Donor related risk factors on the outcome of Living Donor Liver Transplantation

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ABSTRACT
Background & objective: Liver transplantation is an established, effective treatment for acute and chronic end stage liver disease. Donors risk factors should be studied in order not to compromise the procedure of transplantation or to lose candidates for transplantation, the study aims to evaluate the effect of variable donor risk factors on the outcome of Living donor liver transplantation regarding the morbidity and mortality.

Methods: the current study conducted on 48 patients who underwent living donor liver transplantation for End stage liver disease caused by chronic HCV. Morbidity and mortality were assessed at three and twelve months. Obtained data were studied in correlation with various donor related risk factors, a score designed to collect these risk factors, correlate them with recipient morbidity, mortality, and graft rejection.

Results: high rates of graft rejection and recipient mortality was significantly related to older donor age, donor obesity, donor-recipient gender mismatch, hepatic steatosis, and donor graft recipient weight ratio (GRWR) ≤ 0.8. The designed donor risk score of ≥ 7 was expectedly to associate with poor outcome & recipient mortality.

Conclusion: The present study suggested that donor risk factors on the outcome of Living Donor Liver Transplantation in patients espicially with hepatitis C genotype 4.

Key words: donor risk score, Liver Transplant, outcomes, steatosis.

Introduction
Liver transplantation (LT) is an established, effective and often lifesaving treatment for acute and chronic end stage liver disease (ESLD).¹ The transplant procedure remains a technically complex operation, and the application of living donation to the adult recipient population has added another layer of difficulty to an already challenging procedure. In the context of increased candidates for liver transplantation to more and more, transplant programs have begun to consider deceased donor characteristics that were previously considered unacceptable.² With this trend, attention has focused on better defining those donor factors that can exert impact on the outcome of liver transplantation. It is obvious that, in case of patients demanding donors for liver transplantation, an ideal donor is not usually the rule.³

There is valuable body of literature addressing the donor risk factors on living donor liver transplantation (LDLT). It has been reported that donor’s age and other identifiable factors such as obesity seem to strongly affect transplantation outcome, specifically if the recipients harbor hepatitis C virus (HCV).¹ considering fatty livers would be associated with worse outcomes⁵, yet donor steatosis impact is still debatable, few researchers suggested that steatotic graft had no potential implication on graft rejection or recipient survival.⁶ Although, donor risk index(DRI) has been emerged, risk factors in donors should be defined and thoroughly studied in order not to compromise the procedure of transplantation.⁷ Therefore, the study aims to evaluate the effect of variable donor risk factors on the outcome of LDLT regarding the morbidity and mortality. The secondary objective is to construct a scoring model of donor risk on Egyptian liver transplant recipients.

Material & methods:
A prospective study had been conducted on 48 patients with end stage liver disease (ESLD) who underwent liver transplantation at El Manial Cairo- University Hospitals over period of 18 months duration, from 30/6/2013 to 1/1/2015.

Donors data obtained were: donor age, sex mismatch, body mass index(BMI), liver steatosis (assayed using liver biopsy), donor medical and drug history, and graft recipient weight ratio(ORWR). Graft rejection and patient survival were assessed at three and twelve months post LT. The study protocol conformed to ethical guidelines of the 1975 declaration of Helsinki.⁸ it was revised & approved by Internal Medicine Research Ethics Committee, Cairo University. A written informed consent was obtained from all participants in the study.

All patients following living donor liver transplantation for ESLD caused by chronic HCV genotype 4 were included. Whilst, Patients undergoing liver transplantation due to causes other than HCV or pediatric population (age under 12 years)
were excluded.

The donors were subjected to full clinical examination, different laboratory and radiological investigations according to El Manial Cairo- University Hospitals policy. The weight and height of each participant were measured, and the Body Mass Index (BMI) was calculated as (Kg/ m²). Liver function tests including alanine aminotransaminase (ALT), aspartate aminotransaminase, (AST), Total and direct bilirubin, serum albumin, Prothrombin time and concentration, urea and creatinine, serum electrolytes (Na and K), Anti-bilharzial Antibody (Ab) in Urine, Stools analysis and occult blood in stools, Blood grouping and Complete blood count, hepatitis C virus Ab, hepatitis B surface Ag and Hepatitis B core Ab total were done.

Abdominal and pelvic ultrasonography, vascular hepatic Doppler, Magnetic resonance cholangiopancreatography (MRCP) and liver computed tomography volumetry were carried out.

Liver biopsies were obtained from all donors after a written consent, using an automated gun device and under complete aseptic precautions to detect the presence and the degree of hepatic steatosis, then the subjects were divided according to the fat deposition degree yielded by tissue pathology examination into no steatosis (if less than 5 % steatosis), 5-10% steatosis, 10-15% steatosis and >15% steatosis.

Scoring system was planned by the research group to address donor risk factors whether had or not an impact on mortality or rejection encompassing donor age, sex mismatch, body mass index (BMI), degree of graft steatosis (assessed by liver biopsy), donor medical and drug history, and graft recipient weight ratio (GRWR), in order to gather all the important donor demographic, clinical and liver tissue data into a score, hoping to be of value in predicting recipient outcome.

Donor age over 35, BMI of more than 25, donor graft steatosis more than 5%, Donor. GRWR less than 0.8 were given points in ordinal pattern, while presence of DM and/or HTN add 1 to score, sex mismatch add 2 presence of drug history add 1 to score. The total weight of score ranges 5 to 15 points, where increased score indicate poor outcomes as demonstrated in table (1).

### Statistical analysis:

Pre-coded data was entered into the Statistical Package of Social Science Software program, version 21 (SPSS) to be statistically analyzed. Data was summarized using range, mean, and standard deviation for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample t-test and Mann Whitney test for quantitative variables and Chi square test for qualitative ones. P values less than 0.05 were considered statistically significant. Data were tabulated & graphs were used to illustrate some information.

### Results

The study included 48 HCV patients who underwent LDLT (45 males and 3 females), their age ranged between 20 and 62 years with a mean(SD) of 49.4(8.8). Also 48 healthy donors (40 males, and 8 females), their age ranged between 19 and 45 years with a mean (SD) of 29.7(6.1). Demographic & clinical background of the donors summarized in table (2).

In the current study, the incidence of graft rejection was 16.66%, while Mortality frequency was 29.16%.

Impact of donor risk Factors on recipient outcomes showed that there was significant difference between rejected & non rejected as regard high BMI & graft steatosis. However, higher BMI was only related to mortality outcome as shown in table 3 & 4.
Donor risk factors, and their subclassifications, with the impact on recipient mortality and graft survival, either with significant impact or their impact had not reached significant results had been chosen by our research group to build up a scoring system. Each risk factor and their subclassifications were categorized to take points from zero up to three, zero will be given to the absence of these factors, example absence of diabetes and hypertension or drug history, one will be given to either normal state like BMI ≤ 25 kg/m², or < 5 % hepatic steatosis (no steatosis), two and three will be given to any abnormality according to its severity, meaning that three is more severe than two. For each donor, the suggested risk score was applied from 5-13. In 8 cases of recipient graft rejection, donor risk score ranged from 6-10 (7.4 ± 1.4), while it ranged from 5-9 (6.1 ± 1.2) in the non rejected recipients, the difference was highly significant p-value 0.012. In recipient mortality cases “14”, donor risk score ranged from 5-10 (7.2 ± 1.5), while it ranged from 5-9 (6.0 ± 1.1) in surviving recipients again, the difference was significantly high “p-value 0.004”. (table 5 & 6)

From the results obtained from the scoring system, as mentioned above, the statistical point of view was to choose number 7 to be set as cutoff score. “mean ≤7 and >7”. According to the score set by our research team, we tried to correlate the recipient mortality and graft survival rate with the donor risk score. When donor risk score was ≥7, 33.3% of recipients grafts were rejected while rejection was only 6.7% when the risk score was less than 7 with highly statistically significant with “P value 0.04. When donor risk score was ≥7 55.6% of recipients died while mortality was 13.3% when the score was less than 7 with high statistic significance “P value 0.03”.

Discussion
Expansion of the organ donor pool by using grafts with reduced quality has become reality in transplant centers around the world due to increasing donor organ shortage and raising numbers of patients on the waiting lists. This has led to an increased awareness of the associated risks for patient and graft survival.9 A series of attempts to develop objective scores for the assessment of donor liver quality with significant influence on patient and/or graft survival have been made.10,11 In the present study, relation between donor age and recipient graft survival, showed that: when the donor age was less than 35 years 15.8% of the recipients grafts were rejected.
While when the donor age was 35 years or older, 20% of recipients grafts were rejected. Recipient mortality was 26.3%, and 40% when the donor age was younger than 35 years, and older than 35 years respectively.

The use of older donors for liver transplantation has been controversial. Ploeg et al. were the first to identify deceased donor age older than 49 years, as an independent risk factor for the development of Primary Graft Non Function (PGNF) after liver transplantation in a retrospective multivariate analysis. Also a study by DDLT at the University of Bologna, Italy; their data showed the causes of early graft failure in 669 patients who underwent transplantation from older donors was found. Neipp and his colleagues, in 2004, reported that: no distinction between allocation of livers from younger and older donors was found. However, there are many other reports which have failed to corroborate a deleterious effect of increased donor age, Niemeyer and his colleagues, in 2004, reported that: no distinction between allocation of livers from younger and older donors was found.14

Our results did not reach any statistically significant in increased graft rejection rate or recipient mortality rate when the donor and recipient sex were mismatched. Zerbe and his colleagues study could not confirm a negative effect of gender-incompatible LT on graft survival when the data of 16,410 hepatic transplants from 103 hepatic transplant centers overall the study showed that no significant difference of graft survival was found in relation to donor gender.15

In contrary to our study; Varotti and his colleagues analysed the causes of early graft failure in 669 patients who underwent LDLT at the University of Bologna, Italy; their data showed that female recipients, who received grafts from male donors, proved to be an independent risk factor for developing primary graft non-function (PGNF) with p <0.001.16 There was a statistically significant increase in frequency of graft rejection, and recipient mortality in relation to increasing donor BMI. This is in agreement with Perito and his colleagues who evaluated data on pediatric U.S. liver transplants & precluded that severe obesity (BMI>35) in adult donors was found to increase the risk of graft loss and mortality, even after adjustment for recipient, donor, and transplant risk factors.17 In contrary to our results Moss & co hypothesized that selection of donors with BMI greater than 30, normal LTIs and no significant comorbidities may safely participate in LDLT.18

We observed also increase in percentage of graft rejection, and recipient mortality when the GRWRs<0.8. Klein and his colleagues had worked on 41 cases of adult-to-adult LDLT with a GRWR of <0.8 from 2002-15. These were compared to all adult LDLTs with GRWR ≥ 0.8 (n=95) carried out in the same time period. Median follow-up duration was 3.1 years. The 1 and 3-year patient survival for GRWR<0.8 group were 89% and 82% compared to 92% and 88% for the group with GRWR ≥ 0.8.19 However according to Li and his colleagues, no significant difference was found among groups with different GRWRs in 1- and 3-year survival rate.

A statistically significant increasing percentage of mortality and graft rejection( 50% and 35.7 %) respectively when the donor liver is steatotic(>5%) as compared to that when the donor liver was not steatotic(<5%) (20.6% and 9.8 %) respectively (p value 0.037 and 0.078). Cieslak and his colleagues, had performed 269 consecutive orthotopic liver transplantations between 2004 and 2006, they concluded that hepatic steatosis is a risk factor for early hepatic dysfunction after OLT. In contrary to our results Moss & co hypothesized that hepatic steatosis is a risk factor for early hepatic dysfunction after OLT.21 However, the findings of the present study disagree with a previous research done by Fishbien and his colleagues, who identified 40 cases in which the donor liver contained at least 30% steatosis. They concluded that livers with even severe steatosis can be reliably used for transplantation without the fear of high rates of primary nonfunctioning grafts.22

Donor risk factors, with the impact on recipient mortality and graft survival, had been chosen by our research group to build up a scoring system. Each risk factor and their subclasses were categorized to take points from zero up to three, zero will be given to the absence of these factors, example absence of diabetes and hypertension or drug history, one will be given to either normal state like BMI≤25 kg/m², or < 5 % hepatic steatosis (no steatosis), two and three will be given to any abnormality according to its severity, meaning that three is more severe than two. where the statistical point of view was to choose number 7 to be set as cutoff score “mean ≤7 and >7”. According to the score set by our research team. It was observed that when donor risk score was >7, there was shighly statistically significant increase in graft rejection and recipient mortality with “P values 0.04 and 0.03 respectively”.

There is still a high heterogeneity of statistical approaches to the validation of prognostic scores even though Jacob et al. published as early as 2005 uniform quality criteria for the design, validation and reporting of prognostic scores in liver transplantation.23

Data for all 6621 orthotopic liver transplants performed in the Eurotransplant region from 2003 - 2007 were analyzed by Blok and his colleagues;The following donor characteristics were analyzed: age, sex, height, weight, body mass index, cerebrovascular accident (CVA), trauma, anoxia, ICU stay (the period between admission to the ICU and the initiation of cold perfusion); latest and highest serum levels of sodium and alkaline phosphatase; medical history of diabetes mellitus, hypertension, malignancy, drug use, alcohol, and smoking; administration of inotropes, they reported in the same year that they were able to validate the value of the Donor risk index for the prediction of three month, one year and three years graft survival in the Eurotransplant region. Whereas, Schreiber and his colleagues investigated 291 consecutive liver transplants including: 20 (6.9%) split liver transplants, 30(10.3%) acute retransplants, and 25 (8.6%) chronic retransplants. Donor characteristics used in the former study were donor age, donor hospital stay, donorn height, donor BMI, cold ischemic time, warm ischemic time and Serum sodium. The number of donor criteria fulfilled had no statistically significant influence on the primary study endpoints (p >0.05) or on patient survival (p >0.05), they reported that: the Donor-Risk-Index is not applicable to their patients for the prediction of three month mortality, three month patient survival, three month graft survival as well as the necessity of acute retransplantation within thirty days.24

The current study finding should be viewed with the following limitation, the small sized sample & descriptive design of the study, yet it could serve as a pilot study that has to be further validated by large-scale studies in different clinical populations, to validate the role of donor risk score and its impact on recipient mortality and graft survival.

To conclude, Donor age , sex match , body mass index (BMI) , liver steatosis , and Graft Recipient Weight Ratio (GRWR) are donor risk factors that had a high impact on recipient mortality and graft rejection, the present study suggests that donor risk score can be a strong predictor of donor related risk factors and its effect on the outcome of Living Donor Liver Transplantation in Egyptian patients with hepatitis C genotype 4 especially recipient survival and graft rejection.

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