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Pulmonary thromboembolism in liver transplantation: a retrospective review of the first 25 years

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Summary

The evidence on the state of 'haemostasis' at the time of liver transplantation (LT) is conflicting, with recent publications that suggest a hypercoagulable state, in contrast to traditionally held views. These findings raise the issue of thrombo-embolic complications after LT, an area of interest which has received little attention in recent published literature. We therefore conducted a retrospective review of our experience of 3000 liver transplants over 25 years. Our prospective transplant database was reviewed to find all patients who were suspected to have had a pulmonary embolism (PE) during or following LT. Paediatric transplants were excluded. A part of this database was cross referenced against hospital records to corroborate its accuracy. Clinical records of all these patients were reviewed and relevant aspects collated and analyzed. Following exclusion of the paediatric recipients, 2 149 adults were reviewed to find 36 patients in whom a PE was suspected (median age 49), 21 of whom were within 90 days of transplant (median duration 22 days). PE was ruled out in 10, unconfirmed in two, confirmed in eight patients; and in one, air embolism was found. All PEs occurred in hospital, but aetiology of liver failure was varied. Of note, two patients died of an on-table PE and one patient of chronic rejection/disease recurrence (Primary Sclerosing Cholangitis). The remaining five are still alive (median survival of 65 months). Although thromboprophylaxis is now routine in our unit, its use in these patients could not be confirmed from records available. Fifteen PE were suspected and confirmed after 90 days from transplant (six within, and nine out with the first year). Acute PE in the setting of LT has an incidence rate in our series of 0.37% that would appear to be lower than previously reported and lower than one would expect after a 'major complex' category operation. This potentially suggests that the overall haemostatic function in these patients is still weighted towards hypocoagulation with the resultant risk of excessive bleeding. Aetiology of liver disease did not seem to confer a higher risk in our series. The prognosis after post-operative PE appears good although sudden death due to an on-table embolism is a rare but significant risk.

Introduction

Pulmonary embolism (PE) following major abdominal surgery carries significant morbidity and mortality [1]. Despite evidence that suggests that the complex interplay between pro and anticoagulative mechanisms in patients with chronic liver disease undergoing orthotopic liver transplantation (OLT) might increase the recipient's risk of thromboembolism, the incidence of post-operative PE in this group has not been recently studied [2–5]. With

the exception of a report from Ishitani *et al.* 12 years ago, the published literature focussed on the subject, is limited to case series or reports of intra-operative thromboembolic events [6–10]. We therefore reviewed the last 3 000 LT in our centre with an aim to identify the incidence and sequelae of peri-operative PE after LT, in an attempt to find co-relation and learning points.

Methods

This is a retrospective, single centre review of 3000 LT performed over 25 years from 1982 until 2007, based on a database maintained at the Liver Unit, University Hospital, Birmingham. The 851 paediatric LT recipients were excluded. As one would expect, given the wide time span covered by this study there has been variations in operative techniques from the classical 'caval replacement' performed with or without veno-venous bypass to the more recent 'piggyback' technique. The database recorded numbers performed, the technical modalities used, clinical details, as well as complications and mortality. As a measure of quality control or verification, part of the database (the last 500 patients) was cross-referenced by a further, separate retrospective review of the hospital's electronic and radiological records to ensure that the data on the database is complete and accurate. All patients in whom there was either clinical suspicion or radiological confirmation of a PE were selected out to form our main study cohort. The patients who had the event beyond 3 months of the index transplant procedure were excluded, as shown in the CONSORT diagram (Fig. 1). The arbitrary cut-off date of 3 months served to differentiate early (peri-operative) from late PE, as in our opinion PE within the first 3 months were most likely to be secondary to the procedure and to an extent, preventable. In addition, statistically the risk of a postoperative PE has been shown to be the highest in the first 3 months. Moreover it appeared to be a suitable period during which the logistics of increased surveillance were feasible, if required for the prevention or early treatment of the complication.

Clinical records of those selected out with a suspected postoperative PE were collected and further information collated. Demographic and intra-operative data including age, sex, cause of liver disease, co-morbidities, haemoglobin and INR, surgical technique, transfusion requirements for red blood cells, fresh-frozen plasma, platelet, cryoprecipitate during surgery were collected. Postoperative data including post-operative haemoglobin and INR, presentation of PE, other complications and interventions, as well as follow-up and survival were collated and analysed. For the study a patient was deemed to have had a PE if there was a Ventilation/Perfusion (V/Q) scan showing high probability of a PE, or a Computed Tomography Pulmonary Angiography that demonstrated a thrombus (Fig. 2), or a combination of classical, clinical symptoms with supportive evidence from other investigations (e.g. ECG).

Statistical analyses were carried out using GraphPad Prism version 5.0 (Graphpad Software, Avenida de la Playa, CA, USA) and the database was maintained on Microsoft Excel 2000. Kaplan–Meier survival analysis was employed to compare survival between this cohort and the general post-LT population.

Results

Over the last 25 years, 36 patients were suspected of having a PE post-LT among the 2149 adult liver transplant recipients, following exclusion of the paediatric transplants. Fifteen presented more than 90 days after an LT and were excluded from the study.

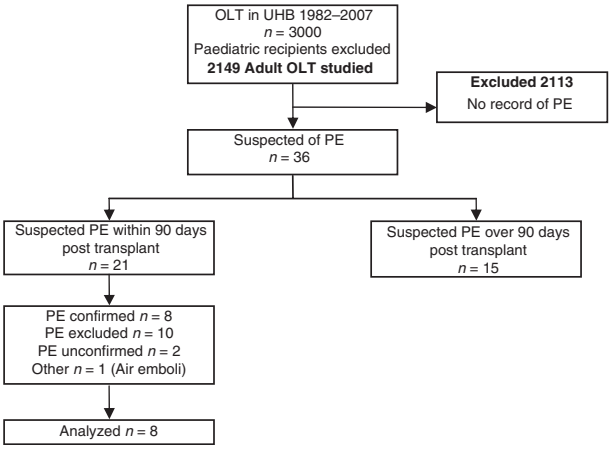

Figure 1 CONSORT diagram of the 3000 transplants studied.

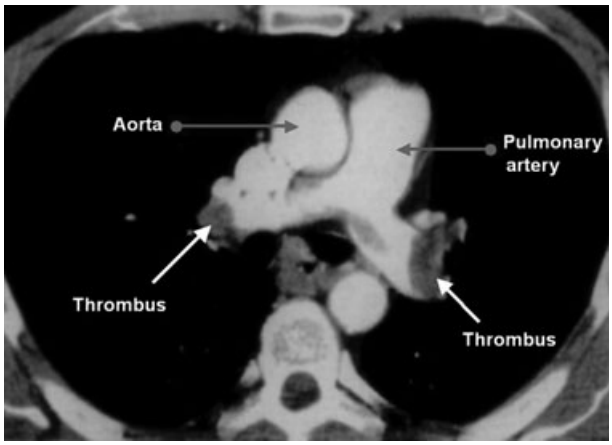

Figure 2 Axial tomography showing filling defects (thrombus) in bilateral pulmonary arteries.

None of those excluded had been in-patients due to or continuous from the index LT operation, at the time of the PE. Twenty-one patients presented within 90 days of transplant. Amongst them, PE was ruled out on further investigations in 10, and unconfirmed in two. In one patient an air emboli was found, leaving eight patients in whom a PE was confirmed (0.37%). In the two patients in whom we were unable to confirm a diagnosis of PE radiologically, further review of the notes revealed no convincing clinical evidence either. They were therefore considered to have not had a PE.

The median ages of the patients were 49 years (range 29–59 years; four men and four women). The aetiology of liver failure was varied [3 × Sero-negative hepatitis (SNH); 2 × Cryptogenic cirrhosis; one each with malignancy, chronic cholestatic liver disease and alpha-1 antitrypsin deficiency). Two of the eight patients with a PE had initially presented in acute liver failure, both secondary to SNH. One of whom later died on-table, with an autopsy confirmed, massive PE. As incidence of PE might be influenced by the pre-operative state, for comparison of severity of liver disease between the patients with a PE and those without, we used their preoperative Model for End-stage Liver Disease (MELD) scores. The MELD in the four patients in whom the MELD was known was 17, 21, 21, and 10. One was transplanted for ALF and hence MELD was not relevant, and the remaining three patients were transplanted before MELD scores were used in transplant assessment. In comparison, median MELD for adult patients undergoing LT in the centre was 15. Owing to the small numbers, no statistical analysis was carried out.

Two patients had pre-existing ischaemic heart disease, one had renal impairment, and another hypothyroidism. None had had previous thromboembolic events. Five had classical caval replacement LT, whilst in three the 'Piggyback' technique was utilised for implantation. There were two LT associated complications- both bile leaks. One required surgical biliary reconstruction with a Roux -en-y hepatico-jejunostomy, and the other required an ERCP and stent insertion. Neither had further complications thereafter. Table 1 tabulates the details of the eight patients in whom the PE was confirmed.

All PEs occurred in hospital. The median time between transplant and PE was 24 days (range 0–50 days). Of the eight in total, two were intra-operative, both of whom died from circulatory collapse due to a massive PE. Both intra-operative deaths occurred post reperfusion. In the first patient the initial sign was a sudden increase in central venous pressure and severe hypotension followed by cardiac arrest soon after skin closure. In the second patient (fulminant SNH), the PE occurred after reperfusion and presented with severe irrecoverable cardiac arrhythmias and secondary loss of cardiac output. Both PE were later confirmed on post mortem examination.

Of the six surviving patients, five presented with classical symptoms of tachypnoea while one presented with ascites and leg swelling. Diagnoses were made by high probability ventilation/perfusion scan in three cases, by Computer tomography pulmonary angiography in two,

Table 1. Details of the eight patients who were confirmed to have had a pulmonary embolus within 3 months of liver transplantation.

Patient No	Age (yrs)/Sex	Year of Transplant	Diagnosis	Pre-operative complications	Technique	Presentation of PE	Time of PE (days)	Survived PE
1	40/M	1988	Malignancy	–	Standard	Ascites + leg swelling	25	Yes
2	47/F	1988	Cryptogenic Cirrhosis	–	Standard	Dyspnoea	50	Yes
3	49/F	1992	Viral Hepatitis	–	Standard	Dyspnoea	5	Yes
4	29/M	1995	Seronegative Hepatitis	Hypothroidism	Standard	Circulation Collapse	0	No
5	53/M	1996	Cryptogenic Cirrhosis	Ischaemic Heart Disease	Standard	Circulation Collapse	0	No
6	59/M	2001	Alpha-1 antitrypsin deficiency	Renal failure	Piggyback	Dyspnoea	40	Yes
7	61/F	2001	Cholestatic	Ischaemic Heart Disease	Piggyback	Dyspnoea	22	Yes
8	29/F	2005	Seronegative Hepatitis	–	Piggyback	Dyspnoea	42	Yes

and in one patient the diagnosis was made clinically after USS showed a deep vein thrombosis and ECG showed sinus tachycardia. Thus of these six patients, two had either clinical or radiological evidence of lower limb venous thrombosis (pedal oedema × 1; Doppler finding × 1). In the others no investigations were done to clarify origin/source of the emboli, but one presumes that they were from the deep veins of the lower limb. All six survived the event, but one died 6 months post-diagnosis of an unrelated cause (chronic rejection/recurrent primary sclerosing cholangitis).

The remaining five are alive to date with a median follow-up of 65 (0–228) months. Figure 3 shows the Kaplan Meier survival estimates as a graph comparing the recipients who did and did not have a PE. All patients apart from the two on-table deaths were treated with long-term warfarin. Since the mid-1990s the thromboprophylaxis measures in our centre has included the use of above knee thromboembolic deterrent stockings on admission to the ward, and sequential calf pumps on-table during the procedure, unless specifically contra-indicated. In the post-operative phase all patients would receive daily, subcutaneous heparin at an appropriate 'prophylactic' dose based on patient weight, started once the INR was below 1.5 and continued until the patient had regained reasonable mobility. We would routinely encourage early physiotherapy assisted exercises that aimed to get the average patient to be able to mobilise unaided to the chair around the time the abdominal drains would be removed i.e. by about the 4th or 5th post-operative day, all being well. For the purposes of the current study we have assumed that all patients received prophylaxis as per protocol, as its use in these patients during the hospital stay following transplant could not be confirmed from records available. From our series, age of transplantation, aetiology of liver disease, technique of liver transplant, graft type, use of peri-operative blood products, pre- and post-LT haemoglobin and INR did not appear to be significant

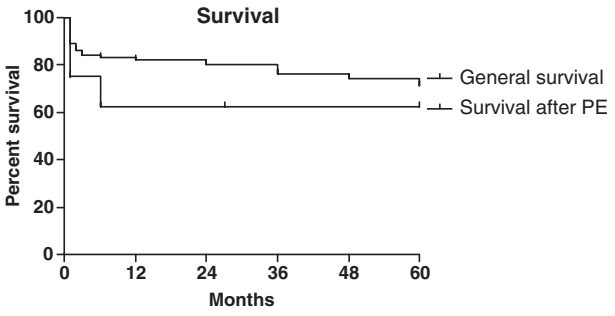

Figure 3 Kaplan–Meier survival analysis comparing 5 year survival estimates between patients who had a pulmonary embolism and those who did not.

risk factors for development of PE in LT although multivariate analysis was not performed on these data. Of the eight with PE, only one patient who had developed acute liver failure secondary to SNH, had received Aprotinin (Trasylol®; Bayer group AG, Germany) intra-operatively. He underwent a piggy back transplant and was found to have had a PE 40 days post-LT. We did not find any patterns in relation to platelet counts in the eight patients with a PE, with the platelet count closest to the event being less than 200 in all eight, and less than 100 in five patients.

Discussion

PE is a well-recognised post-operative complication of patients undergoing surgery [11]. It is the most common cause of preventable death in surgical patients and the risk of PE depends on a combination of patient's predisposing factors and type of surgery [12]. Patient risk factors include previous venous thromboembolic disease (TED), malignancy, medical therapy, underlying haematological conditions, obesity, increasing age and female sex. Surgical risks factors include the complexity of surgery, general anaesthetic and venous trauma sustained during surgery [13].

In large published studies, the incidence of TED in abdominal surgery was 29% and the rate of clinical PE around 1.6%, with a mortality rate of 0.9% without prophylaxis [14,15]. According to a landmark paper that attempted to classify risk of TED in surgical patients, most of our transplant patients would be in the 'highest risk' cohort for post-operative PE wherein the median risk is in the range of 4–10% for clinical and 1–5% for fatal PE [16]. The risk of PE is highest within the first week of surgery, and remains elevated for up to 3 months [11]. The advent of pharmacological (e.g. low molecular weight heparin) and mechanical (pneumatic compression devices) TED prophylaxis have significantly reduced this rate by 51% and 57% respectively [13,17]. However unlike in other gastrointestinal surgery, the risk in LT is hard to predict and is probably variable, as the delicate balance of haemostasis is disturbed in these patients by the disease aetiology, surgery and therapeutic intervention.

Traditionally it had been felt that the overall haemostatic function in the LT recipient is abnormal with the resultant risk of life threatening bleeding during or after surgery as surgical trauma inflected could be considerable. However more recently, studies have suggested that liver failure is associated with hypercoagulation rather than hypocoagulation or at the least haemostasis may not be as abnormal in cirrhosis as previously thought [3]. Indeed, a recent Danish population based case–control

study found an almost doubled risk of TED in patients with liver disease compared to the general population [4]. This has led to the present view of 'rebalanced haemostasis' suggested by Warnaar *et al.*, owing to the defects in both pro and anticoagulant systems [5]. However both these authors point out that despite this finding, the overall ability of this 'rebalanced' system to maintain haemostasis when stressed, is still reduced. Whilst liver disease might not be as anti-thrombotic as first thought, additional factors such as blood loss, sepsis and vitamin K deficiency leads to the oft observed coagulopathy [18]. Thus although the risk of excessive haemorrhage is not removed it does raise the risk of peri-operative TED, and therefore the need for prevention utilising protocol driven TED prophylaxis. It is important to note that current tests of haemostasis measure mainly pro-coagulant systems and are relatively insensitive to anti-coagulant factors barring Thromboelastography® potentially [5].

Various putative risk factors for the development of PE during LT have been suggested, including veno-venous bypass, vascular clamping, anti-fibrinolytic drugs, central venous catheters, etc. Activation of coagulation factors due to venous stasis, tissue injury/ischaemia also contribute to a pro-thrombotic state [19,20]. In addition arrhythmias from insertion of intravascular catheters, administration of anti-fibrinolytic agents and blood products is said to encourage thrombosis. However in a systematic review of intra-operative PEs, none of these factors appeared to be universally present in a high percentage of patients [21]. Aetiology of liver disease might have a role to play in this fine balance such as the finding of increased level of anti-phospholipid antibodies in hepatitis C positive patients, rendering them pro-coagulant [6]. Cholestatic liver diseases such as primary sclerosing cholangitis or primary biliary cirrhosis might also create a hypercoagulable state. However a higher incidence of PE was not borne out in our series in these disease groups. No discussion on haemostasis during or TED after LT is complete without mention of the much debated anti-fibrinolytic therapy. Despite being currently out of flavour due to concerns regards increased risk of TED and renal damage, a recent review has not supported these concerns [22].

Finally it is important to note that all of the above factors numerous and complex as they may be, are by no means exhaustive. A host of miscellaneous, hard to define or measure factors such as donor or graft derived, genetic pro-coagulant tendencies; intra-operative transfusion of haemostasis related therapies; the hypercoagulation of systemic sepsis, etc. might co-exist to complicate matters further. The low incidence of PE in our series potentially suggests that the overall haemostatic function in these patients is still weighted towards hypocoagulation with the resultant risk of excessive bleeding. However the numerous factors involved we believe would make accurate predictions difficult. The balance is more likely to be patient specific and even period specific with variations in the same patient during the whole process.

As mentioned before, the current literature in this field has so far been mostly concentrated to intra-operative thromboembolic events [7–10]. Thromboembolic events can occur at any stage of LT, but there is a slight predominance during the reperfusion phase [9]. The quoted incidence ranges from 1.2% to 6.25% depending on the series, but the numbers reported in each study are limited [8]. The analysis by Lerner and colleagues have shown that the death rate from PE is around 30% [9]. Only one previous study reported on the incidence of PE as a post-operative complication of LT, quoting an incidence of 1% [6].

Our study with its prospective data collection and large patient cohort and mature transplant experience, highlights the previously unrecognised low incidence of PE (0.37%) in patients undergoing LT. Previous studies have quoted higher incidences but have studied fewer patients (299 patients in the study by Ishitani *et al.*) or involved relatively nonselective patient cohorts [6,16]. The reason for the previously noted, relatively higher incidence of intra-operative as opposed to the postoperative PEs might be better intra-operative monitoring and the greater risk in the reperfusion phase as alluded to before [7,9,23,23]. An alternative explanation for the low incidence noted in our study might be enhanced fibrinolysis. Intravascular thrombi especially if small and clinically insignificant might undergo spontaneous dissolution as noted by Gologorsky *et al.* in their series of seven patients with intra-operative PEs [8]. It is also important to highlight that the current study covers a time span of 25 years during which period there has been dramatic changes in clinical practice. It is likely that PE would have been under-diagnosed in the early years when both awareness regards the possibility of such a diagnosis and the means to detect or confirm it were limited, leading to a potential underestimation of its overall prevalence in the current study.

In other abdominal surgeries, the highest risk of symptomatic venous thromboembolism (VTE) is within a week of surgery [13]. In our study the median time to a post operative PE was 24 days. This difference or delay maybe reflective of coagulopathy associated with initial liver dysfunction of the newly implanted graft. Nonetheless, the diligent use of anti-thromboembolic prophylaxis maybe contributive to this low figure.

The present study does suffer other limitations in addition to the one raised above. First, although the database was created prospectively, radiological records of the patients were collected retrospectively. Secondly as the

period of the study covered 25 years, clinical data on the earlier cases is limited and variations in clinical practice and operative techniques, could have potentially created biases that influenced the incidence. Third, data on peri-operative anti-thromboembolic measures are currently not prospectively entered into the transplant database. There is a presumption that all patients in the database had received anti-thromboembolic prophylaxis where appropriate, following protocol driven anti-thromboembolic measures instituted gradually in our centre from the mid-1990s. Information on measures used prior to this is lacking but is likely to have been absent. Finally although the age of transplantation, aetiology of liver disease, technique of liver transplant, graft type, use of peri-operative blood products, pre and post-OLT haemoglobin and INR did not appear to be significant risk factors for development of PE in OLT, multivariate analysis was not performed on these data due to the small numbers of positive patients.

Conclusion

Acute PE in the setting of OLT has an incidence rate (0.37%) in our series that appears to be lower than one would expect after a 'major complex' category operation. This potentially suggests that the overall imbalance in haemostasis is still tipped in favour of hypocoagulation, in most cases after LT. However it is important to bear in mind the various pro-coagulant factors that bear influence in these patients and to be vigilant to such phenomenon and take adequate prophylaxis where appropriate as these factors might also have a role to play in inflow vessel vascular thrombosis. No specific liver disorder appeared to pose greater risk to VTEs in our series. The prognosis after post-operative PE appears to be good with a median survival of 65 months in our series although, sudden death due to an on-table embolism is a rare (incidence rate 0.09%) but significant risk.

Authorship

TPC: designed study, collected data, analyzed data, wrote paper; KC: collected data, wrote paper; BG: analyzed data; SRB, DM, DFM: helped in conducting study; JACB: designed study, supervised project, edited paper.

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