Thrombocytopenia in cirrhosis: Impact of fibrinogen on bleeding risk

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AIM
To investigate the relationship between baseline platelet count, claus fibrinogen, maximum amplitude (MA) on thromboelastography, and blood loss in orthotopic liver transplantation (OLT).

METHODS
A retrospective analysis of our OLT Database (2006-2015) was performed. Baseline haematological indices and intraoperative blood transfusion requirements, as a combination of cell salvage return and estimation of 300 mls/unit of allogenic blood, was noted as a surrogate for intraoperative bleeding. Two groups: Excessive transfusion (> 1200 mL returned) and No excessive transfusion (< 1200 mL returned) were analysed. All data analyses were conducted using IBM SPSS Statistics version 23.

RESULTS
Of 322 OLT patients, 77 were excluded due to fulminant disease; redo transplant or baseline haemoglobin (Hb) of < 80 g/L. One hundred and fourteen (46.3%) were classified into the excessive transfusion group, 132 (53.7%) in the no excessive transfusion group. Mean age and gender distribution were similar in both groups.
A number of factors contribute to thrombocytopenia in disease and is associated with significant morbidity. Thrombocytopenia (defined as platelet count $< 50 \times 10^{9}/L$) as the predictor and Haemorrhage as the outcome showed an odds ratio of 1.393 (95%CI: 0.758-2.563; $P = 0.286$). Review of receiver operating characteristic curves showed an area under the curve (AUC) for platelet count of 0.604 (95%CI: 0.534-0.675; $P = 0.005$) as compared with AUC for fibrinogen level, 0.678 (95%CI: 0.612-0.744; $P \leq 0.001$). A multivariate logistic regression shows United Kingdom model for End Stage Liver Disease ($P = 0.006$), Hb ($P = 0.022$) and Fibrinogen ($P = 0.026$) to be statistically significant, whereas Platelet count was not statistically significant.

**CONCLUSION**

Platelet count alone does not predict excessive transfusion. Additional investigations, e.g., clauss fibrinogen and viscoelastic tests, provide more robust assessment of bleeding-risk in thrombocytopenia and cirrhosis.

Key words: Thrombocytopenia; Cirrhosis; Haemostasis; Fibrinogen; Liver transplantation

Core tip: Current literature describing bleeding risk in thrombocytopenia and cirrhosis does not take into account the impact of fibrinogen. The minimal platelet count to form a clot with normal strength is unknown, and would be influenced by fibrinogen. Viscoelastic testing, particularly maximum amplitude (MA, thromboelastography) or maximum clot-firmness (MCF, thromboelastometry), reflects platelet-fibrinogen interaction and allows assessment of clot strength. Low platelet count and low fibrinogen levels lead to low MA/MCF and correlate strongly with increased bleeding tendency. Assessment of platelet count alone does not accurately predict bleeding, but is useful in conjunction with other indices such as clauss fibrinogen and MA/MCF.

INTRODUCTION

Thrombocytopenia is a common finding in patients with advanced liver disease. In most instances it is well tolerated but it is traditionally thought to increase the likelihood of surgical or traumatic bleeding. Moderate thrombocytopenia (defined as platelet count $< 50 \times 10^{9}/L$) occurs in approximately 13% of those with liver disease and is associated with significant morbidity. A number of factors contribute to thrombocytopenia in liver disease, including low thrombopoietin levels, and sequestration of platelets in hypersplenism as a result of portal hypertension.

Derangements of other haematological indices in cirrhosis include prolongation of prothrombin time (PT), prolongation of activated thromboplastin time (APTT) and dysfibrinogenemia. Conventionally, these changes were thought to lead to an increased bleeding risk. Over the last 10 years, however, a new paradigm of haemostasis in liver disease has been described. There is now considered to be a “rebalancing” with a reduction in procoagulant molecules being accompanied by a reduction in anticoagulant molecules. Thrombin generation is normal, or even increased and patients with cirrhosis are now considered to have an elevated risk of thrombosis rather than have complications of bleeding.

Standard tests of coagulation such as PT and APTT do not accurately reflect coagulation status in vivo, as they cannot assess cellular contributions or the effects of anticoagulant molecules. In-vitro studies in cirrhosis have shown a compensatory increase in levels of Von Willebrand Factor (vWF) - a platelet adhesion protein and reductions in ADAMTS-13, the cleavage enzyme responsible for the breakdown of vWF. Additionally, platelet hyperactivity has been reported in cholestatic liver disease. A systematic review evaluating platelet function concluded that in patients with cirrhosis, primary haemostasis is not defective.

Whole blood viscoelastic testing provides valuable information about dynamic clot formation. It measures changes in clot tensile strength with time and is used in goal-orientated algorithms to target transfusion. Clot strength is assessed by maximum amplitude (MA) or maximum clot firmness (MCF) and is influenced by both platelet count and by fibrinogen level. MA or MCF can be maintained in the face of low platelet counts by normal or increased levels of fibrinogen. Whole blood global viscoelastic tests such as thromboelastography (TEG) or thromboelastometry (ROTEM) may provide more clinically relevant information about coagulation profiles in liver disease. Increasingly observed blood transfusion free orthotopic liver transplantation (OLT) suggests that conventional tests of coagulation are inadequate in predicting bleeding.

Studies of low platelet count in cirrhosis suggest that thrombin generation may be reduced in cases of severe thrombocytopenia. In-vitro studies, however, have shown that a platelet count of 20-30 $\times 10^{9}/L$ is likely to be adequate to initiate haemostasis and generate enough thrombin to allow normal MA on TEG. Despite a reduction in thrombin production, clot strength is likely to be adequate if the appropriate substrates for clot formation are present. Moderate reductions in platelet count, therefore, do not necessarily indicate an increased risk of bleeding in liver disease.

British Haematology Society guidelines for the use of platelet transfusions and consensus guidelines for percutaneous image guided interventions recommend the prophylactic transfusion of platelets to a count of $> 50$
\( \times 10^9/L \) prior to liver biopsy to prevent complications of bleeding. In view of current knowledge of coagulation and haemostasis in cirrhosis, the objectives of this study were to investigate the relationship between baseline platelet count, clauss fibrinogen, MA on TEG and the volume of blood transfused in patients undergoing orthotopic liver transplantation.

**MATERIALS AND METHODS**

**Study design**
A retrospective study of patients who had undergone OLT at the Centre for Hepatobiliary Surgery, Royal Free London between 2006 and 2015 was conducted. The cohort of patients reviewed had transplantation for chronic end stage liver disease, with or without hepatocellular carcinoma. Data from their intraoperative course was retrieved from a database formed as part of standard care. Those with acute fulminant liver failure, paracetamol overdose or redo transplantation were excluded. Patients with starting haemoglobin of less than 80 g/L were also excluded in view of an increased risk of intraoperative blood transfusion. Data was anonymised and institutional research and development departmental approval was obtained for its use.

Patient demographic data, baseline haematological results, number of packed red cell units transfused intra-operatively and volume of cell salvaged blood returned to patients was retrieved electronically.

**Measurements**
Baseline variables were retrieved from the OLT database and included patient characteristics such as age, gender, diagnosis and severity scoring with United Kingdom model for End Stage Liver Disease (UKELD score). Baseline clinical measurements were point-of-care (i.e., Medical diagnostic testing at the point of care) samples taken at the time of anaesthesia for liver transplantation from arterial catheters and measurements included haemoglobin concentration (Hb) and platelet count by pocH-100i full blood count analyser (Sysmex Europe GmbH). TEG variables were from TEG® 5000 (Haemonetics, Braintree, MA, United States. United Kingdom TD in particular MA on heparinase TEG was assessed. Heparinase TEGs were used for analysis to remove any influence that may have been exerted by endogenous heparinoids and to standardize results. Laboratory Clauss fibrinogen levels using ACL-TOP 700 (Werfen, United Kingdom) were obtained prior to transplantation and did not exceed 24 h prior to anaesthetic start time. All assays are controlled and monitored using laboratory quality assurance processes.

As a surrogate for intraoperative blood loss, an estimation of 300 mL of blood in a packed red cell unit given to patients was made, and the volume summated with cell salvage return volume to give a total volume of blood returned. Patients were divided into 2 groups according to total volume of blood returned: \( \leq 1200 \) mL (no excessive transfusion) and \( > 1200 \) mL (excessive transfusion).

**Statistical analysis**
Descriptive statistics were performed on baseline variables and comparisons made between excessive transfusion (ET) and no excessive transfusion (NET) groups. Univariate logistic regression was performed for each variable independently as the predictor, and ET as the binary outcome. Receiver operating characteristic (ROC) curves for baseline platelet count and for baseline clauss fibrinogen were also constructed and area under the curves calculated. Binomial logistic regression with each variable as the predictor and ET as the outcome was also performed. Predicted probabilities from the binomial logistic regression were used for further ROC analysis. The relationship between platelet count and blood volume returned as well as fibrinogen and blood volume returned was further investigated by linear regression modeling. All data analyses were conducted using IBM SPSS Statistics version 23. All statistical analyses were reviewed by Ms Fatima Jichi, a trained biostatistician with the department of Biostatistics, University College London.

**RESULTS**

**Baseline demographics**
Results for 323 patients were reviewed and of these 37 patients had either acute, fulminant liver failure or a redo-liver transplant and were excluded. A further 40 patients had a baseline Hb less than 80 g/L and were also excluded. Of the remaining 246 patients, 114 (46.3%) had excessive transfusion and 132 (53.7%) had no excessive transfusion.

Mean patient ages were 53 years (± 1 SD 10.04 years) and were similar in ET and NET groups. The gender distribution of patients was 72.8% male and 27.2% female with a similar divide in both groups. Mean UKELD was 56 (± 10.55) in the ET group and 51 (± 5.08) in the NET group \((P \leq 0.001)\). Liver disease due to Infection (33.3%) or Alcohol (29.6%) was the commonest aetiology. Interestingly, primary sclerosing cholangitis (PSC) was more common in the NET group (18.9%) vs the ET group (7.9%). \( \chi^2 \) analysis of aetiologies in both groups revealed \( \times \chi^2 = 18.81, P = 0.016 \). Baseline Hb, platelet count, clauss fibrinogen and hep MA were all statistically significantly different between the two groups (Table 1).

A comparison of patient demographics and baseline measurements between those with platelet count < 50 and those \( \geq 50 \times 10^9/L \) is described in Table 2. Baseline fibrinogen was statistically significantly different between those with low platelet count (mean = 1.78 ± 0.62) and those without (2.45 ± 1.15, \( P \leq 0.001)\). Baseline hep MA was also significantly different in the 2 groups (35.28 ± 9.49 vs 47.85 ± 11.93, \( P \leq 0.001)\). The total volume of blood returned was not significantly different between
Table 1  Baseline demographics for patients with chronic liver disease who have undergone orthotopic liver transplantation

| Diagnosis          | n  | Male | Female | Gender | Mean | SD | Median | IQR | Range | n  | P value |
|--------------------|-----|------|--------|--------|------|----|--------|-----|-------|-----|---------|
| ALD                | 44  | 24   | 19     |        | 41.6| 9.5| 35.0   | 21  | 60    | 44  | 0.612-0.744; P ≤ 0.001 |
| Infectious         | 40  | 23   | 17     |        | 39.3| 8.8| 34.2   | 22  | 54    | 40  | 0.001 |
| NASH               | 4   | 2    | 2      |        | 41.5| 8.2| 40.0   | 3   | 50    | 6   | 0.001 |
| PSC                | 9   | 5    | 4      |        | 38.3| 5.5| 36.0   | 6   | 51    | 8   | 0.001 |
| PBC                | 2   | 1    | 1      |        | 56.5| 15.2| 49.0   | 23  | 79    | 4   | 0.001 |
| AIH                | 4   | 2    | 2      |        | 38.3| 7.4| 34.0   | 6   | 50    | 5   | 0.001 |
| Wilsons            | 1   | 1    | 0      |        | 41.5| 8.2| 40.0   | 0   | 50    | 1   | 0.001 |
| Haemochromatosis   | 1   | 1    | 0      |        | 41.5| 8.2| 40.0   | 0   | 50    | 1   | 0.001 |
| Misc               | 8   | 2    | 6      |        | 38.3| 7.4| 34.0   | 6   | 50    | 4   | 0.001 |
| Fibrinogen (g/L)   |     |      |        |        | 1.96| 0.9| 1.5    | 0.4 | 2.3   | 1.96| 0.001 |
| Hep MA (mm)        |     |      |        |        | 41.5| 7.4| 34.0   | 6   | 50    | 1   | 0.001 |
| Total blood returned (mL) |     |      |        |        | 3323| 487| 1802   |     |       | 2536| 0.286 |

Table 2  Comparison of baseline demographics according to baseline platelet count cut off value of 50 × 10^3/L

| Platelet count | n  | Platelet count | P value |
|----------------|-----|----------------|---------|
| < 50           | 53  | 21.5%          | 0.013   |
| ≥ 50           | 193 | 78.5%          |         |
| Age (yr)       | Mean| 51.23          | 9.04    |
| SD             | 10  |                |         |
| Median         | 52.38|              | 55.26   |
| Range          | 52  |                | 50      |
| Gender         |     |                |         |
| Female         | 40  | 75.5%          | 0.62    |
| Male           | 13  | 24.5%          | 0.09    |
| UKELD          | Mean| 54.16          | 52.72   |
| SD             | 5.06|                | 6.47    |

the 2 groups (P = 0.69).

A logistic regression analysis (Table 3) was performed to ascertain the independent effects of age, gender, UKELD, baseline Hb, baseline platelet count, baseline platelet count < 50 × 10^3/L or ≥ 50 × 10^3/L as a binary value, baseline claus fibrinogen level and baseline heparinase MA on likelihood of excessive transfusion. UKELD (P ≤ 0.001), HB (P ≤ 0.001), platelet count (P = 0.007), claus fibrinogen (P ≤ 0.001) and Hep MA (P = 0.001) were all statistically significant. A cut off value of platelet count less than 50 was not a good predictor of excessive transfusion (P = 0.286).

Review of ROC curves showed an area under the curve (AUC) for platelet count of 0.604 (standard error: 0.036; 95%CI: 0.534-0.675; P = 0.005). AUC for fibrinogen level was 0.678 (standard error: 0.034; 95%CI: 0.612-0.744; P ≤ 0.001) (Figure 1).

A multivariate logistic regression with all covariates with P ≤ 0.1 from univariate logistic regression added to a model, shows UKELD (P = 0.006), HB (P = 0.022) and Fibrinogen (P = 0.026) to be statistically significant. Platelet count was not statistically significant (Table 4).

The AUC from ROC curve analysis of predicted probabilities from multivariate logistic regression was 0.749 (standard error: 0.032; 95%CI: 0.686-0.812; P ≤ 0.001), suggesting that variables need to be considered together to better predict excessive transfusion (Figure 2).

Further investigation of the relationship between baseline platelet count and total volume of blood returned to patients showed that for every 1 point increase in platelet count, a 4.9 mL (P = 0.19) reduction in total
blood volume returned was achieved. For every 1-point increase in fibrinogen level, however, a reduction of 525.95 mL ($P \leq 0.001$) of blood returned to the patient was achieved (Table 5).

**DISCUSSION**

**Principle findings**

Guidelines recommend the prophylactic transfusion of platelets to achieve a count of $50 \times 10^9/L$ prior to invasive procedures such as liver biopsy. Understanding of haemostasis in the cirrhotic population has altered with the concept of a “rebalanced” haemostatic profile in liver disease. This study evaluated differences in baseline platelet count, fibrinogen levels, viscoelastic tests and blood transfusion requirements in those undergoing OLT for chronic liver disease. Patients in our study were divided according to whether they received excessive blood transfusion or not. On comparison, the 2 groups were well matched for gender and age, although UKELD was found to be significantly different. Severity of liver disease, in the form of Childs-Pugh score and Model for end stage liver disease (MELD) scoring, is associated with a prediction of increased intraoperative transfusion requirement$^{[12]}$. This may explain the difference in UKELD between the 2 groups.

It was interesting to note a higher preponderance of PSC as the aetiology of liver disease in those not requiring excessive transfusion. Hypercoagulable haemostatic profiles have been described for those with biliary cirrhotic disease and in general this population does not have thrombocytopenia or low fibrinogen$^{[5]}$.

A statistically significant difference in baseline Hb, platelet count, Clauss fibrinogen and MA on heparinase TEG was observed between those who received excessive transfusion vs those who did not. This highlights an association with bleeding risk and indicates that possibly all of these measurements would be useful in predicting increased blood transfusion requirements.

Logistic regression performed to evaluate the probability of excessive transfusion with each variable shows clearly that a platelet threshold value of $50 \times 10^9/L$ is not a good predictor of blood transfusion in this population. Although there has been a previously described association between a reduction in thrombin generation with a reduction in platelet count$^{[8]}$, the cut off value of platelets requiring transfusion in cirrhosis is likely to lie significantly below $50 \times 10^9/L$ described in guidelines. One small prospective study of liver biopsy in severe thrombocytopenia associated

**Table 3  Univariate logistic regression**

|                | Odds ratio | 95%CI       | $P$ value |
|----------------|------------|-------------|-----------|
| Age            | 1.004      | 0.979-1.029 | 0.76      |
| Gender         | 1.288      | 0.730-2.271 | 0.382     |
| UKELD          | 1.130      | 1.076-1.188 | < 0.001   |
| Hb             | 0.97       | 0.954-0.986 | < 0.001   |
| Platelet count | 0.994      | 0.990-0.998 | 0.007     |
| Platelets (Binary cut off < 50 and $\geq 50$) | 1.903 | 0.758-2.563 | 0.286     |
| Fibrinogen     | 0.523      | 0.388-0.703 | < 0.001   |
| Hep MA         | 0.963      | 0.942-0.984 | 0.001     |

UKELD: United Kingdom end-stage liver disease score; Hb: Haemoglobin; Hep MA: Maximum amplitude on heparinise TEG.

**Table 4  Multivariate logistic regression with covariates $P < 0.1$ from univariate logistic regression**

|                | OR  | 95%CI       | $P$ value |
|----------------|-----|-------------|-----------|
| UKELD          | 1.081| 1.023-1.143 | 0.006     |
| Hb             | 0.977| 0.958-0.997 | 0.022     |
| Platelets      | 0.999| 0.994-1.004 | 0.700     |
| Fibrinogen     | 0.682| 0.487-0.955 | 0.026     |
| Hep MA         | 0.986| 0.957-1.015 | 0.338     |

OR: Odds ratio; UKELD: United Kingdom end-stage liver disease score; Hb: Haemoglobin; Hep MA: Maximum amplitude on heparinise TEG.

**Table 5  Relationship between baseline platelet count and baseline clauss fibrinogen and blood returned to patients (linear regression)**

| Model             | Regression coefficient B | 95%CI       | $P$ value |
|-------------------|--------------------------|-------------|-----------|
| Platelet count    | 2280.72-4.99             | -9.142-0.829| < 0.001   |
| Fibrinogen        | 3014.63-525.95           | -776.88-275.02| < 0.001   |

**Figure 1  Receiver operating characteristics for baseline platelet count and baseline clauss fibrinogen. A: Platelets; B: Fibrinogen; ROC: Receiver operating characteristic.**
with haematological malignancy suggests the likely cut off value lies below $30 \times 10^9/L$.

Much of the literature describing bleeding risk in cirrhosis and thrombocytopenia does not take into account fibrinogen level. The minimal platelet count required for normal clot strength is unknown and is markedly affected by fibrinogen. MA on TEG is a composite reflection of platelet-fibrinogen interaction and can be used to assess clot strength. Assessment of MA shows that even in the face of a low platelet count, adequate clot strength may still be achieved if fibrinogen is normal or raised. A combination of low platelet count and low fibrinogen level always results in low MA and is strongly associated with an increased bleeding tendency. Platelet count alone is not a true indicator of clot strength; therefore, if baseline platelet count is low, assessment of MA is useful in guiding whether to replace fibrinogen or to transfuse platelets. Thrombocytopenia predominately leads to a reduction in blood clot strength displayed as MA on TEG, but fibrinogen also contributes to clot firmness. The effect of the administration of fibrinogen concentrates in thrombocytopenia, at a count of $30 \times 10^9/L$, in the pig model has been studied. Velik-Salchner et al. showed an improvement in impaired clot formation and a reduction in blood loss in thrombocytopenia with the addition of fibrinogen.

The impact of fibrinogen on bleeding risk can be observed in the results of this study. Baseline clauss fibrinogen level is likely to have a greater protective effect than the other baseline haematological variables (OR: 0.52; 95%CI: 0.388-0.705; $P \leq 0.001$). Similarly, Odds ratios for fibrinogen on multivariate analysis are the lowest when compared with other variables (0.682, 95%CI: 0.487-0.955) (Table 4). On comparison of AUCs on ROC curve analysis, baseline fibrinogen level is a better predictor of excessive transfusion than platelet count. Interestingly, linear regression analysis shows a $52.95$ mL reduction in blood returned to patients with each 1-unit increase in baseline fibrinogen level (i.e., 1 g of fibrinogen factor concentrate) (Figure 1). In comparison, 1 pool of platelets (one adult therapeutic dose) increases platelet count by $20 \times 10^9/L$, equating to a $99.8$ mL reduction in blood transfusion if the linear model is used. ROC analysis of predicted probabilities on multivariate analysis show an AUC greater than that of platelet count alone, indicating a better predictive value on assessing all the demographic and haematological variables simultaneously (Figure 2).

**Strengths and weaknesses of the study**

Although there are a number of in-vitro investigations into the associations between thrombocytopenia and fibrinogen concentration and clot strength, there is a lack of evidence relating to the influence of the two in vivo. There is also a lack of substantial evidence to validate a cut off value for prophylactic platelet transfusion in the cirrhotic population. This study highlights the contribution of fibrinogen in reducing the risk of excessive blood transfusion, and therefore bleeding risk.

Excessive transfusion was used as a surrogate for intraoperative bleeding in this study. Measurement of blood loss in suction and weight of swabs would provide more accurate information with regard to blood loss, but this information was unavailable retrospectively. Furthermore, OLT is complex surgery with other influences on haemorrhage apart from the haemostatic picture. These include presence of portal hypertension and varices, difficult operative dissection with multiple adhesions, surgical technique (i.e., Caval replacement surgery or “piggy back” technique for reperfusion) and the volume of fluid given to the patient. Baseline low haematocrit values increase the likelihood of requiring intraoperative blood transfusion. Low haematocrit also has an impact on lamellar flow in blood vessels and therefore a disturbance in primary haemostasis may occur in anaemia. We excluded those with baseline haemoglobin of $< 80 \text{ g/L}$ for this reason.

Although the results of our study point to the usefulness of measuring baseline clauss fibrinogen in conjunction with platelet count and assessment of TEG, we are unable to assess for specific cut off values for baseline platelet count and fibrinogen level. Results would require validation against external data sets to allow for cut off values, requiring further prospective research.

**Implications of study**

The transfusion of platelets is not without risk. Complications of platelet transfusion include allergic or anaphylactic reactions, haemolytic and non-haemolitic transfusion reactions, transfusion related acute lung injury and septic transfusion reactions of bacterial origin. Furthermore, in liver transplantation, platelets have been shown to be involved in ischaemic reperfusion injury by interactions with activated sinusoidal endothelium and induction of apoptosis. Perioperative platelet transfusion has been identified as an independent risk factor for adverse post-operative outcomes. In a large retrospective analysis of patients undergoing cardiac surgery, those receiving platelets were at an increased risk of postoperative infection, stroke and multiorgan failure.

The availability of platelets, largely due to short storage life, can also be limited. By demonstrating a lack
of association between excessive blood transfusion and a threshold platelet count of 50 × 10^9/L, the question of unnecessary prophylactic platelet transfusion arises. If an increase in fibrinogen levels by 1 g reduces the volume of blood transfused significantly, the usefulness of fibrinogen concentrate rather than platelet transfusion should be considered. Fibrinogen concentrate appears to have a better safety profile than cryoprecipitate and fresh frozen plasma, particularly when considering the risk of blood borne infection. Other advantages of its use include the accuracy and rapidity of its administration[23].

In conclusion, further prospective evaluation to assess for the true baseline platelet count at which bleeding risk is increased needs to be performed. Studies have described an increase likelihood of bleeding associated with invasive procedure with low platelet counts (< 75 × 10^9/L), but it is important to note that these studies failed to assess the contribution of fibrinogen to clot strength in cases of thrombocytopenia[24]. Additional haematological indices such as Clauss fibrinogen and the use of viscoelastic testing may provide a more robust assessment of bleeding risk in thrombocytopenia associated with cirrhosis.

ACKNOWLEDGMENTS

We would like to appreciate Dr. Eleanor Galtrey and Dr. Simon Goddard, Anaesthetic fellows, for their contribution in obtaining and processing data for this study. We also appreciate Felicity Blake, Point of Care laboratory manager for her continuing support in facilitating point of care assessment in patients undergoing OLT.

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P- Reviewer: Manolakopoulos S, Procopet B, Wong GLH
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