present study, we evaluated the preoperative thrombophilia profile in healthy liver donors and established the need for screening protein S, protein C, antithrombin, and lupus anticoagulant during preoperative evaluations for living donor liver transplantation. This screening aims to ensure donor safety and prevent postoperative thrombotic complications.

A limitation of this study is that we did not confirm the serological deficiencies of protein C, protein S, and antithrombin on two occasions. Confirmation is essential to rule out biological variability and transient deficiencies. Furthermore, these deficiencies should be verified at the genetic level. We also did not examine clinical outcomes in donors with abnormal thrombophilia screens.

Conclusion

Pre-operative thrombophilia profile in living liver donors from Pakistan revealed significant prevalence of hereditary thrombophilia markers within the donor population. Since thrombophilia is not detected by conventional laboratory methods (PT/APTT, Fibrinogen levels, D dimers), extended thrombophilia screening protocol for LLDs is essential for identifying at risk individuals guiding appropriate perioperative thromboprophylaxis and ultimately improving the safety of both donors and recipients undergoing LLDT

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