Liver Transplantation and Outcome Predictors in Critical Care Unit

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Abstract

Background and Study Aims: In the absence of cadaveric donor liver transplantation, living-donor liver transplantation (LDLT) is an alternative option for patients with end-stage liver disease. This may help to decrease waiting time. A shorter waiting time may reduce the risk of dying or of further deterioration that could render the patient too sick to undergo successful transplantation. This study aims at determination of early predictors for morbidity and mortality in these patients.

Patients and Methods: A Retrospective study enrolled 30 recipients, 24 males (80%) and 6 females (20%) who underwent Living Donor Liver Transplantation (from October 2004 to December 2008) at Cairo University Hospital. For all patients complete laboratory profile is done daily, as well as CRP and serum level of FK. Other laboratory work includes bilirubin level, hemoglobin and hematocrite levels in the surgical drains. Continuous assessment of haemodynamics was done.

Results: From the 30 recipients, 24 males (80%) and 6 females (20%) Their mean age was 35±20 years old, ranging from 1 to 63 years old. The mortality rate was 26.7% (8 patients), causes of death were sepsis (62.5%), rejection (25%), and portal vein thrombosis (12.5%). There was positive impact of serum CRP levels during the early post-operative days, as an indicator of infection and inflammation, on the outcome and survival after LDLT (p=0.0001). CRP levels within normal range (5.16±3.6), had good outcome than patients with elevated CRP levels (22.09±7.9). Recipients of younger aged donors (29.2±5.3 years), had better outcome than those with more elderly donors (40.0±2.6 years). Tachycardic patients upon ICU admission always have a poor prognosis in comparison with patients that are not (p=0.008). platelet count was significantly higher in survivor with mean 108 vs 58.33 in non survivor p=0.02. Another predictor for outcome was the length of ICU stay post-operatively and outcome after LDLT (p=0.003).

Conclusion: A smooth ICU course after liver transplant is dependent on satisfactory graft function, which can be assessed by clinical parameters, some can be predictor for outcome as heart rate, laboratory test as CRP, stable platelet counts, declining transaminases.


Introduction

CIRRHOSIS is a slow and progressive liver dysfunction with significant impact on all body systems. The functioning transplanted liver represents the determinant of organ system recovery and gives the patient a new life. Whereas, in the event of graft dysfunction or failure of the transplanted liver, the patient will continue to be in multi-organ failure and will require an enhanced level of critical care support [1].

The pathophysiology of ESLD patients has important impact on their critical care treatment, particularly in the postoperative state. As a standard practice, all the modalities of monitoring and medication are continued into the postoperative period, the degree of which will be decided depending on the progress of the patient [1].

Though it is the degree of functioning of the transplanted liver that largely determines the other system functions, their dysfunction may be an outcome of an independent entity [2].

The current study aims at determination of early predictors for morbidity and mortality in these patients. Further more we will try to identify factors that influence the ICU stay in this category.

Material and Methods

Design: Retrospective study.

Setting: The ICU of Critical Care Department of Cairo University.

According to the ethical commettie, this study enrolled 30 recipients patients who underwent

Abbreviations:

LDLT : Living Donor Liver Transplantation.
FK : Tacrolimus.
CRP : C-Reactive Protein.
ESLD : End Stage Liver Disease.
TPO : Thrombopoietin.
Liver Transplantation & Outcome Predictors

Living Donor Liver Transplantation (from October 2004 to December 2008) at Cairo University Hospital. From these 24 patients were males (80%) and 6 were females (20%). For all patients complete laboratory profile was done daily, including complete blood count, coagulation profile, liver enzymes, total protein, albumin, kidney functions, electrolytes, CRP and serum level of FK. Other laboratory work includes bilirubin level, hemoglobin and hematocrite levels in the surgical drains. Continuous assessment of haemodynamics was done by assessment of arterial blood pressure, heart rate, temperature, respiratory rate, daily urine output, and central venous pressure monitoring. APACHE II was calculated. Detection of any complication redorded and Duration of stay.

Statistical analysis:
Patients’ data were tabulated and processed using SPSS Statistical Package for Social Science version (16) for Microsoft Windows.

Data were statistically described in term of range, mean±SD, median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples. Correlation between various variables was done using Spearman rank correlation equation for non normal variables. A probability value (p-value) less than 0.05 was considered statistically significant.

Results
This study is a retrospective study involving 30 recipients, 24 males (80%) and 6 females (20%) who underwent Living Donor Liver Transplantation (October 2004 to December 2008) at Cairo University Hospital. Their mean age was 35±20 years old, ranging from 1 to 63 years old. The mortality rate was 26.7% (8 patients), causes of death were sepsis (62.5%), rejection (25%), and portal vein thrombosis (12.5%).

There was positive impact of serum CRP levels during the early post-operative days, as an indicator of infection and inflammation. There is significant good positive correlation $r$ 0.5 between the levels of serum CRP and level of serum bilirubin levels in the post-operative period (p=0.002).

Patients who develop renal impairment post-operatively, showed strong correlation between creatinine level and the serum FK level ($r$ 0.52) (p=0.027) and good correlation between blood urea level and serum FK level ($r$:0.4 $p$=0.027).

Also we have noticed that patients that develop variable degrees of renal impairment during the post-operative period are associated with higher level of AST and ALT as there is (p-value as regard AST was 0.039, and as regard ALT was 0.013).

There is good inverse relation between FK level and the ALT, $r$ -0.42, $p$ 0.03 there is good correlation between FK level (6.3±1.8) and duration of post operative ICU stay (11.7±10.8 days) ($r$=0.4) ($p$=0.03). The higher the FK level the longer the post poperative ICU stay.

By dividing patient according to outcome into 2 groups; group 1 survival patients, group 2 non survival patients. It was found that there was significant difference between both group as regard APACHE score being 6.87 in survivors vs 19.89 in non survivors $p$ 0.0001 and. Mean arterial blood pressure was significantly higher in group 2 where mean was 154.5 vs 123.2 in group 1with $p$ 0.002, also it was noticed that Tachycardic patients upon ICU admission always have a poor prognosis in comparison with patients that are not ($p$=0.008), as survivors had a mean heart rate of (92.39±9.99), while non survivors (104.4±18.27), throughout the post-operative period.

Also in this study CRP level was significantly higher in non survival than survival group.

As regarding CRP and its effect on the outcome and survival after LDLT. It was noticed that patients with CRP levels within normal range (5.16±3.6), had good outcome than patients with elevated CRP levels (22.09±7.9) ($p$=0.0001).

Platelets can be used as predictor to outcome as platelet count was significantly higher in group 1 with mean 108 vs 58.33 in group 2 $p$=0.02.

Another predictor for outcome after LDLT was the length of ICU stay post-operatively ($p$=0.003). Survived cases had a shorter duration of postoperative ICU stay (8.27±4.1 days), compared to non survivors (21.0±17.29 days).

Although this study showed no correlation between the age of the recipient and the outcome after LDLT ($p$=0.1), a significant relation between the age of the donor and the survival of his recipient. Recipients of younger aged donors (29.2±5.3 years), had better outcome than those with more elderly donors (40.0±2.6 years) ($p$=0.01).

Discussion
Although there have been moves towards avoidance of ICU admission after transplantation, Inten-
sive care units (ICUs) remains as one of the main corner stones in liver transplantation as most patients still spend part of their post-operative course in the ICU [3,4].

Many scoring systems have been implied to quantify the severity of illness of patients admitted to the ICU and to predict their survival and hospital discharge [8]. Such prognostic scoring systems include the Simplified Acute Physiology Score (SAPS), the Mortality Probability Model (MPM) and the Acute Physiology and Chronic Health Evaluation (APACHE) scoring system [6-8].

Mortality models are likely to underestimate mortality in selected patient subpopulations. For example, studies of kidney transplant recipients and patients with malignancies admitted to the ICU have shown the inability of the APACHE and SAPS scoring systems to accurately predict mortality in these patient groups [9-12].

Although Mark et al., have found that APACHE II scoring system doesn’t identify survivors in a large group of patients admitted to the ICU after OLT [16], in this study APACHE II score was significantly different (p=0) between survivors (6.8±2.2) and non survivors (19.8±12.2). Mark et al., have attributed the poor performance of APACHE II in this population to possible errors in data acquisition, interpretation, and application of the APACHE II equation. Also mortality after OLT (orthotopic liver transplantation) may result from the sequelae of rejection, which (except for primary non-function) are unlikely to be seen during a patient’s post-OLT ICU stay. Similarly, opportunistic infection arising in the setting of immunosuppression may lead to patient demise, though is unlikely to manifest on the first ICU day. Intraoperative resuscitation and therapy will “normalize” many physiologic derangements. As laboratory and physiologic data acquired before admission to the ICU are not included in calculation of the APACHE II, ICU calculations may underestimate the severity of illness of an OLT recipient [16].

The primary cause of death after liver transplantation is infection [17]. Infections are common in the early posttransplant period, arising from intravascular lines, lung, urinary tract, surgical wound, and the biliary system [18]. This study showed that there is a strong relation between the mean serum CRP levels in the post-operative period, as early predictor of infection, and outcome of patients after LDLT (p=0.002). This result goes with Gupta D et al. [19] results as they found that CRP and PCT values are uniformly increased in postoperative LDLT recipients. They peak on second postoperative day and then start decreasing. Patients with Clinically significant infections (CSI) have higher values as compared to non-CSI patients and hence a higher cut off may be warranted to support their role as an early marker of sepsis. Also this study showed that most of the non-survived patients have elevated serum CRP levels post-operatively (22.09±7.9). While the survived patients showed relatively low CRP level (5.16±3.6). Also this go with An HJ et al. [20] result who found that CRP would be considered as a useful and cost-effective biomarker to predict outcomes after transplantation of HCC, particularly in patients over the Milan criteria.

Also this study showed that patients with non elevated levels of CRP (9.7±2.5), upon ICU admission, also had lower serum bilirubin level (4.6±3.3), post-operatively. No study had studied this relation.

Also there was significant relation between the mean serum CRP levels in these patients and the duration of their post-operative ICU stay. Patients with elevated CRP levels had longer durations of stay (21.0±17.29 days). Also there was a significant relation between the mean serum bilirubin level in the post operative period and the mean serum levels of CRP where r=0.5 and p=0.002 this results can be explained by Suzana M et al., who found that patient with high CRP level at ICU admission had more severe organ dysfunction, longer ICU stays, and higher mortality rates than those with normal CRP level on ICU admission [21].

Smith et al., reviewed adult OLT database for patients who survived >30 days. Prolonged length of stay (PLOS) was defined as hospitalization >30 days following OLT. Of 521 OLT recipients, 68 (13%) had PLOS with a median duration of 50 days versus only 10 days for patients discharged within 30 days [22]. This study revealed that Survived cases (73.3%) had a shorter duration of postoperative ICU stay (8.27±4.1 days), while non survived cases (26.7%), had a longer duration of ICU stay (21.0±17.29 days) (p=0.003). This can be attributed to higher rate of complications among the non survivors which necessitated longer ICU stay [22].

Further more there is a strong correlation between the rate of rise of serum FK level and the corresponding duration of post-operative ICU stay (p=0.033). The good correlation between FK level
and length of stay this may explained by higher level of FK in impaired renal function due to its nephrotoxicity and decrease its clearance this may increase incidence of complication and may increase risk of infection.

It is known that liver enzymes start to be elevated post-operatively and gradually return to normal values along the course of few days post-operatively. This study revealed a good correlation of serum FK level results in rapid decline of the level of the liver enzyme ALT, which is the most specific liver enzyme \( r=0.42 \) \( (p=0.020) \). Again, the earlier control of rejection phases may halt the complications in the early post-operative period.

This study showed that patients with variable degrees of renal impairment post-operatively, compared to those with normal renal function, had a higher level of the serum FK in the post-operative period \( (p\text{-value for urea level was 0.027, and for Creatinine level was 0.003}) \). Logically, this is due to decreased rate of FK clearance in patients with impaired renal functions.

Furthermore, we have shown that patients with abnormally elevated serum Creatinine levels post-operatively, had higher serum level of transaminases post-operatively \( (p\text{-value for AST was 0.039, and for ALT was 0.013}) \), which may be attributed to defective clearance of these enzymes by the impaired renal function.

This study showed that Upon ICU admission and through the first few days post-transplant, patients with mean heart rate within the normal range \( (22 \text{ patients with mean heart rate } 92.39\pm9.99) \) have a good outcome, while patients with mean heart rate exceeding the normal range \( (8 \text{ patients with mean heart rate } 104\pm18.27) \) did not survive. As heart rate reflect underlying hidden cause that may vary from mild to severe cause.

The age of the recipient did not affect the outcome after LDLT in this study. However, this study showed that there is a significant relation between the age of the donor and the survival of his recipient post-transplant \( (p=0.01) \). Recipients of younger aged donors \( (29.2\pm5.3) \), had better outcome than those with more elderly donors \( (40.0\pm2.6) \). This go with Lake JR et al., who had similar results as they found that Donor age, which was not a risk factor in patients with HBV, was the strongest predictor of graft loss and death in patients with HCV, starting with donors >40 years. Donor age >60 years was the strongest predictor of graft loss and death in patients without viral hepatitis [23] and Morioka D et al., found that higher donor age \( (>or=50 \text{ years}) \) were indicated as independent factors predictive of graft failure (graft loss or death) in the multivariate analysis [24]. But this against what Ronald W et al. [25] said that despite initially donor age 50 years was thought to be associated with poor graft outcomes, their study had shown that aged donors \( (50 \text{ years}) \) without additional risk factors have similar outcomes to younger donors and age itself should not be a contraindication to liver donation. Donor age of more than 70 years, however, was found to be associated with lower patient and graft survival [25]. Also Ikegami T et al., found that Partial liver grafts, even though left lobe grafts, from older donors can be used safely with caution in LDLT.

Regarding platelets count, this study showed that higher platelets level was in survivor than non survivors this may be explained by better graft function and release of thrombopoietin (TPO). Thrombopoietin is a glycoprotein hormone produced mainly by the liver and the kidney that regulates the production of platelets by the bone marrow. It stimulates the production and differentiation of megakaryocytes, the bone marrow cells that fragment into large numbers of platelets [27]. This study confirmed earlier findings by Peck-Radosavljevic et al. [28] that the number of platelets in patients with end-stage cirrhosis increases after OLT finding of a parallel increase in the synthesis of liver-derived clotting factors and of TPO levels between days 1 and 4 after OLT supports the concept that TPO is synthesized by the new liver in sufficient quantities. Eyraud D et al. [29] also found that the number of platelets in platelet rich plasma (PRP) rises significantly after liver transplantation, with a non-statistical impact on aggregometry. None of them correlated this to outcome.

Conclusion:

A smooth ICU course after liver transplant is dependent on satisfactory graft function, which can be assessed by clinical parameters, some can be predictor for outcome as heart rate, laboratory test as CRP, stable platelet counts, declining transaminases.

References


