Review Article

Primary graft dysfunction after liver transplantation

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BACKGROUND: **Primary graft dysfunction (PGD) causes complications in liver transplantation, which result in poor prognosis. Recipients who develop PGD usually experience a longer intensive care unit and hospital stay and have higher mortality and graft loss rates compared with those without graft dysfunction. However, because of the lack of universally accepted definition, early diagnosis of graft dysfunction is difficult. Additionally, numerous factors affect the allograft function after transplantation, making the prediction of PGD more difficult. The present review was to analyze the literature available on PGD and to propose a definition.**

DATA SOURCE: **A search of PubMed (up to the end of 2012) for English-language articles relevant to PGD was performed to clarify the characteristics, risk factors, and possible treatments or interventions for PGD.**

RESULTS: **There is no pathological diagnostic standard; many documented definitions of PGD are different. Many factors, such as donor status, procurement and transplant process and recipient illness may affect the function of graft, and ischemia-reperfusion injury is considered the direct cause. Potential managements which are helpful to improve graft function were investigated. Some of them are promising.**

CONCLUSIONS: **Our analyses suggested that the definition of PGD should include one or more of the following variables: (1) bilirubin ≥10 mg/dL on postoperative day 7; (2) international normalized ratio ≥1.6 on postoperative day 7; and (3) alanine aminotransferase or aspartate aminotransferase >2000 IU/L within 7 postoperative days. Reducing risk factors may decrease the incidence of PGD. A majority of the recipients could recover from PGD; however, when the graft progresses into primary non-function, the patients need to be treated with re-transplantation.**

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KEY WORDS: **graft function; primary graft dysfunction; initial poor function; primary non-function; liver transplantation**

Introduction

Liver transplantation (LT) has evolved from a risky procedure associated with a high mortality and morbidity to a standard and predominantly effective treatment for patients with end-stage liver diseases, and one-year graft survival averages more than 80% at the majority of treatment centers.[1, 2] Because of the increased gap between liver resources and its requirements, marginal organs/donors are used routinely for the sickest transplantation recipients. Severe complications, such as primary graft dysfunction (PGD), can develop in this situation. Recipients with graft dysfunction usually experience a longer intensive care unit (ICU) and hospital stay, increased mortality and higher graft loss than those without graft dysfunction. Numerous conditions can affect the initial function of the allograft after transplantation. Therefore, understanding and detecting these conditions earlier and predicting early graft dysfunction are very important in decreasing the mortality and morbidity caused by PGD after LT. Unfortunately, because there is no uniform definition of PGD, the various definitions (supported by different transplant centers and involving many factors associated with PGD) impede or confuse the recognition of PGD as a complication of LT. Therefore, our aims are, by reviewing the relevant literature, to propose a definition, to identify risk factors, to summarize clinical features, and to recommend the management of PGD.

There is no consensus on the definitions of PGD,

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initial poor function (IPF), and primary non-function (PNF). However, it is universally accepted that PGD of the liver consists of IPF and PNF, which exhibit different degrees of severity; IPF and PNF are different stages of PGD. IPF is a borderline syndrome and directly influences the survival of the liver allograft. The majority of grafts at IPF are reversible because of their considerable regeneration potential; however, once grafts progress to PNF, the grafts will ultimately progress to graft loss. PNF is characterized by hepatic cytolysis, rapidly rising levels of transaminases, the absence of bile production, severe liver-related coagulation deficiency, high lactate levels, hepatic hemodynamic instability, hypoglycemia and acute renal and respiratory failure.[3-5]

IPF

Currently, there is no universal definition of IPF; different studies use different endpoints and scoring systems (Table 1). Most studies assess IPF based on time intervals during the first postoperative days or weeks and use liver-related laboratory parameters such as alanine aminotransferase (ALT) and asparate aminotransferase (AST) and prothrombin activity.[6-11] Ploeg et al[6] defined IPF as an AST of more than 2000 IU/L, a prothrombin time greater than 16 seconds, and an ammonia level greater than 50 μmol/L between postoperative days 2 and 7. This definition is widely used because it includes AST (indicating hepatocyte injury) and prolonged prothrombin time (indicating reduced synthetic ability). Nanashima and colleagues[7] recommended that an ALT and/or AST is greater than 1500 IU/L for 2 consecutive measurements within the first 72 hours after LT, whereas Dhillon et al[8] suggested that an average level of transaminase greater than 986 IU/L on postoperative day 2. Pokorny et al[3] used AST plus clotting factor support and bile production to evaluate IPF. Broering et al[9] defined primary poor function as ALT or AST >2000 IU/L or fresh frozen plasma being substituted for more than 5 days postoperatively. Nemes et al[12] selected the quotient of serum bilirubin (μmol/L) and prothrombin (percent) at postoperative day 5 to define IPF, González et al[13] used peak serum ALT values, mean bile output and lowest prothrombin activity to score early postoperative graft function. But in these studies the cutoff levels for the parameters were chosen arbitrarily based on the experiences of different centers. Statistically, the Nanashima criteria demonstrate a high concordance with the González criteria for the definition of early postoperative graft function and for predicting graft and patient survival.[14] However, similar tests for predicting graft function can have unequal predictive efficacy for IPF defined by González et al compared with the prediction of IPF defined by Ploeg et al.[15] Moreover, in the study conducted by Heise et al,[10] the incidence of IPF varied according to the scoring systems.

Although a number of the criteria described above demonstrated a high consistency in defining early postoperative graft function and predicting graft and

Table 1. Definitions of IPF

References	Definitions of IPF
Pokorny et al[3]	AST >2500 IU/L, clotting factor support >2 days, and bile output <20 mL/d
Ploeg et al[6]	AST >2000 IU/L, PT >16 sec, and NH_3 >50 μmol/L on postoperative days 2-7
Nanashima et al[7]	ALT or AST >1500 IU/L on two consecutive measurements within the first 72 h
Dhillon et al[8]	Definition based on liver enzymes [(ALT+AST)/2] on postoperative day 2: Good function <285 IU/L Average function 285-986 IU/L IPF>986 IU/L
Broering et al[9]	ALT or AST or glutamate dehydrogenase >2000 IU/L; or fresh frozen plasma had to be substituted for >5 days postoperatively
Heise et al[10]	Survival based classification system calculated by ALT, AST, bile output and prothrombin activity on days 1, 3, 7, 14: Berlin A (good function): sum of score 4 or 5 Berlin B (moderate): 6 Berlin C (IPF): 7 or 8
Cieślak et al[11]	ALT or AST >2500 IU/L or prothrombin index <50% during first 7 days
Nemes et al[12]	Quotient of serum bilirubin (μmol/L) and prothrombin (percent) at postoperative day 5 was greater than 1
González et al[13, 14]	Graded initial liver function based on ALT, bile output and prothrombin activity measured in the first 72 hours after LT: IPF: sum of score 7-9 Moderate dysfunction: 5 or 6 Good function: 3 or 4
Olthoff et al[16]	When one or more of the following variables were present: (1) Bilirubin ≥10 mg/dL on postoperative day 7 (2) INR ≥1.6 on postoperative day 7 (3) ALT or AST >2000 IU/L within the 7 postoperative days
Lock et al[17, 18]	Liver function classified by two LiMAx (maximal liver function capacity) readouts within 24 hours after transplantation: PNF: LiMAx <60 μg/kg per hour with normal graft perfusion IPF: LiMAx 60-120 μg/kg per hour Fair: LiMAx 120-240 μg/kg per hour Good: LiMAx >240 μg/kg per hour

ALT: alanine aminotransferase; AST: asparate aminotransferase; PT: prothrombin time.