An Epidemiologic Study of Early Renal Replacement Therapy after Orthotopic Liver Transplantation

GABRIEL CONTRERAS,* GALO GARCES,† ANDREW A. QUARTIN,‡ CYNTHIA CELY,§ MARK A. LAGATTA,§ GASPAR A. BARRETO,§ DAVID ROTH,§ and EMILIO GOMEZ,§

Divisions of *Nephrology and †Pulmonary and Critical Care Medicine, Veterans Affairs Medical Center, Miami, Florida; and the ‡Internal Medicine Residency Program and §Division of Nephrology, University of Miami, Miami, Florida

Abstract. The preoperative impairment of renal function is associated with the need for postoperative renal replacement therapy (RRT) in patients undergoing liver transplantation. The principal goal of this investigation was to identify other factors apparent before or during transplant that were independently associated with the need for RRT in the early posttransplant period. A total of 260 consecutive adult patients who received a primary liver transplant were studied. Twenty-eight patients required early RRT (RRT initiated within 1 wk of transplant); 23 for control of volume overload. Preoperative blood urea nitrogen (odds ratio [95% CI], 1.52 [1.15 to 2.01] per 10 mg/dl), serum creatinine (1.91 [1.06 to 3.44] per 1 mg/dl), and urine output (0.12 [0.03 to 0.44] L/d) were independently predictive of the need for early RRT and in combination formed a parsimonious model that discriminated well (area under the receiver operating characteristic curve, 0.877) and had excellent fit ($P = 0.699$ to reject model fit). No other potential predictors meaningfully improved predictions of which patients would require early RRT. Patients requiring early RRT consumed more healthcare resources than patients who did not require early RRT, spending more time in intensive care (15 ± 13 d versus 7 ± 11 d; $P < 0.001$) and in the hospital (34 ± 27 d versus 19 ± 20 d; $P < 0.001$). The need for early RRT was strongly associated with death before hospital discharge (29% mortality versus 4% mortality among all others; $P < 0.001$). The data demonstrate that dependency on RRT in the first week after orthotopic liver transplantation stems almost entirely from preoperative renal dysfunction.

Each year more than 4000 patients undergo orthotopic liver transplantation (OLT) in the United States (1). Among adults, liver transplantation is currently indicated for many cases of both fulminating hepatic failure and end-stage liver disease with or without hepatorenal syndrome. In recent years, patients suffering cirrhosis secondary to hepatitis C virus have constituted an increasing proportion of the OLT candidate population.

The impairment of renal function appears to be an important clinical event in patients undergoing liver transplantation. A recent prospective study demonstrated that acute renal failure (ARF) and the need for renal replacement therapy (RRT) after OLT were significant risk factors for in-hospital mortality (2). In that study, 19% of patients awaiting OLT suffered ARF. Not only did renal failure occur preoperatively, but as many as 30% of patients were reported to suffer ARF in the postoperative period (2).

The need for RRT after OLT can be reasonably classified as early or late according to its temporal relationship with surgery, probably reflecting distinct clinical entities. Patients who undergo OLT often enter surgery with some degree of renal insufficiency, and during the procedure they may endure the additional insults of a systemic inflammatory response, hemorrhage, and massive infusion of crystalloids, colloids, and blood products (3,4). It thus seems likely that preoperative and intraoperative factors would be the principal determinants of the need for RRT in the early postoperative period. Beyond 7 d after OLT, renal insufficiency seems likely to be of different origins, because the effects of preoperative and intraoperative renal insults should have already been manifested. Rather, it seems likely that the need for RRT in this later period would probably be due to insults suffered in the postoperative period, including sepsis, contrast nephropathy, and nephrotoxicity from calcineurin inhibitors (2,5).

Although preoperative renal insufficiency is known to be associated with the need for postoperative RRT (5–8), no previous study has provided estimates of adjusted risks associated with other factors that may influence the need for RRT after OLT. The principal goal of this study was to identify risk factors for early RRT after OLT after adjusting for preexisting renal failure. The effects of the need for RRT on in-hospital resource use and mortality were also analyzed in this study.

Materials and Methods

Study Population

The study population consisted of adults who received a primary OLT at Jackson Memorial Hospital between March, 1994, and April, 1998, had complete records for purposes of analysis, survived at least...
7 d after transplantation, and did not receive RRT in the 7 d before OLT. The institutional review board on human research approved the protocol waiving the need for informed consent.

Data Collection

The Liver Transplant Program maintains a database that includes information on age, gender, ethnicity, hepatic pathology, type of surgical procedure (piggyback or conventional), use of venovenous bypass, blood product units infused intraoperatively, bone marrow infusion, United Network of Organ Sharing (UNOS) status, warm ischemia time, and cold ischemia time. Data regarding preoperative urine flow (from the preceding 24 h), BUN, serum creatinine, hematocrit, total bilirubin, prothrombin time, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and BP were extracted from the same database when available or from the patients’ medical records. An acute physiology score (APSIII) was calculated from data in the hospital record from the 24 h after surgery, using the weightings of the Acute Physiology and Chronic Health Evaluation III model (9). For patients started on RRT during the first 24 h after surgery, the time window for use of data in the APSIII was truncated when RRT began. Data regarding the use and timing of RRT was obtained from the medical record. Lengths of stay in the hospital and intensive care unit were extracted from the hospital’s computerized records, as was vital status at discharge.

Statistical Analyses

Early RRT was defined as the institution of ultrafiltration, dialysis, and/or hemodialfiltration within the first 7 d after OLT. Initiation of RRT after 7 d was defined as late RRT. Patients classified as having received early RRT were excluded from analyses of late RRT.

The principal analysis was performed using multivariate logistic regression, with receipt of early RRT as the outcome variable. Factors considered as possible predictors of the need for early RRT included liver pathology, age, gender, ethnicity, warm and cold ischemia times, UNOS status, bone marrow infusion, preoperative BP, surgical technique, use of venovenous bypass, units of blood products infused intraoperatively, and preoperative hematocrit, prothrombin time, albumin, total bilirubin, AST, and ALT. Because both previous investigation and clinical sensibility suggest that the need for RRT is linked to preoperative renal function, a baseline model was constructed that included preoperative BUN, creatinine, and urine flow as covariates. Each possible predictor was then added individually to the baseline model, and those that showed a trend toward improved model performance \((P < 0.10)\) for change in model \(\chi^2\) were considered for further analysis. Independently significant predictors were then identified by adding covariates to the baseline model in a forward stepwise fashion, selecting the predictor that most improved model performance at each step and stopping when no remaining predictors significantly improved model performance \((P < 0.05)\) for change in model \(\chi^2\). Model discrimination was assessed by using the area under the receiver operating characteristic curve, and goodness of fit was evaluated by using the method of Hosmer and Lemeshow.

Comparisons of categorical variables between groups were performed by using \(\chi^2\) tests. Comparisons of continuous variables between two groups were performed using the \(t\) test when distributions were approximately normal and variances approximately equal, the Aspin-Welch test when distributions were approximately normal but variances unequal, and the Wilcoxon Rank Sum test when distributions were not normal. The effect of RRT on survival was assessed by using multiple logistic regression adjusted for the APSIII. All statistical analyses were done by using the NCSS 2000 software package (NCSS, Kaysville, UT), with the exception of goodness-of-fit tests, which were done by using Minitab statistical software (Minitab, State College, PA).

Results

Demographics

Three hundred thirty-five adults underwent OLT at Jackson Memorial Hospital between March, 1994, and April, 1998. Five patients were excluded from analysis because they received RRT before OLT, four patients expired within 1 wk of OLT (none having received RRT in the postoperative period), and an additional 66 patients were excluded because of incomplete data. A total of 260 patients were therefore included in this analysis. All of our patients received induction immunosuppression with steroids and calcineurin inhibitors, with 95% receiving tacrolimus and the other 5% cyclosporine. Twenty percent of the patients received purine analogs (19% mycophenolate mofetil and 1% azathioprine). Only 3% of the patients received either muromonab-CD3 (2%) or dacluzimab (1%) as part of their immunosuppressive regimen.

The most common cause of hepatic failure was hepatitis C (43% of patients). Patients were 51 ± 12 yr of age (mean ± SD) and predominantly white (67%) men (57%). Twenty-three patients were listed as UNOS status I preoperatively, and 70 as UNOS status II. Preoperative renal status was characterized by urine flow of 1.159 ± 0.840 L/d, BUN of 19 ± 18 mg/dl, and creatinine of 1.3 ± 0.9 mg/dl. Preoperative hepatic function was characterized by a prothrombin time of 17.0 ± 9.1 s, total bilirubin of 6.6 ± 9.9 mg/dl, AST of 251 ± 570 U/L, ALT of 193 ± 536 U/L, and albumin of 3.1 ± 0.7 g/dL. Allogeneic bone marrow from the donor was infused at the time of OLT in 124 patients (48%), and 64 ± 48 units of blood products were infused during each procedure. Eighteen patients (7%) died before leaving the hospital (Table 1).

Twenty-eight patients (11%) received early RRT and 15 patients (6%) received late RRT (Figure 1). Early RRT was instituted in 23 (82%) of 28 patients for control of volume overload. Although hypervolemia was the impetus to implement RRT in this group, both BUN (48 ± 34 mg/dl before OLT; 70 ± 43 mg/dl before RRT; \(P = 0.014\)) and creatinine (2.5 ± 1.8 mg/dl before OLT; 3.7 ± 2.6 before RRT; \(P = 0.004\)) rose significantly before the initiation of early RRT. BUN and serum creatinine were also significantly higher than baseline in the late RRT group at the time RRT was started (BUN 121 ± 38 mg/dl \([P < 0.0001]\); creatinine 3.5 ± 1.8 mg/dl \([P < 0.0008]\)).

Predictors of Need for Early RRT

As anticipated, preoperative BUN and creatinine were much higher among patients requiring early RRT than among patients not requiring this therapy (BUN, 48 ± 34 mg/dl versus 16 ± 12 mg/dl \([P < 0.001]\); creatinine, 2.5 ± 1.8 mg/dl versus 1.2 ± 0.5 mg/dl \([P < 0.001]\)), and urine flows were much lower (0.545 ± 0.379 L/d versus 1.233 ± 0.850 L/d; \(P < 0.001\)). Other factors identifiable in the preoperative or intraoperative period that were associated with the need for early RRT included the preoperative mean arterial pressure, hemat-
ocrit, total bilirubin, and prothrombin time, as well as UNOS status, use of venovenous bypass, and the total number of units of blood products infused during surgery (Table 1). Preoperative albumin, AST, and ALT, as well as age, ethnicity, gender, allogenic bone marrow infusion, type of liver disease, surgical technique, and operative ischemic times appeared unrelated to the need for early RRT.

Development of the baseline model using multivariate logistic regression revealed that preoperative BUN (odds ratio [95% CI], 1.52 [1.15 to 2.01] per 10 mg/dl), creatinine (odds ratio, 1.91 [1.06 to 3.44] per 1 mg/dl), and urine output (odds ratio, 0.12 [0.03 to 0.44] per L/d) were independently predictive of the need for early RRT (Table 2). The baseline model discriminated well (area under the receiver operating characteristic curve, 0.877), and goodness of fit was excellent ($P = 0.699$ to reject model fit) (Figure 2). Race, preoperative mean arterial pressure, total bilirubin, prothrombin time, AST, and the number of units of blood products infused intraoperatively

![Figure 1](image.png)
all showed a trend toward association with the need for early RRT ($P < 0.10$ for each covariate), and these covariates were therefore considered for entry into the full model predicting need for early RRT.

Forward stepwise model construction added preoperative mean arterial pressure, the number of units of blood products infused intraoperatively, AST, and white race as additional predictors for the baseline model (Table 2). Despite the use of these four additional predictors, the full model only negligibly improved discrimination beyond that of the baseline model (area under the receiver operating characteristic curve, 0.884), and it fit the data no better ($P = 0.569$ to reject model fit).

Relationship of Early RRT to Hospital Resource Use and Mortality

Patients who required early RRT consumed significantly more healthcare resources than patients who did not require early RRT, spending more time in an intensive care unit postoperatively (15 ± 13 d versus 7 ± 11 d; $P < 0.001$), in the hospital postoperatively (34 ± 27 d versus 19 ± 20 d; $P < 0.001$), and on mechanical ventilatory support (11 ± 10 d versus 4 ± 9 d; $P < 0.001$). After being started on RRT, patients who received early RRT continued to receive such support for 12 ± 18 d.

Receipt of early RRT was strongly associated with death before hospital discharge (29% mortality among patients receiving early RRT, 4% mortality among all others, $P < 0.001$). However, early RRT status did not significantly improve a logistic regression model of hospital mortality based on APSIII from the first 24 h of the postoperative period ($P > 0.25$ for model improvement with addition of early RRT status). This suggests that early RRT is a marker of mortality risks rather than a cause of mortality.

Late RRT

Of all the preoperative, intraoperative, and postoperative factors studied, univariate logistic regression identified only the number of units of blood products infused intraoperatively (odds ratio, 1.15 [1.04 to 1.27] per 10 units; $P = 0.0008$) and APSIII from the first 24 h of the postoperative period (odds ratio, 1.07 [1.03 to 1.11] per point; $P = 0.0048$) as significantly related to the need for late RRT. Preoperative BUN, creatinine, and urine output appeared unrelated to the need for late RRT ($P > 0.10$ for each). A model based on only intraoperative blood product infusions and postoperative APSIII weakly discriminated between patients who required late RRT and those who did not (area under the receiver operating characteristic curve, 0.685). All patients who required late RRT were diagnosed as being septic before the initiation of RRT. Eight (53%) of 15 patients requiring late RRT expired before leaving the hospital, compared with 10 (4%) of 245 who did not require late RRT ($P < 0.001$ for difference between groups).

Discussion

Our study confirms previous findings that the need for postoperative RRT is associated with increased in-hospital mortality and resource use (2). Our data demonstrate that dependency on RRT originating in the first week after OLT is attributable to preoperative renal function and that later dependency on RRT is most likely based on postoperative factors. The need for early and late RRT was associated with in-hospital mortality rates of 29% and 53%, respectively. Compared with recipients who did not receive early RRT support,
patients who received this therapy remained twice as long in both the intensive care unit and hospital wards and received mechanical ventilatory support for three times as long.

In our study of 260 adults who received primary OLT, 43 (17%) received RRT after surgery. The previously reported incidence of the need for RRT after OLT has ranged from 5% to 35% (2,5,6). This wide range is probably due in part to the lack of gold standard criteria to initiate RRT, the presence or absence of hepatorenal syndrome in studied populations, the experience of the transplant centers, the size of the study samples, and inconsistent definitions of the time interval during which RRT was considered to be related to transplantation. In one study, Gonwa et al. (5) reported that postoperative hemodialysis was required in 35% of hepatorenal syndrome recipients but in only 5% of nonhepatorenal syndrome recipients. Fraley et al. (2) reported that 20% of liver transplant recipients required some type of acute dialytic support postoperatively. In another study of 116 consecutive liver transplants, 27 (23%) developed early ARF and 11 (9%) of them required RRT (6).

Our study demonstrates that most patients at increased risk of postoperative need for early RRT can be identified before transplant simply by considering the preoperative BUN, serum creatinine, and urine flow. Taking into account three additional preoperative factors (mean arterial BP, AST, and race) and one intraoperative factor (units of blood products infused) did not usefully improve the ability to anticipate which patients would require early RRT, despite these additional factors statistically significantly improving the fit of the logistic regression.

The observed mutual independence of preoperative BUN, serum creatinine, and urine flow as predictors of the need for early RRT is worthy of discussion. BUN and serum creatinine are generally thought of as estimates of glomerular filtration, and preoperative oliguria presumably predicts the inability to handle a fluid load. The independent contribution of these three markers may result in part from differences in practice patterns among consulting nephrologists. However, we suspect that physiologic factors associated with end-stage liver disease are more likely to explain the need to consider all three markers. Serum creatinine, probably the preferred single marker of filtration in the heptically intact population, is often low in the hepatic failure patient because of decreased muscle mass, even when filtration is compromised. BUN may at times be artificially elevated because of occult gastrointestinal hemorrhage and increased catabolism or decreased because of low protein intake and liver failure. Assessing filtration in these patients by using routine laboratory markers is therefore problematic, and without a more specific (and nonroutine) marker of preoperative glomerular filtration, it is not surprising that BUN and serum creatinine remain independently significant predictors of the need for early RRT. Low urine output anticipates inability to tolerate large fluid loads that may be particularly dangerous to OLT patients, as increasing central venous pressure may lead to liver congestion and graft failure. This would therefore be considered by most nephrologists to be an indication for RRT independent of glomerular filtration.

Other perioperative factors, including age, gender, UNOS status, type of liver disease, hematocrit, total bilirubin, albumin, ALT, surgical technique, bone marrow infusion, and operative ischemic times, appeared unrelated to the need for early RRT. Of particular interest, we found that the use of venovenous bypass actually was associated with a modest increase in the risk of need for early RRT in univariate analysis, although this association vanished once preoperative renal function was taken into account. Our finding contrasts with Brown et al. (10) who found that renal perfusion pressure was preserved during the anhepatic stage with venovenous bypass and that urine output remained stable throughout the surgery. Although venovenous bypass is often used to reduce renal venous congestion due to elevated inferior vena cava pressure and to maintain hemodynamic stability, which theoretically protects the kidneys, in a randomized clinical trial, Grande et al. (11) found that venovenous bypass was not associated with any clear benefit in preserving the renal filtration function or predicting the need for early RRT after OLT. Therefore, systematic use of venovenous bypass does not seem warranted.

Preoperative renal dysfunction was not predictive of the need for late RRT. Rather, acute renal failure necessitating late RRT appeared to be an epiphenomenon of multisystem organ failure. All 15 patients who required late RRT were diagnosed as being septic before the initiation of RRT, in contrast to the early RRT population, none of whom were septic at the time RRT was initiated. For this reason, we believe that late renal insufficiency requiring RRT is a clinically distinct entity from early renal insufficiency requiring RRT after OLT. The 7-d interval chosen in this investigation therefore appears applicable for future studies of renal dysfunction after OLT.

Our study has several limitations, but we believe they do not invalidate its conclusions. Most importantly, this was a retrospective study, relying on the clinical decision to provide RRT rather than prespecified criteria for renal insufficiency. Although this allows some variability in criteria for RRT, it probably more accurately reflects clinical application of the therapy than would a criteria set designed for study. Our survival and resource use data are limited to the postoperative hospitalization period. The effect of the need for RRT on long-term outcomes has not been analyzed here and may prove to be important. Finally, our analysis is limited with respect to exploring other potential causes of renal dysfunction requiring RRT, in particular injury caused by rejection, relaparotomy, and nephrotoxic agents such as calcineurin inhibitors, intravenous contrast, and antibiotics. However, the excellent performance of models that do not include these factors in predicting the need for early RRT make it unlikely that they are major contributors to risk. By contrast, these postoperative factors may well play a role in predicting the need for late RRT.

On the basis of 4000 OLT performed each year and assuming an 11% frequency of the need for early RRT, we estimate that approximately 440 recipients would require RRT after transplantation in the United States. According to the length-of-stay results of our study, the effect of such events would be to increase total intensive care unit stay by approximately 3500 d and total hospital stay by approximately 6600 d. This would result in an increase in hospital healthcare cost likely
exceeding 20 million dollars. This supports the findings of Brown et al. (12) that preoperative renal function is the most important predictor of cost of OLT.

Our findings provide impetus to seek postoperative management regimens more protective of kidney function in patients with pre-existing renal dysfunction. These patients did not require RRT preoperatively; therefore, it may be that such regimens could reduce cost, morbidity, and mortality in this especially vulnerable population. As shown by Gonwa et al. (5), a calcineurin-sparing protocol using azathioprine maintains renal function in those patients who present with pre-existing renal dysfunction before OLT. Perhaps this or a similar approach should be used for patients at high risk for needing early RRT.

In summary, we found that the risk for RRT in the week after OLT depends on preoperative renal function and that other factors identifiable in the preoperative and intraoperative periods do not significantly contribute to this risk. Early RRT is associated with increased in-hospital mortality and resource use. We have identified a high-risk subgroup of patients likely to require early RRT, thereby allowing the communication of such risk to patients and the focusing of perioperative care efficiently in this high-risk subgroup. Further studies are needed to define pathogenetic mechanisms and additional predictors and to develop therapeutic strategies to reduce morbidity and mortality in OLT recipients.

Acknowledgments

We thank Debbie Weppler and Ine M. Fernandez for providing the database support from the transplant center. We also thank Dr. Carlos A. Vaamonde and Dr. Murray Epstein for helpful editorial comments and discussions.

References