

REOPERATIONS FOR INTRAABDOMINAL BLEEDING FOLLOWING DECEASED DONOR LIVER TRANSPLANTATION

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Intraabdominal hemorrhage remains one of the most frequent surgical complications after liver transplantation.

The aim of the study was to evaluate risk factors for intraabdominal bleeding requiring reoperation and to assess the relevance of the reoperations with respect to short- and long-term outcomes following liver transplantation.

Material and methods. Data of 603 liver transplantations performed in the Department of General, Transplant and Liver Surgery in the period between January 2011 and September 2014 were analyzed retrospectively. Study end-points comprised: reoperation due to bleeding and death during the first 90 postoperative days and between 90 postoperative day and third post-transplant year.

Results. Reoperations for intraabdominal bleeding were performed after 45 out of 603 (7.5%) transplantations. Low pre-transplant hemoglobin was the only independent predictor of reoperation ($p=0.002$) with the cut-off of 11.3 g/dl. Postoperative 90-day mortality was significantly higher in patients undergoing reoperation as compared to the remaining patients (15.6% vs 5.6%, $p=0.008$). Post-transplant survival from 90 days to 3 years was non-significantly lower in patients after reoperation for bleeding (83.3%) as compared to the remaining patients (92.2%, $p=0.096$). Nevertheless, multivariable analyses did not reveal any significant negative impact of reoperations for bleeding on short-term mortality ($p=0.589$) and 3-year survival ($p=0.079$).

Conclusions. Surgical interventions due to postoperative intraabdominal hemorrhage do not appear to affect short- and long-term outcomes following liver transplantation. Preoperative hemoglobin concentration over 11.3 g/dl is associated with decreased risk of this complication, yet the clinical relevance of this phenomenon is doubtful.

Key words: liver transplantation, bleeding, reoperation, mortality, outcomes

Long-term outcomes of liver transplantation are continuously improving which is associated with increased experience of transplant centers and improvements in surgical techniques, immunosuppressive treatment, postoperative management, and long-term patient care (1, 2). Now, 5-year patient and transplanted organ survival rates are 70-75% and 66-71%, respectively (1, 2). Regardless of improvement in the long-term outcomes, postoperative complications occur even in 80% of recipients in the first month following liver transplantation. It has been found that the frequency of severe post-

operative complications defined as III or higher degree according to the Clavien-Dindo classification reaches up to 60% (3, 4). Reoperations by reason of early postoperative complications are performed in even 29-45% of the patients (5, 6). It should be noted, however, that there are significant differences in early outcomes of liver transplantation between particular transplantation centers (3).

Intraabdominal bleedings are undoubtedly one of the most common causes of surgical interventions in patients in the early post-transplant period (5). This is associated with

extensiveness of the operation, frequent occurrence of blood clotting disorders and portal hypertension. It has been estimated that the intraabdominal bleeding rate after liver transplantation was 5-21% (3, 7, 8, 9). Results of studies available in transplant literature show a negative impact of the need to carry out the reoperation and occurrence of other severe postoperative complications on long-term outcomes of liver transplantation (5, 6, 10).

The aim of the study was to define risk factors for reoperation due to intraabdominal bleeding after liver transplantation, and determine effect of early surgical interventions due to bleeding on resulting long-term outcomes.

MATERIAL AND METHODS

Totally, 1498 liver transplantations were performed in the Department of General, Transplant and Liver Surgery, Medical University of Warsaw from December 1989 to September 2014. Data of 603 liver transplantations carried out from January 2011 to September 2014 were analyzed retrospectively. The primary study end-point was intraabdominal bleeding in the postoperative period requiring surgical intervention. Secondary end-points included death during the first 90 postoperative days and between 90 postoperative day and third post-transplant year. Adopted end-points were used to determine postoperative mortality and 3-year patient survival except for postoperative mortality, respectively.

Quantitative and qualitative variables were presented as medians and interquartile ranges (IQRs), respectively, and as numerosness and percentages. A chi-square test was used to compare postoperative mortality between the group of the patients who had been subjected to the reoperations due to bleeding and the patients who had not experienced those complications. The risk factors for reoperation due to bleeding were determined by using of the logistic regression. The cut-off points for qualitative variables for reoperation prediction were determined on the basis of an analysis of curves presenting receiver operating characteristics (ROC). The long-term survivals were determined with the use of the Kaplan-Meier method. The log-rank test was used to compare

survival curves. Proportional hazards regression analysis by Cox was used to determine risk factors for patient and transplanted organs survivals. Odds ratios (ORs), hazard ratios (HRs), and areas under a ROC curve (AUROC) were presented along with 95% confidence interval (95% CI). We adopt the significance level $p=0.05$. Statistical calculations were done using STATISTICA 12 software (StatSoft Inc., Tulsa, OK, USA).

RESULTS

Basic characteristics of 603 liver transplantations taken for analysis are presented in tab. 1. The reoperations for intraabdominal bleeding were necessary after 45 out of 603 transplantations (7.5%). The risk factors for the reoperation due to bleeding are presented in tab. 2. Univariable analyses shown that the factors significantly associated with the complication included the Model for End-stage Liver Disease (MELD) score ($p=0.003$), hemoglobin level ($p=0.001$), and intraoperative erythrocyte mass ($p=0.009$) and plasma transfusions ($p=0.010$). However, multivariable analysis shown that the hemoglobin level was the only independent risk factor for the reoperation due to intraabdominal bleeding (OR 0.78 for increase in the hemoglobin level by 1 g/dL; 95% CI 0.66 – 0.91, $p=0.002$). The optimal cut-off point for the hemoglobin level ≤ 11.3 g/dL was determined on the basis of the ROC curve (fig. 1). Sensitivity, specificity, negative and positive predictive values were 63.4%, 59.1%, 11.5%, and 95.1%, respectively.

Postoperative mortality in the group of the patients who had undergone the reoperations due to bleeding (7/45; 15.6%) was significantly higher ($p=0.008$), as compared with the remaining patients (31/558; 5.6%). The risk factors for 90-day mortality included the need to carry out the reoperation due to bleeding ($p=0.011$), MELD scores ($p<0.001$), re-transplantations ($p<0.001$), classical surgery technique with the excision of the retrohepatic segment of the inferior vena cava and temporary veno-venous extracorporeal circulation ($p<0.001$), and intraoperative erythrocyte mass ($p<0.001$) and plasma ($p<0.001$) transfusions (tab. 3). Multivariable analysis shown that the independent risks to die in 90 days following transplantation were only the MELD score and

Table 1. Characteristics of 603 transplantations included in the study

Factors	n (%) or median (interquartile range)
Recipient age (years)	52 (39-59)
Male sex of recipient	370 (61,4%)
MELD	12 (9-17)
BMI (kg/m ²)	24,7 (21,8-27,7)
Laboratory test before transplantation	
INR	1,22 (1,09-1,44)
hemoglobin level (g/dl)	11,7 (10,2-13,3)
platelet count (10 ³ /mm ³)	91 (61-154)
fibrinogen concentration (mg/dl)	239 (165-346)
HCV infection	202 (33,5%)
HBV infection	131 (21,7%)
Alcoholic liver disease	113 (18,7%)
HCC	129 (21,4%)
Re-transplantations	45 (7,5%)
Classical transplant technique	104 (17,2%)
Intraoperative transfusions of:	
erythrocyte mass (units)	4 (2-7)
plasma (units)	6 (4-9)
Duration of cold ischemia organ (hours)	9 (7,8-10,3)
Donor age (years)	49 (37-57)

MELD – ang. Model for End-stage Liver Disease; BMI – ang. body mass index; INR – ang. international normalized ratio; HCV – ang. hepatitis C virus; HBV – ang. hepatitis B virus; HCC – ang. hepatocellular cancer

Table 2. Analyses of the risk of reoperation due to bleeding following liver transplantation

Factor	OR	95% PU	p
Recipient age	0,99	0,97 – 1,01	0,334
Male sex of recipient	0,84	0,62 – 1,14	0,252
MELD	1,05	1,02 – 1,08	0,003
BMI	1,01	0,93 – 1,09	0,899
Laboratory test before transplantation			
INR	1,07	0,81 – 1,43	0,626
hemoglobin level (g/dl)	0,76	0,65 – 0,90	0,001
platelet count	1,11	0,82 – 1,49	0,572
fibrinogen concentration	0,94	0,74 – 1,20	0,636
HCV infection	1,00	0,72 – 1,38	0,980
HBV infection	1,09	0,76 – 1,55	0,646
Alcoholic liver disease	1,12	0,78 – 1,62	0,535
HCC	0,88	0,60 – 1,31	0,540
Re-transplantations	0,94	0,51 – 1,72	0,833
Classical transplant technique	1,19	0,82 – 1,72	0,360
Intraoperative transfusions of:			
erythrocyte mass	1,06	1,01 – 1,10	0,009
plasma	1,06	1,01 – 1,11	0,010
Duration of cold ischemia organ	1,04	0,89 – 1,22	0,634
Donor age	1,00	0,98 – 1,02	0,722

intraoperative erythrocyte mass transfusions (p=0.002). Taking into account the role of these independent risk factors it has been found that effect of the reoperation due to bleeding on the risk of early death was statistically insignificant (OR 1.18; 95% CI 0.65 – 2.12; p=0.589).

If early postoperative deaths were ruled out, the 3-year survival in the group of the patients who had undergone transplantations was

83.3% and was insignificantly lower than the remaining patients (92.2%; p=0.096; fig. 2). The risk factors for death from 90 days to 3 years following transplantation are presented in tab. 4. The results of the univariable analyses shown significant importance of male sex of the recipient (p=0.039), re-transplantation (p=0.028), improving experience of the center (p=0.007), intraoperative erythrocyte mass

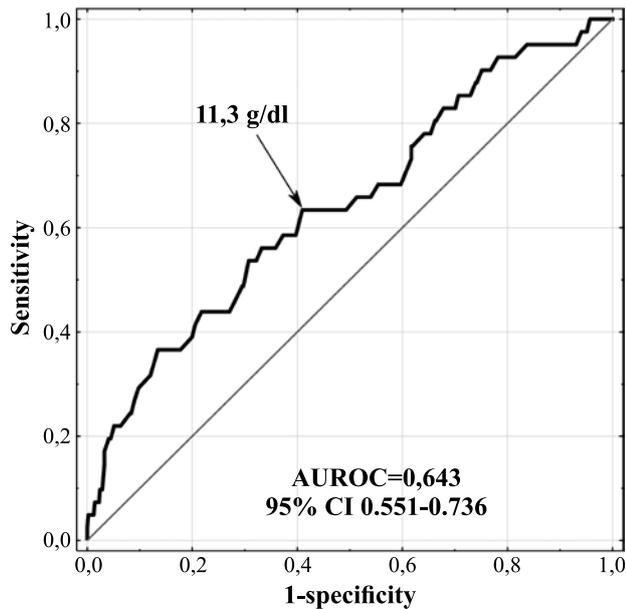


Fig. 1. Receiver operating characteristics curve for preoperative hemoglobin level to predict reoperation for intraabdominal bleeding following liver transplantation

($p=0.0018$) and plasma ($p=0.0036$) transfusions, and age of the donor ($p=0.0012$). The independent risk factors for death during this period only included re-transplantation ($p=0.003$) and age of the donor (0.027). Considering these two independent risk factors the relationship between the need to the reoperation due to bleeding and long-term survival was above the statistical significance level (HR 2.59; 95% CI 0.89 – 7.50; $p=0.079$).

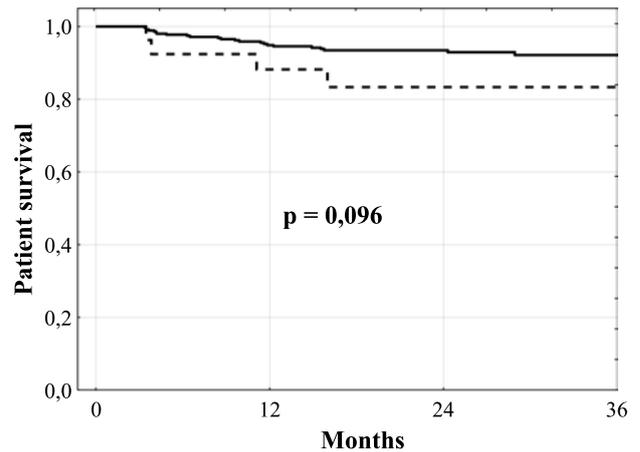


Fig. 2. General 3-year survival curves following transplantation except for postoperative mortality. Dashed line indicates survival of patients subjected to reoperations due to intraabdominal bleeding and full line indicates the remaining patients

DISCUSSION

Intraabdominal bleeding following deceased donor's liver transplantation is a severe complication with a high mortality rate. Reoperations for intraabdominal bleeding in this group of patients are technically difficult because of associated coagulopathy, difficulties in determining the source of bleeding and maintaining homostasis. In presented material the intraabdominal bleeding rate was 7.5% and was in the low range given by transplant literature (3, 7, 8, 9, 11, 12, 13).

Table 3. Analyses of risk factors for postoperative mortality (to 90 days) following liver transplantation

Factors	Univariable			Multivariable		
	OR	95% PU	p	OR	95% PU	p
Reoperation due to bleeding	1,77	1,14-2,75	0,011			
Recipient age	1,00	0,98-1,03	0,849			
Male sex of the recipient	0,98	0,70-1,37	0,913			
MELD	1,08	1,04-1,11	<0,001	1,07	1,03-1,10	<0,001
BMI	1,00	0,91-1,09	0,906			
HCV infection	0,95	0,67-1,36	0,796			
HBV infection	0,73	0,45-1,18	0,193			
Alcohol liver disease	0,70	0,41-1,19	0,189			
HCC	0,91	0,59-1,38	0,645			
Re-transplantation	2,33	1,56-3,47	<0,001			
Experience of the center	1,00	0,99-1,01	0,802			
Classical transplant technique	1,99	1,41-2,79	<0,001			
Intraoperative transfusions of:						
erythrocyte mass	1,10	1,05-1,15	<0,001	1,08	1,03-1,13	0,002
plasma	1,11	1,05-1,16	<0,001			
Duration of cold ischemia organ	1,03	0,86-1,25	0,725			
Donor age	1,00	0,98-1,02	0,869			

Table 4. Analyses of risk factors for survival from 90 days to 3 years after liver transplantation

Czynniki	Univariable			Multivariable		
	HR	95% PU	p	HR	95% PU	p
Reoperation due to bleeding	2,41	0,83-6,97	0,104			
Recipient age	1,01	0,98-1,04	0,505			
Male sex of the recipient	2,78	1,05-7,33	0,039			
MELD	1,02	0,97-1,07	0,435			
BMI	1,05	0,97-1,14	0,246			
HCV infection	1,50	0,70-3,22	0,292			
HBV infection	0,94	0,38-2,33	0,895			
Allcohol liver disease	0,87	0,33-2,30	0,779			
HCC	1,62	0,71-3,71	0,250			
Re-transplantation	3,29	1,14-9,51	0,028	5,31	1,78-15,84	0,003
Experience of the center	1,55	1,13-2,14	0,007			
Classical transplant technique	1,43	0,54-3,77	0,474			
Intraoperative transfusions of:						
erythrocyte mass	1,06	1,01-1,11	0,018			
plasma	1,06	1,00-1,12	0,036			
Duration of cold ischemia organ	1,11	0,92-1,34	0,281			
Donor age	1,04	1,01-1,08	0,012	1,04	1,00-1,08	0,027

The risk of intraabdominal bleeding causing the need to perform the reoperation was significantly associated with the degree of liver failure directly before transplantation expressed as the MELD score, intraoperative blood-based products transfusions, and preoperative hemoglobin level. Other authors reported that there is also a relationship between the MELD score and the blood-based products transfusions and risk of bleeding following transplantation (12, 13). Surprisingly, the preoperative hemoglobin level below 11.3 g/dL was the only independent risk factor. However, this observation has low positive predicate value so it is not clinically important. It should be noted that data available in literature indicate that in liver transplantations the preoperative hemoglobin level is in inverse proportion to the need to perform intraoperative blood-based transfusion (14).

The postoperative mortality rate in the group of the patients who had undergone the reoperation due to intraabdominal bleeding was 15.6% and corresponded to the rate reported by other authors (5, 13). Although the mortality rate was significantly higher than the remaining patients, multivariable analysis did not confirm that there is the independent impact the need to perform the reoperation on the risk of early death. Thus, the observed difference is probably associated with the fact that higher MELD score before transplantation and larger intraoperative erythrocyte mass transfusions in patients subjected to the reoperations due to bleeding into the peritoneal

cavity simultaneously were the independent risks of postoperative death. Results obtained by other authors and our previous studies carried out in the Department of General, Transplant and Liver Surgery, Medical University of Warsaw confirm that both risk factors have a significant impact on the risk of early deaths following transplantation (15-19).

The reoperations for intraabdominal bleeding were not associated with lower long-term survival rates in the patients in the univariable analyses and taking into account impact of other independent risk factors as well. Higher risk to die in extended period of time was observed in the case of re-transplantation and transplantation of organs obtained from elderly donors. Donor age and re-transplantation as well as are considered to be associated with worse outcomes of liver transplantation so our results accord with data available in literature (20-24).

CONCLUSIONS

In summary, it is not possible to assess in detail the risk of intraabdominal bleeding requiring the reoperation on the basis of pre- and intraoperative factors. The need to perform the reoperation due to intraabdominal bleeding following liver transplantation is associated with the increased risk of postoperative death but reoperation itself is not the independent risk factor. This complication does not have a significant impact on risk to die at a later time.

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