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Anaemia in patients with chronic liver disease and its association with morbidity and mortality following liver transplantation.

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Pre-operative anaemia and the need for intra-operative transfusion have been associated with increased morbidity and mortality following cardiac and major non-cardiac surgery. Anaemia is highly prevalent in patients with severe chronic liver disease. Whether this correlates with an altered morbidity and mortality following liver transplant has not been established.

Methods

Prospectively collected data was analysed for the period 1998-2012. Donor and recipient characteristics, blood profiles and complications were recorded. Graft and patient survival was calculated. All patients were followed up for 1 year or until death. Pre-operative haemoglobin levels were correlated with patient demographics and outcome using a binary logistic regression analysis.

Results

Pre-operative anaemia, according to WHO criteria, occurred in 73% of patients. Anaemia was more common with advanced liver disease (higher MELD score). As MELD score increased, Haemoglobin levels dropped. Anaemic patients were more commonly transfused ($p<0.001$), spent longer ventilated (7 day vs 5 days, $p=0.005$) and required longer ITU stays (8 days vs 6 days, $p = 0.015$). Pre-operative anaemia did not correlate with patient morbidity or mortality.

Conclusions:

Reduced haemoglobin levels reflect the severity of chronic liver disease but are not an independent risk factor for a poor outcome following liver transplantation.

Introduction:

Liver transplantation is the only effective treatment available to patients with end stage chronic liver failure. Liver transplantation is highly effective but is a major surgical procedure with a 1 year mortality rate of 14% (1). Reducing the post-operative mortality rate is a major goal in liver transplant surgery.

Anaemia is a common finding in surgical patients occurring in approximately 30.4% of patients undergoing non-cardiac surgery (2). Pre-operative anaemia has been identified as an independent risk factor for post-operative morbidity and mortality in several surgical fields (2)(3)(4)(5). In the setting of cardiac surgery, a haemoglobin level of less than 12mg/dL has been shown to increase the risk of surgical mortality three fold and the incidence of significant post-operative morbidity five fold (6). The mechanism linking anaemia with poor outcome is unknown. Reduced tissue oxygenation, increased haemodilution and increased incidence of transfusion have been implicated as possible mechanisms of a reduced physiological ability to cope with the stress of major surgery (6).

Anaemia is common in patients with advanced chronic liver disease. 75% of patients undergoing treatment for hepatitis C virus are anaemic (7). The pathology of anaemia in severe liver disease is diverse including acute and chronic blood loss into the GI tract, malnutrition, haemolysis and treatment of viral hepatitis (8)(9). As the underlying pathophysiology of the liver disease is so variable in this group of patients, the underlying type of anaemia in patients with chronic liver disease may similarly vary from iron deficiency to Vitamin B12 and folate deficiency (8)(10) making correction of anaemia difficult. Correction of haemoglobin levels in patients with Hepatitis C can be achieved with Erethropoetin (7).

With the current median waiting time between being listed for transplantation to undergoing transplantation being 4-5 months in the UK (11), there is ample time to correct pre-operative anaemia prior to transplantation.

Although anaemia has been investigated as a predictor of the need for intra-operative transfusions in liver transplantation (12)(13), the significance of pre-operative anaemia to the early outcomes of liver transplant surgery has not been established and was the aim of this study

Methods:

A prospectively collected liver transplant database was reviewed between the years of 1998 and 2012 to allow significant sample size and adequate follow up data. All donor types (DBD, DCD, split and domino grafts) were included in the analysis. Re-transplantations were also included.

Haemoglobin levels were measured in peripheral venous blood (Sysmex XE-2100, Sysmex Corporation, Milton Keynes, UK) on the day of admission for liver transplant along with full biochemistry profiles including a Model for End-Stage Liver Disease (MELD) score.

Transplant procedure:

Grafts were identified and retrieved through NHS blood and transplant (NHSBT) by the designated regional teams within the UK National Organ Retrieval Service (NORS). All grafts were retrieved according to the national standards for organ retrieval from deceased donors (NHSBT) (14). Grafts were routinely perfused in situ with cold University of Wisconsin (UW) solution (Organ Recovery Systems, Chicago).

Both piggy-back and caval replacement techniques for liver transplantation were utilised. Veno-venous bypass was not routinely employed.

1 mg of methylprednisolone (Pharmacia) was given intravenously during the anhepatic phase. All patients were monitored via invasive central and venous blood pressures.

Post operative management:

Post-operatively all patients were managed in the intensive care unit.

Haemoglobin levels were maintained below 10g/L to reduce the risk of graft thrombosis.

Platelets and fresh frozen plasma were administered only if there was active bleeding associated with a coagulopathy or thrombocytopaenia. Patients were routinely started on subcutaneous thromboprophylaxis on the first post-operative day.

All patients underwent a Doppler ultrasound scan of the liver vessels on the first, third and fifth post-operative day and underwent routine daily bloods including liver function tests.

Patients were extubated on the first post-operative day unless there was a clinical need for ongoing respiratory support.

Standard immunosuppression therapy was commenced on day one post-operatively.

Pre-operative anaemia:

Haemogloblin levels were documented on the day of admission for liver transplant and patients were classified as anaemic according to the World Health Organisation (WHO) definition of male <13g/dL or female <12g/dL (15). The need for intra-operative Red Cell Concentrate (RCC) transfusion was determined by the anaesthetic team and was based on blood loss, systemic haemodynamics and haemoglobin level on routine arterial blood gas analysis. Clotting factor replacement was based on blood loss and near patient coagulation monitoring using Thromboelastography (TEG) readings.

Mortality:

Patient mortality was defined as death from any cause and was calculated at 30 days, 90 days and at 1 year post transplantation.

Morbidity:

Post-operative morbidity included, graft loss within 3 months, the need for organ support (respiratory and renal), biliary complication (leak and stricture), hepatic artery thrombosis (HAT), portal vein thrombosis (PVT) and post-operative infective episodes (bacterial/fungal/viral). Infective complications were only included when a positive culture was documented.

Donor, transplant and recipient factors:

When regression models were performed, pre-operative haemoglobin was adjusted for the donor variable age, the transplant variables - length of cold ischaemic time and length of vascular anastomosis time and the recipient variables - age, gender and pre-operative MELD score.

MELD score and its relationship with haemoglobin:

To further explore the relationship between pre-operative haemoglobin levels and MELD score, MELD was broken down into the individual components that are used to calculate it – serum creatinine, serum bilirubin and INR (16). Data regarding recent dialysis in the last week was missing and as such the UNOS modification of altering creatinine accordingly was not used.

Statistical analysis:

Results were analysed on the Statistical Package for the Social Sciences (SPSS) version 21, IBM. Univariate comparisons between anaemic and non-anaemic groups were performed using chi-squared tests for dichotomous variables and independent

samples t-tests for continuous variables for parametic data and Mann-Whitney U tests for non-parametric data.

A binary logistic regression model was used to adjust haemoglobin values for donor, transplant and recipient factors when the outcome measured was dichotomous and a linear regression model was used when the outcome was a continuous variable.

A spearman's bivariate correlation was used to correlate haemoglobin values with individual components of MELD score.

A p value of <0.05 was considered to be significant.

Results

Data was analysed on 795 patients (416 Female/377 Male/1 Unknown) undergoing liver transplant between 1998 and 2012. Minimum follow up was 30 days or until death, maximum follow up was 1 year. The median donor age was 43 (31-53). The majority of grafts were from donors after brain death (DBD) (97%). The median cold ischaemic time was 604 mins (454-744). 99.6% of grafts were preserved in commercial University of Wisconsin preservation fluid (Organ Recovery Systems, Chicago). Further donor and transplant variables are described in Table 1. The median recipient age at time of transplantation was 50 years (41-57) and the median pre-operative MELD score was 16 (12-22) Further recipient characteristics are given in Table 2. The main indications for transplantation were hepatitis C virus (HCV) related cirrhosis (23%) and alcoholic liver disease (ALD) (18%). Other indications are given in Table 3.

Median pre-operative haemoglobin level was 11 mg/dL (9.6-12.5).

100 patients (7.8%) died within 30 days of their transplant, 141 patients (11.1%) died within 90 days of their transplant and 218 patients (17.9%) died within 1 year of their transplant.

Incidence of pre-operative anaemia:

When calculated according to WHO classification (15), 580 patients (73%) were anaemic on the day of admission for liver transplantation. Anaemia was prevalent across all indications for transplantation ranging from 44-100% (Table 2). Anaemic patients were younger [50(40-57) vs 51(44-58), p=0.026], were more likely to be female, had more advanced liver disease as measured by MELD score [17(13-24) vs

13(9-17), p<0.001] and poorer pre-operative renal function as measured by creatinine levels (p<0.001) (Table 4).

Pre-operative anaemia and post transplant outcomes:

On univariate analysis, anaemia did not correlate with 30 day (p=0.305), 90 day (p=0.170), or 1 year mortality (p=0.162). As the majority (73%) of patients were classified as anaemic, haemoglobin was further explored as a continuous variable. Patients who died within 30 days had a significantly lower median pre-operative haemoglobin levels than patients that survived [10.6(9.1-11.6)g/dL vs 11.2(9.6-12.5)g/dL, p=0.004]. This significance was continued at 90 days [10.6(9.4-12.1)g/dL vs 11.2(9.6-12.5)g/dL, p=0.015] and at 1 year [10.7(9.6-12.3)g/dL vs 11.2(9.7-12.5)g/dL, p=0.021].

The presence of pre-operative anaemia was associated with a increased incidence of blood transfusion (P<0.001) and median number of units transfused (5 vs 2, p<0.001), an increased stay in ITU (p=0.015) and an increased need for respiratory support (p=0.005) but was not associated with an increased risk of post-operative complication rates including graft loss at 3 months (Table 5).

A binary logistic regression analysis was performed to analyse whether pre-operative haemoglobin levels were an independent risk factor for post-operative mortality when adjusted for other donor, transplant and recipient variables. Pre-operative haemoglobin levels correlated with increased 1 year mortality (p=0.046) but not with mortality at 30 days (p=0.277) or 90 days (p=0.124) (Table 6).

Pre-operative haemoglobin levels were inversely correlated with MELD scores ($p<0.001$). As the MELD score increased (Figure 1), the pre-operative haemoglobin level was lower by 0.398g/dL/unit MELD score. When MELD scores were excluded from the regression analysis, pre-operative haemoglobin levels correlated significantly with mortality at all time points ($p=0.028$, $p=0.010$, $p=0.001$) (Table 7).

To explore which individual factors of the MELD score influenced haemoglobin levels, a linear regression analysis was performed including pre-operative INR, bilirubin and creatinine levels. Pre-operative creatinine levels ($p<0.001$), INR ($p<0.001$) and bilirubin levels ($p=0.007$) were each significantly correlated with pre-operative haemoglobin levels. For every increase in pre-operative creatine levels, serum haemoglobin levels dropped by 0.298g/dL/micromol/L creatinine while for every increase in bilirubin levels, serum haemoglobin levels dropped by 0.311g/dL/micromol/L bilirubin and for every increase in INR, haemoglobin levels dropped by 0.345g/dL/unit INR.

Discussion:

This study is the first to analyse the role of pre-operative anaemia as a risk factor for mortality and the development of post-operative complications in liver transplant surgery. It has shown that pre-operative anaemia, as defined by the WHO classification, is not an independent risk factor for early post-operative mortality or the development of post-operative complications in this large cohort of patients undergoing liver transplantation. Anaemic patients are significantly more likely to require a blood transfusion and spend longer in ITU.

The incidence of anaemia, according to the WHO definition (15), in patients undergoing liver transplantation was high at 73%. This is in keeping with other studies of anaemia in patients with end stage liver disease (7). The aetiology of anaemia in chronic liver disease is diverse; folate and vitamin B12 deficiency, hypersplenism, haemodilution, bone marrow suppression caused by ethanol or viruses, autoimmune haemolysis, renal insufficiency and variceal bleeding may all contribute (17). Anaemia is postulated to increase bleeding risk through reduced platelet activation and aggregation, and worsening the hyperdynamic circulation(18).

Our analysis suggests the anaemia is secondary to the severity of the chronic liver disease. We recorded a strong correlation between pre-operative haemoglobin level and MELD score. MELD is multifactorial and is calculated based on a patient's INR, serum creatinine and bilirubin levels (16). To help identify the association between pre-operative haemoglobin levels and MELD score an analysis of individual factors of the MELD score and haemoglobin values was performed. This identified that both hepatic and renal dysfunction were associated with reduced haemoglobin levels.

These findings are important for two reasons. Anaemia is strongly associated with renal dysfunction (19) and can be successfully treated with erythropoietin (EPO) (19)(20). A previous study investigating anaemia in patients under treatment for advanced Hepatitis C demonstrated that anaemic patients, with advanced liver disease, could be successfully treated with daily EPO injections (21). During the period of a patient waiting for a liver transplant, underlying low haemoglobin values could be corrected reducing the need for intra-operative transfusions and potentially improving outcome.

The major limitation of this study is that, along with the majority of other studies on pre-operative anaemia, it does not identify the underlying mechanism of the increased risk of post-operative mortality but suggests it may be secondary to severity of liver disease. Although it may be possible to correct low haemoglobin levels pre-operatively, if the mechanism of increased risk of post-operative mortality is secondary to more advanced liver disease, it will not lead to decreased mortality levels post-operatively.

Correction of pre-operative anaemia may reduce the need for blood transfusion in this group of patients and may lead to a reduced requirement for intensive care support which would represent a cost saving for the health service. A full economic costing of the effect of correcting pre-operative haemoglobin levels would therefore be warranted.

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Table 1: Median donor and transplant characteristics (interquartile range)

Age		43 (31-53)
Type of Donor	Deceased brain death	752
	Deceased cardiac death	33
	Domino	8
	Split	3
Length of time in ITU		3 (2-5)
Cold ischaemic time (minutes)		604 (454-744)
Implantation warm ischaemic time (minutes)		43 (37-49)

Table 2: Median recipient characteristics (interquartile range)

Gender	Male	377
	Female	416
Age		50 (41-57)
Pre operative MELD score		16 (12-22)
Pre-operative creatinine (micromoles/L)		90 (75-116)
Preoperative haemoglobin (g/dL)		11.0 (9.6-12.5)

Table 3: Indication for transplantation

Indication for transplantation	number	Percentage anaemic
Hepatitis C Cirrhosis	182	67.6%
Alcohol Liver Disease	145	76.7%
Primary Biliary Cirrhosis	82	65.9%
Primary Sclerosing Cholangitis	61	82.0%
Acute Liver Failure (unknown cause)	60	66.7%
Hepatitis B Cirrhosis	57	59.6%
Cryptogenic Cirrhosis	39	76.9%
Auto-immune Hepatitis	23	65.2%
Hepato-cellular Carcinoma (Cirrhosis)	20	55.0%
Hepatic Artery Thrombosis	20	95.0%
Other	19	89.5%%
Acute Liver Failure (paracetamol)	14	100%
Metabolic Diseases	12	75.0%
Primary Graft Non-Function	11	100%
Familial Adenomatous Polyposis	9	44.4%
Biliary Complication	8	75.0%
Chronic Rejection	7	85.7%

Other	4	50.0%
Budd Chiari Syndrome	4	50.0%
Wilson's Disease	3	100%
Ductopenic Rejection	3	100%
Other Malignancy	3	66.7%
Non-Thrombotic Infarction	2	100%
Hepato-Cellular Carcinoma (non-cirrhtoic)	2	50.0%
Polycystic Disease	1	100%

Table 4: Recipient pre-operative characteristic and their association with pre-operative anaemia

	No pre-operative anaemia (n=215)	Pre operative anaemia (n=580)	P value
Gender			0.004
Male	83	294	
Female	130	286	
Recipient age	51 (44-58)	50 (40-57)	0.026
MELD score	13 (9-17)	17 (13-24)	<0.001
Creatinine level (micromoles/L)	92 (75-118)	89 (75-115)	<0.001

Table 5: Univariate analysis of anaemia and the incidence of post operative morbidity and mortality

Outcome measure	No pre operative anaemia (n=215)	Pre-operative anaemia (n=580)	P value
30 day mortality	9 (4%)	37 (6%)	0.305
90 day mortality	11 (5%)	48 (8%)	0.17
1 year mortality	18 (9%)	50 (9%)	0.162
3 month graft loss	20 (9%)	69 (12%)	0.375
Need for RRT	27 (13%)	100 (17%)	0.127
ITU days	5.88	8.45	0.015
Ventilated days	4.51	7.07	0.005
Bacteraemias	9 (4%)	28 (5%)	0.850
Fungal infection	2 (1%)	9 (1%)	1.00
Viral infection	4 (2%)	8 (1%)	0.744
Hepatic Artery Thrombosis	7 (3%)	29 (5%)	0.342
Portal Vein Thrombosis	0 (0%)	3 (1%)	0.567
Biliary stricture	4 (2%)	18 (3%)	0.467
Bile leak	13 (6%)	42 (7%)	0.638
Need for intra op transfusion	120 (56%)	510 (88%)	<0.001
Median units transfused	2	5	<0.001

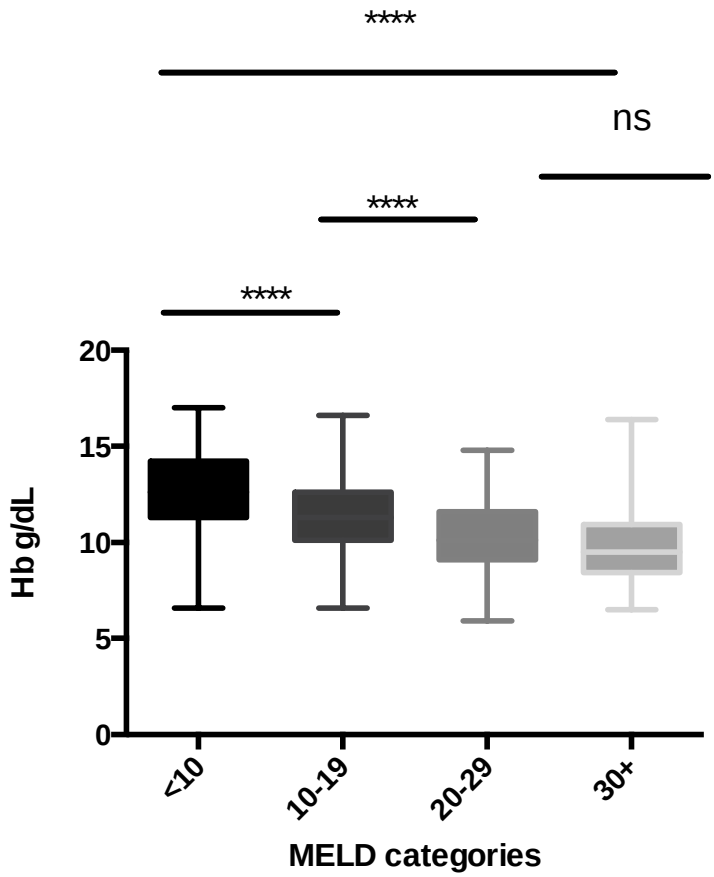
Table 6: Binary logistic regression analysis when MELD is included in the analysis.

Variable	30 day mortality (p values)	90 day mortality (p values)	1 year mortality (p values)
MELD	0.002	0.011	0.003
Pre-operative haemoglobin	0.277	0.124	0.046
Recipient gender	0.123	0.062	0.030
Recipient age	0.377	0.640	0.057
Donor age	0.527	0.164	0.119
Donor type	0.996	0.996	0.883
Cold ischaemic time	0.235	0.118	0.284
Vascular anastomosis time	0.180	0.123	0.178

Table 7: Binary logistic regression analysis showing pre-operative haemoglobin levels correlate with post-operative mortality when MELD is not included in the analysis.

Variable	30 day mortality (p values)	90 day mortality (p values)	1 year mortality (p values)
Pre-operative haemoglobin	0.028	0.010	0.001
Recipient gender	0.122	0.047	0.023
Recipient age	0.948	0.891	0.222
Donor age	0.597	0.231	0.174
Donor type	0.996	0.298	0.907
Cold ischaemic time	0.160	0.106	0.237
Vascular anastomosis time	0.210	0.154	0.221

Figure 1: Median haemoglobin values grouped by MELD scores:



**** p<0.001

Highlights:

- Anaemia is highly prevalent in patients undergoing liver transplant (73%)
- Unlike in other major surgery, anaemia is not associated with an increased risk of mortality post liver transplant.
- Haemoglobin levels are inversely correlated with MELD scores.
- When MELD scores are removed from the analysis, low haemogloblin levels are associated with higher mortality suggesting that anaemia may reflect worse pre-operative burden of disease.