Recipient-Related Preoperative and Intraoperative Risk Factors for Primary Graft Dysfunction After Orthotopic Liver Transplantation

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ABSTRACT

Introduction. Primary graft dysfunction (PGD) is a multifactorial syndrome related to the most adverse outcomes after liver transplantation. Ischemia–reperfusion injury is recognized as the predominant cause of this complication. PGD may be subdivided into early allograft dysfunction, diagnosed by the presence of a serum bilirubin level ≥10 mg/dL (171 μmol/L), International Normalized Ratio ≥1.6, or alanine and aspartate transaminase levels ≥2000 IU/L on the seventh postoperative day; and primary nonfunction, defined as either a need for retransplantation or patient death within the first 7 days. We aimed to determine the preoperative and intraoperative risk factors for PGD.

Materials and Methods. We enrolled 109 patients who underwent orthotopic liver transplantation between 2012 and 2016. Analysis included inter alia: biochemical parameters, morphology, blood transfusions, as well as intraoperative fluctuations of blood pressure.

Results. Fourteen percent of patients were diagnosed with PGD. Using logistic regression and multivariate and receiver operating characteristic and area under the curve analysis, a preoperative neutrophils level above 4030/μL (OR = 4.03, P = .012) and decrease of the mean arterial pressure after reperfusion were recognized as the major independent PGD risk factors.

Conclusions. A high preoperative neutrophils level may be a novel recipient-related risk factor for PGD. A decrease of the arterial blood pressure after graft reperfusion may influence the development of PGD.

LIVER transplantation is a life-saving treatment for patients suffering from end-stage liver disease. This major surgery is associated with a large number of serious complications because of the complexity of the intervention and the serious condition of the qualified patient. Primary graft dysfunction (PGD) is a severe event during the first days after liver transplantation that is associated with a poor prognosis and high mortality. PGD can be divided into primary graft nonfunction (PNF) and early allograft dysfunction (EAD). Despite numerous studies on both complications, no clear, unified definitions can be found for them in the literature. PNF is most often defined as either the need for retransplantation or recipient death within the first 7 postoperative days. EAD is diagnosed based on elevated serum bilirubin and alanine (ALT) and aspartate (AST) transaminase levels, as well as International Normalized Ratio level measured on days 2–10 after transplantation, with different cut-off points depending on the author's criteria [1]. Nevertheless, regardless of the definition applied, PGD describes a severe, life-threatening condition and because of its poor outcome, identifying preoperative and intraoperative risk factors for PGD is

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exceedingly important. It could also facilitate a selection of high-risk patients with introduction of appropriate management to avoid or alleviate this serious complication. So far several presumable PGD risk factors were distinguished, most of which were related to the donor and the surgical procedure, such as extended donor criteria, donor age, liver steatosis, blood loss and blood transfusions during surgery, as well as cold and warm ischemia time [2]. Taking into account the complexity of this multifactorial syndrome, a lack of established diagnostic criteria, and acknowledged risk factors we aimed to detect the independent recipient-related preoperative and intraoperative risk factors for PGD in our cohort of patients.

PATIENTS AND METHODS

We conducted a retrospective analysis of 109 (64 men and 45 women, including, 10 retransplantations) consecutive patients who underwent orthotopic liver transplantation (OLTx) performed via the piggyback technique in the Department of General, Vascular and Transplant Surgery Medical University of Silesia in Katowice (Poland) between 2012 and 2016. Preoperative recipient and donor-related data, as well as the intra- and postoperative variables, were collected from patients' medical histories and anesthesia carts. Analysis included inter alia: length of operation and anhepatic phase, hemodynamic fluctuations, biochemical parameters, morphology, blood transfusions, and diuresis (Table 1).

Primary graft nonfunction was defined as either the need for retransplantation or death within 7 postoperative days. Early allograft dysfunction was identified when one of the following was present: serum bilirubin level ≥10 mg/dL on the seventh postoperative day, International Normalized Ratio ≥1.6 on the seventh postoperative day, or ALT and AST level >2000 IU/L within the first 7 postoperative days.

Statistical analysis included a univariate logistic regression to assess odds ratios (OR) with 95% confidence intervals (CIs). All variables with $P < .05$ were included in the multivariate regression model created by backward elimination with the Wald test. For all significant variables the cut-off points were determined by receiver operating characteristic (ROC) and area under the curve (AUC) analysis. Descriptive statistics were expressed as mean values with standard deviations for continuous variables and percentages for discrete ones.

RESULTS

The mean recipient age was 49.4 ± 12. Progression of end-stage liver disease was assessed with a mean Model for End-Stage Liver Disease (MELD) score of 18.3 ± 8. Its etiology included viral hepatitis (37%, n = 40), toxic and alcoholic liver disease (24%, n = 26), primary sclerosing cholangitis (PSC, 10%, n = 11), primary biliary cirrhosis (PBC, 6%, n = 7), and autoimmune hepatitis (12%, n = 13). The prevalence of hepatocellular carcinoma was 25% (n = 27). Primary graft dysfunction occurred in 14% of cases (n = 15), with 9% (n = 10) EAD and 5% (n = 5) PNF. Results of logistic regression analysis of the preoperative and intraoperative risk factors are presented in Table 1. The most predisposing PGD etiology turned out to be PBC (OR: 5.625, $P = .03$). Among biochemical and morphological variables, the ALT level (OR: 1.001, $P = .046$) and number of neutrophils (OR: 1.140, $P = .017$) reached statistical significance, whereas only the latter one was found to be significant in the multivariate analysis (Wald statistic: 5.58, $P = .018$). In ROC/AUC analysis the cut-off point for neutrophils was estimated at the level of 4030/μL (AUC: 0.68, $P = .025$) with OR = 4.03 ($P = .012$) for this threshold. The most favorable intraoperative risk factor for PGD was mean blood pH (OR: 0.01, $P = .03$) and hemodynamic instability expressed via a mean arterial pressure (MAP) early after reperfusion (OR: 0.937, $P = .02$) and reperfusion hemodynamic instability defined by a decrease of MAP after unclamping of the portal vein (OR: 1.046, $P = .039$). Post-reperfusion syndrome (PRS), defined as a decrease in MAP >30% below the baseline value, for at least 1 minute within the first 5 minutes after reperfusion occurred in 12% (n = 13) of cases. Among them only the absolute MAP value early after reperfusion turned out to be a significant, independent risk factor in the multivariate analysis (Wald statistic: 5.43, $P = .019$). The cut-off point determined at 83.3 mm Hg had high sensitivity, but lower specificity, with $P = .07$ (AUC: 0.633).

DISCUSSION

Only few studies so far have investigated key risk factors for graft dysfunction after liver transplantation. Previous results varied, probably owing to different examined populations, difference in surgical technique, or distinct PGD definition criteria. The analysis presented here revealed a preoperative number of neutrophils above 4000/μL as an independent recipient-related PGD risk factor. Ischemia–reperfusion injury (IRI) is a well-established pathomechanism of early graft dysfunction [3]. One of the detrimental phenomena influencing the severity of IRI is the inflammatory reaction comediated by neutrophil infiltration and activation with cytokines and chemokine synthesis, as well as release of reactive oxygen species. Furthermore, by blocking the small capillaries, neutrophils are responsible for the no-reflow phenomenon impairing graft reperfusion and exacerbating tissue damage. Subsequently, the feedback loop of neutrophil recruitment is triggered, leading to an intensification of the inflammatory response and tissue damage reflected in acute graft failure [4]. The detrimental role of neutrophils in the development of hepatic ischemia–reperfusion injury was already confirmed in multiple studies [5,6]. Consequently, as was proven in our analysis, the high preoperative level of neutrophils can be a valuable predictor of the occurrence of PGD after OLTx. Among the intraoperative variables analyzed, a decrease of arterial blood pressure after portal reperfusion was the most essential independent PGD risk factor. Hemodynamic instability after liver graft reperfusion is called postreperfusion syndrome, defined as a decrease in MAP >30% below the baseline value, for at least 1 minute, occurring within the first 5 minutes after reperfusion [7]. Multiple studies investigated the pathophysiology and potential risk factors responsible for the occurrence of PRS; however, information on the established criteria and management is missing [7,8]. Nevertheless, most reports

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