Original Article

Post-operative hypertension, a surrogate marker of the graft function and predictor of survival in living donor liver transplant recipients: A retrospective study

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ABSTRACT

Background and Aims: *De novo* hypertension (HTN) in liver transplantation recipients is a known entity. We investigated haemodynamic behaviour after a liver transplant to see if it can predict survival to discharge from the hospital. **Methods:** electronic records of Haemodynamic parameters and laboratory investigations of 95 patients of living donor liver transplant (LDLT) were retrospectively analysed. **Results:** Twenty-three patients were operated for acute liver failure (ALF) and 72 patients for chronic liver disease (CLD). Eight patients of CLD and four of ALF did not survive. CLD patients had statistically significant rise in systolic blood pressure from the post-operative day (POD) 1 to POD 4 and diastolic blood pressure (DBP) from POD 3 to POD 6. Heart rate (HR) significantly decreased from POD 3 to POD 5. Haemodynamic parameters returned to baseline values within 20 days. Diastolic HTN had a positive predictive value of 100% for survival with 100% sensitivity and specificity. Systolic HTN had a positive predictive value of 100% for survival (sensitivity-89%, specificity-100%). ALF patients had a significant decrease in HR from POD 2 to POD 10. Bradycardia (HR ≤60/min) had a positive predictive value of 100% for survival with a sensitivity of 45% and 58% in CLD and ALF, respectively, with a specificity of 100% in both the groups. Non-survivors had no significant change in haemodynamics. In CLD group, International Normalised Ratio had statistically significant, strong negative correlation with DBP. **Conclusion:** Haemodynamic pattern of recovery may be used for predicting survival to discharge after LDLT.

Key words: Diastolic hypertension, living donor liver transplantation, post-liver transplantation, systolic hypertension

INTRODUCTION

Liver transplantation (LT) has become the treatment of choice for patients with decompensated chronic liver disease (CLD) and acute liver failure (ALF) of various aetiologies. Patients undergoing LT are known to develop the '*de novo* hypertension (HTN)', with a reported incidence of 60–70%.[1,2] Haemodynamic behaviour in the short-term, immediately after liver transplant and before discharge from hospital is, however, less studied. The key to successful patient management after surgery lies in close observation of the recovery parameters including the haemodynamic behaviour and to develop reasoning to merit the observations. We hypothesised that haemodynamic change after Living donor liver transplantt (LDLT) reflects graft function and may be used to predict 'survival to discharge' from hospital. We, therefore,

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retrospectively analysed the data of liver transplant recipients at our institute to explore any possible correlation between the haemodynamic behaviour of the patients after LT while they are still in the hospital and their recovery and outcome in terms of 'discharge from hospital'.

METHODS

The study was approved by the Institute's Ethical Committee. The study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki. All liver grafts were donated by first or second degree relatives of the patients and were approved by the authorisation committee. The requirement for written informed consent was waived by the Institutional Review Board. Electronic data records of automated blood pressure and heart rate (HR) were retrieved for systolic and diastolic blood pressure (SBP, DBP) and HR. Haemodynamic variables were noted from the day inotropes and vasopressor were withdrawn. The mean value of three highest readings every 24 h, was used for SBP, DBP and HR. Systolic and diastolic HTN was defined as SBP >140 mmHg and DBP >90 mmHg. While bradycardia was defined as 'present' when there were three or more readings of HR <60 beats/min. Coagulation parameter, International Normalised Ratio (INR) of prothrombin time and daily trough levels of tacrolimus were retrieved from the electronic hospital information system for each patient. Data were collected for every day for the first 10 days after surgery while the patients were in Intensive Care Unit (ICU), and then for the post-operative day (POD) 15 and 20. SBP, DBP, HR and INR values on the day preceding the LT surgery were taken as the baseline values for comparison.

For the purpose of analysis, data of the patients were divided into two groups. CLD group for patients with de-compensated CLD and the ALF group for patients with ALF. Systolic HTN was marked 'present' when mean of three highest readings of SBP in a day was more than 140 mmHg. Diastolic HTN was marked as 'present' when mean of three highest DBP recordings was more than 90 mmHg, each lasting for 2 or more days. Bradycardia was marked 'present' when there were 3 or more readings of HR ≤60 beats/min in a day and not associated with hypotension requiring treatment. Subgroup analysis was performed for non-survivors of either group.

Data were analysed using the Shapiro–Wilk test for the normality of distribution. Pearson correlation was applied to the data normally distributed, whereas Kendall's Tau's *b* test was applied to data not distributed uniformly. Paired *t*-test was used for the significance of the change in haemodynamic variables from the baseline values. The value of $P < 0.05$ was considered statistically significant. 2 × 2 contingency table was used to calculate positive and negative predictive value of haemodynamic variables and their sensitivity and specificity for predicting 'survival to discharge' after LT.

RESULTS

Ninety-five patients were operated on for LDLT surgery. Twenty-three patients were of ALF, whereas remaining 72 patients were operated on for decompensated CLD. Twelve patients did not survive, eight in the CLD group and four in the ALF group. Vasopressor/inotrope was tapered off on POD 0 in all the patients. Vasopressor/inotrope support was reinstituted while they were still in ICU in 12 patients out of whom 10 did not survive [Table 1]. No patient, in either group was on any antihypertensive medication at the time of being considered for LT. Analgesia was assessed using 10 cm visual analogue scale (VAS). VAS values corresponding to the time when patient had HTN or bradycardia was looked to rule out pain as the cause of haemodynamic changes observed. Analgesia was judged adequate in all the patients (VAS ≤3) at all-time points. The data for the haemodynamic variables SBP, DBP and HR were normally distributed in both the groups, while the data for the INR were not normally distributed, in either group.

Table 1: Demographics

Variable	Number	Survivors at 1 month	Non-survivors at 1 month	De Novo Systolic Hypertension	De Novo Diastolic Hypertension	De Novo Bradycardia HR <60/minute	Patients requiring hemodialysis after LDLT	Reinstitution of inotrope/ vasopressor
Total No. of patients operated for LDLT	95	83 (87%)	12	57	64	40	2	16
Chronic Liver disease	72	64 (89%)	8	57	64	29	2	12
Acute Liver failure	23	19 (83%)	4	0	0	11	0	4

LDLT – Living donor liver transplant

In CLD group, there was statistically significant rise in SBP compared to the baseline (117 ± 13 mmHg), starting POD 1 (128 ± 15 mmHg) till POD 4 (150 ± 15 mmHg) (P = 0.00). SBP returned towards baseline gradually but was still higher than baseline at POD 15 (124 ± 12 mmHg) and at POD 20 (123 ± 11 mmHg) (P = 0.01). DBP also increased significantly over baseline (71 ± 8 mmHg), on POD 3 (76 ± 12 mmHg) (P = 0.02) till POD 6 (75 ± 11 mmHg) (P = 0.04) after a decline on POD 1 (65 ± 10 mmHg). DBP returned towards baseline by POD 7 (74 ± 10 mmHg) (P = 0.17) [Table 2]. The HR displayed an opposite trend. HR decreased significantly compared to the baseline value (83 ± 15 beats/min) on POD 3 (74 ± 12 beats/min) till POD 5 (73 ± 15 beats/min) (P = 0.001) and returned to base line value on POD 6 (79 ± 17 beats/min) (P = 0.19) [Table 3 and Figure 1].

In the CLD group, systolic HTN was seen in 79% (57/72) and diastolic HTN was seen in 89% of patients. About 90% of patients who survived had systolic HTN (57/64) and 100% of the patients who survived had diastolic HTN (64/64) [Table 1]. Diastolic HTN had a positive predictive value of 100% for 'survival to discharge' with 100% sensitivity and specificity. Systolic HTN had a positive predictive value of 100% for 'survival to discharge' with a sensitivity of 89% and specificity of 100% [Table 4].

In the ALF group, there was no statistically significant difference, compared to the baseline value, in SBP and DBP, but the HR decreased significantly from the baseline values (103 ± 28 beats/min) on POD 2 (83 ± 23 beats/min) (P = 0.001) till POD 10 (90 ± 18 beats/min) (P = 0.04) [Tables 2 and 3].

More than three incidences of bradycardia in a day, each with HR ≤60 beats/min and not associated with hypotension requiring treatment, were seen in 51% of patients with CLD and in 58% of patients of ALF [Table 1]. All the patients who survived had episodes of bradycardia which were not associated with a decrease in blood pressure and were, therefore, not

Table 2: Systolic and Diastolic Blood pressure (mean±standard deviation)

Day	CLD-SBP	ALF-SBP	Non-survivors-SBP	CLD-DBP	ALF-DBP	Non-survivors-DBP
PRE-OP/baseline	117±13	115±19	112±18	71±08	67±14	70±13
PO DAY 1	128±15*	118±14	113±10	65±10	62±07	59±13
PO DAY 2	140±19*	117±14	116±14	70±11	66±10	60±14
PO DAY 3	150±17*	118±15	125±21	76±12*	66±12	64±10
PO DAY 4	150±15*	120±14	129±25	76±09*	69±13	66±14
PO DAY 5	145±16*	125±14	124±16	77±10*	71±11	67±14
PO DAY 6	140±15*	126±13	125±17	75±11*	73±11	71±12
PO DAY 7	139±15*	124±14	124±21	74±10	70±12	63±17
PO DAY 8	135±15*	121±12	115±19	75±10	66±09	58±11
PO DAY 9	132±15*	122±13	125±08	75±12	69±09	68±12
PO DAY 10	128±15*	119±14	119±14	73±11	67±12	63±13
PO DAY 15	124±12*	122±15	126±17	72±11	70±08	69±12
PO DAY 20	123±11*	114±14	126±05	73±10	65±11	71±10

* student t test comparing with baseline value; P<0.05; CLD – Decompensated chronic liver disease; ALF – Acute liver failure; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; PO Day – Post operative Day

Table 3: HR and INR in CLD, ALF and Non-survivors, (mean±standard deviation)

Day	CLD-HR	ALF-HR	Non-survivors-HR	CLD-INR	ALF-INR	Non-survivors-INR
PRE-OP/baseline	83±15	103±28	93±32	2.39±1.81	4.27±2.97	4.14±3.12
PO DAY 1	88±14	95±17	96±17	2.89±0.83	2.88±1.15	3.11±1.01
PO DAY 2	79±15	83±23*	98±19	2.45±0.70	3.18±1.45	3.58±1.44
PO DAY 3	74±12*	84±23*	87±22	1.88±0.56	2.44±1.07	2.97±1.55
PO DAY 4	73±14*	83±26*	92±28	1.73±0.82	2.18±0.88	2.79±1.46
PO DAY 5	73±15*	85±22*	90±25	1.51±0.39	2.14±1.34	2.96±1.76
PO DAY 6	79±17	85±17*	103±22	1.47±0.59	1.68±0.58	2.54±1.15
PO DAY 7	82±17	92±19*	97±26	1.35±0.56	1.59±0.54	2.89±1.65
PO DAY 8	81±15	91±18*	89±37	1.31±0.60	1.68±0.79	2.86±1.43
PO DAY 9	83±14	86±19*	82±22	1.25±0.52	1.63±0.90	2.57±1.34
PO DAY 10	86±13	90±18*	95±30	1.20±0.40	1.60±0.81	2.80±1.26
PO DAY 15	84±14	93±20	87±21	1.10±0.27	1.26±0.35	1.54±0.14
PO DAY 20	85±12	97±22	92±5	1.20±0.51	1.19±0.22	1.85±0.28

* student t test comparing with baseline value; P<0.05; INR – International normalized ratio of prothrombin time; CLD – Decompensated chronic liver disease; ALF – Acute liver failure; HR – Heart Rate; PO Day – Post operative Day

Table 4: Predictive value of haemodynamic variables for 'survival to discharge' in CLD and ALF

Parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Denovo systolic hypertension (CLD)	89	100	100	53
Denovo diastolic hypertension (CLD)	100	100	100	100
Bradycardia (CLD)	45	100	100	19
Bradycardia (ALF)	58	100	100	33

CLD – Decompensated chronic liver disease; ALF – Acute liver failure

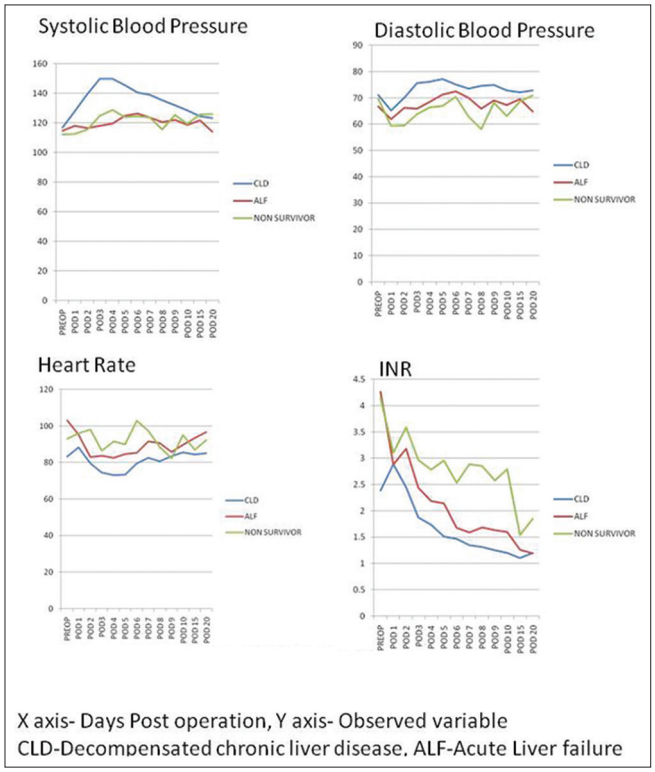

Figure 1: Graphical trend of observed variables

treated. Bradycardia had a positive predictive value of 100% for survival with a sensitivity of 45% and 58% in CLD and ALF, respectively, with a specificity of 100% in both the groups [Table 4].

Non-survivors from either group did not exhibit any significant change in their haemodynamics over the baseline values, including SBP, DBP and HR [Tables 2, 3 and Figure 1].

INR in survivors but not in the non-survivors of either group consistently decreased compared to baseline values over the study duration [Table 3 and Figure 1].

In the CLD group, the INR values had statistically significant, strong negative correlation with the DBP ($r = -0.66$, $P = 0.01$). There was, however, weak negative correlation of INR with the SBP ($r = -0.16$; $P = 0.59$) and weak positive correlation with the HR ($r = 0.14$, $P = 0.62$) [Table 5].

In the ALF group, INR values had a strong negative correlation with the SBP ($r = -0.52$, $P = 0.06$), medium negative correlation with the DBP ($r = -0.31$, $P = 0.29$) and a weak positive correlation with the HR ($r = 0.28$, $P = 0.32$). None of these correlations in ALF group, however, could reach the level of statistical significance [Table 5].

Mean tacrolimus blood levels of the patients for the duration of the study were well within the prescribed limits (5–15 mcg/L) at all the time points of observation. Two patients with pre-existing hepatorenal syndrome required haemodialysis for decreased urine output with raised serum creatinine levels. One patient out of these two survived with improvement in the renal functions while the other patient succumbed to subsequent multi-organ dysfunction and sepsis.

The cause of death in all the non-survivors was sepsis following multi-organ failure after LDLT surgery.

DISCUSSION

In this study, we observed that following LDLT, systolic and DBPs increased and HR decreased over pre-transplant values. These haemodynamic changes returned to baseline by POD 20. The pattern of haemodynamic changes was different for CLD patients than for the patients of ALF and these changes in the haemodynamics were not seen in non-survivors. INR values consistently decreased over the period in the patients who survived. The study also demonstrated the direct correlation of INR with SBP and DBP while the negative correlation of INR with HR.

Median ICU/HDU stay for the LDLT recipients in our hospital is 10 days and the median hospital stay is 26 days. Therefore, the data for the haemodynamic variables and laboratory investigations were retrieved for every day for first 10 days after surgery, till the patient was in ICU and then for POD 15 and 20. Day of arrival in ICU after the surgery was considered as POD 0. In all the patients, inotropes and vasopressors used during the surgery were tapered off on POD 0. In

Table 5: Pearson's Correlation (*r*) of haemodynamic variables with International Normalized ratio (INR)

Variable	CLD	ALF
SBP	*r*=−0.16; *P*=0.59	*r*=−0.52; *P*=0.06
DBP	*r*=−0.66; *P*=0.01*	*r*=−0.31; *P*=0.29
HR	*r*=+0.14; *P*=0.62	*r*=+0.28; *P*=0.32

Pearson's correlation; *r*=0. 5 to 1=High correlation; 0.3 to 0.5=Medium correlation; 0.1 to 0.3=low correlation; *Statistical significance *P*<0.05; CLD – Decompensated chronic liver disease; ALF – Acute liver failure; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HR – Heart Rate

CLD group, two patients who survived, nor-adrenaline was restarted on POD 15 and 17, respectively, due to clinical features suggestive of sepsis, but it was tapered off over next 24 h in each.

De novo HTN in LT recipients is a known phenomenon.[1,2] Diagnosis of HTN in LDLT recipients at our hospital was based on the recommendations of the seventh report of the joint national commission on prevention, detection, evaluation and treatment of high blood pressure, for the general population.[3] In patients undergoing LT, it has been attributed to the recovery of the vasomotor tone (secondary to improving graft function) and to the use of the calcineurin inhibitors (CNIs) (cyclosporine, tacrolimus) for immunosuppression, because of their effect on afferent renal arteriolar vasoconstriction.[4] The immunosuppression regimen in our institute consists of a combination of tacrolimus, mycophenolate and methylprednisolone. This combination allowed reduced doses of individual drugs and hence reduced side effects of individual drugs as both CNI's and Steroids have known hypertensive potential.[5-10] The potential for development of HTN due to tacrolimus (31–38%) however is less[7,8] compared to cyclosporine (58–82%).[2,6]

Tacrolimus blood levels were well within the prescribed therapeutic limits at all-time points of observation in all the patients. Three out of ninety-five patients had increase in serum creatinine and two of these also had decreased urine output. These two patients with decreased urine output and raised serum creatinine levels required haemodialysis while the third patient with only rise in serum creatinine, improved with conservative measures. Tacrolimus-induced renal dysfunction was, therefore, excluded as a possible cause for the hypertensive response observed in our patients.

Patients with the end-stage liver disease have decreased central blood volume and autonomic dysfunction marked by increased circulating catecholamines with decreased baroreceptor sensitivity.[11] Increased circulating catecholamine causes desensitisation and down-regulation of the adrenergic receptors such that there is blunted response to even potent vasopressors/inotropes.[11] Following LT, renin levels are known to decrease, reflecting normalisation of the circulating blood volumes.[12] We postulated that following successful LDLT, redistribution of the body fluids with normalisation of the central blood volume cause decrease in blood levels of circulating catecholamines, thereby allowing re-sensitisation and regeneration of the adrenergic receptors to cause HTN as was seen in our patients of CLD group. Similar to our findings, Schreen D and Caramelli B studied patients of liver transplant and observed them for haemodynamic changes for 48 h after transplant. They also found that mean blood pressure begins to rise after surgery and reaches statistical significance 24 h after surgery and remained elevated even at 48 h.[13]

In the ALF group, however, neither did the survivors nor did the non-survivors have systolic or diastolic HTN after LDLT surgery. Disease not being chronic, the autonomic dysfunction is probably less severe in patients of ALF compared to patients with CLD. With no significant change in autonomic function, the resultant rise of SBP and DBP over the baseline would, therefore, be not significant after LDLT as was seen in our patients of ALF.

Parasympathetic autonomic dysfunction along with increased angiotensin II (AGII) levels have been documented in patients with cirrhosis of the liver.[14] The increased AGII levels interact with parasympathetic control of the HR, thereby reducing the vagal discharge and the HR variability.[13] Following LT, we hypothesise that AGII levels decrease causing a concomitant increase in the vagal discharge. This increased vagal discharge could manifest as bradycardia. In our patients, three or more episodes of bradycardia in a day with HR decreasing to ≤60 beats/min was seen in 51% of patients in CLD group and in 58% of patients in ALF group. The overall decline in HR, compared to the baseline values was for a lesser number of days in patients of CLD group (POD 3–6) compared to the patients with ALF (POD 2–10). We could not find any explanation for this observation. Correlation between the HR and INR was weak in both the groups. However, statistical analysis returned a positive predictive value of 100% for bradycardia for survival with a sensitivity of 45% and 58% in CLD and ALF, respectively, with a specificity of 100% in both the groups.

Dysfunction of the circulating blood volumes, AGII levels and the autonomic dysregulation would have persisted in the absence of a functioning liver allograft in the patients who did not survive. Possibly, therefore, in these patients, we did not find any changes in SBP, DBP and HR.

Predictors of outcome after transplant are desirable for resource management and prognostication. Various factors that may affect the outcome and survival after LT surgery have been investigated. Correlations of survival after transplant (short-and long-term) have been derived with 'model for an end-stage liver disease' score at listing for LT, and with donor factors such as age, co-morbidity, degree of fatty infiltration of the liver, and also with warm and cold ischaemia time of the liver graft.[15] Besides pre-operative factors, intraoperative variables (like duration of surgery and usage of blood products) have also been correlated with the outcome and survival after LT surgery. Disease-specific survival models have also been derived and are reflective of the affect of the severity and the characteristics of the affecting disease.[16-18] The factors affecting outcome are shared by both living donor and deceased donor LT surgery except that warm and cold ischaemia intervals are predictably shorter with living donor and that the graft weight to recipient weight ratio is a consideration in living donor LT.

Summation of effects of the pre-operative and intraoperative variables after LT surgery is desirable, to take stock of intervention and to prognosticate the immediate outcome. In this study, we found a signature pattern of haemodynamic after LDLT and that diastolic HTN and bradycardia are statistically significant, strong predictors of 'survival to discharge'. This study also found statistically significant, the strong correlation of DBP with the INR in CLD patients.

The limitation of our study besides the small number of patients is that we could not follow our patients beyond the 20 days post-liver transplant because of its retrospective nature. A prospective study with a longer follow-up of these patients could provide the actual incidence of HTN developing subsequently in the LDLT patients and relation between survival and the haemodynamics in the long-term.

CONCLUSION

In view of findings of this retrospective study, we suggest that the occurrence of post-operative HTN may be used as a surrogate marker of the graft function and predictor of survival to discharge in live related liver transplant recipients.

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Conflicts of interest
There are no conflicts of interest.

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