Risk factors of acute renal failure after liver transplantation

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The objective of this study was to determine the risk factors of postoperative acute renal failure (ARF) in orthotopic liver transplantation (OLT). We reviewed 184 consecutive OLT. Postoperative ARF was defined as a persistent rise of 50% increase or more of the S-creatinine (S-Cr). The patients were classified as early postoperative ARF (E-ARF) (first week) and late postoperative ARF (L-ARF) (second to fourth week). Preoperative variables were age, sex, comorbidity, indication for OLT, Child–Pugh stage, united network for organ sharing status, analysis of the blood and urine, and donor's data. Intraoperative variables were systolic arterial pressure, mean arterial pressure, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance index. Surgical technique, number of blood products transfused, need for adrenergic agonist drugs, and intraoperative complications were also important. Postoperative variables were duration of stay in the intensive care unit, time on mechanic ventilation, liver graft dysfunction, need for adrenergic agonist drugs, units of blood products infused, episodes of acute rejection, re-operations, and bacterial infections. Firstly we carried out a univariate statistical analysis, and secondly a logistic regression analysis. The risk factors for E-ARF were: pretransplant ARF (odds ratio (OR) = 10.2, $P = 0.025$), S-albumin (OR = 0.3, $P = 0.001$), duration of treatment with dopamine (OR = 1.6, $P = 0.001$), and grade II–IV dysfunction of the liver graft (OR = 5.6, $P = 0.002$). The risk factors for L-ARF were: re-operation (OR = 3.1, $P = 0.013$) and bacterial infection (OR = 2.9, $P = 0.017$). The development of E-ARF is influenced by preoperative factors such as ARF and hypoalbuminemia, as well as postoperative factors such as liver dysfunction and prolonged treatment with dopamine. The predicting factors of L-ARF differ from E-ARF and correspond to postoperative causes such as bacterial infection and surgical re-operation.

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Postoperative acute renal failure (ARF) is a serious clinical problem in orthotopic liver transplantation (OLT). The true incidence is not known due to the differences in the selection of patients and in the criteria and methods used to evaluate renal function. The rate of ARF after OLT varies between 51 and 94%,[1–3] and between 8 and 17% need renal replacement therapy (RRT).[3,4] Moreover, postoperative ARF results in a high mortality, which has been linked to the serum creatinine (S-Cr) peak,[2] the need for postoperative dialysis,[4] the duration of RRT,[5] and the presence of other co-morbidities such as sepsis, encephalopathy, and coagulopathy.[6]

Various factors may influence, to a different extent, the origin of ARF after OLT. Some depend on the clinical state of the recipient before transplant and others stem from intraoperative hemodynamic changes and postoperative complications.[3,7,8] Postoperative ARF has been divided, arbitrarily, into early postoperative ARF (E-ARF) and late postoperative ARF (L-ARF) depending on how long after the operation it occurs, and etiopathogenic differences have been suggested, although these have not been reliably confirmed. To date there is no specific treatment available for ARF. Preventive measures such as careful adjustment of drug doses and of the hydroelectrolytic balance, together with dialysis in the serious cases, are the most effective therapeutic measures. Consequently, there is a growing interest in identifying the risk factors for ARF after OLT, which would allow a better understanding of the illness and enable preventive measures to be adopted.

The objective of this study was to identify the independent risk factors of both E-ARF and L-ARF in patients who had undergone OLT in our hospital.

RESULTS

Fifty-seven (30.9%) patients had E-ARF and 34 (19.1%) L-ARF, with an overall incidence in the first month after surgery of 48%. The most frequent etiologies of E-ARF were ischemic acute tubular necrosis and pre-renal ARF, whereas those of L-ARF were multifactorial ARF, followed by cyclosporine nephrotoxicity and sepsis-associated ARF (Table 1).

Table 1 | Etiology and clinical data in liver transplantation patients with early and late ARF

	E-ARF (*N*=57)	L-ARF (*N*=37)	*P*
Etiology of ARF			
Prerenal azotemia	18 (32)	5 (13)	<0.05
Ischemic ATN	24 (42)	1 (3)	<0.001
Hepatorenal syndrome	0	1 (3)	NS
Cyclosporine nephrotoxicity	0	8 (22)	<0.001
Sepsis-associated ARF	1 (2)	7 (19)	<0.01
Multifactorial ARF	14 (25)	15 (40)	NS
Clinical of ARF			
Oliguria	14 (25)	9 (24)	NS
Peak S-Cr (mg/dl)	2.2 (1.5–5.9)	2 (1.4–5.6)	NS
Duration of the ARF (days)	5 (1–21)	7 (2–20)	NS
Patients in dialysis	15 (26)	7 (19)	NS
Need of dialysis (days)	6 (1–14)	4 (2–6)	<0.001

The values are the number and (%) of patients.
Results of quantitative data are expressed as median (and range).
ATN, acute tubular necrosis; ARF, acute renal failure; E-ARF, early acute renal failure; L-ARF, late acute renal failure; NS, not significant; S-Cr, serum creatinine.

Patients with E-ARF and L-ARF showed similar clinical manifestations with regard to the following variables: oliguria, maximum S-Cr, the percentage of patients undergoing dialysis, and the duration of ARF. However, the duration of RRT was significantly longer in patients with E-ARF (Table 1). The mean S-Cr, on the 30th day post-OLT, was 1.4 mg/dl in E-ARF group, 1.86 mg/dl in the L-ARF group, and 1 mg/dl in patients without ARF. Two patients in the L-ARF group received dialysis temporarily on the 30th day post-OLT. In the first month post-transplant, 17 patients died, six (10.5%) from the E-ARF group, seven (20.5%) from the L-ARF group, and four from the group without any postoperative ARF. The global postoperative mortality was greater in patients with ARF than in those without ARF, 13 (16.7%) vs 4 (3.8%), respectively ($P<0.01$).

Univariate analysis for E-ARF

The E-ARF and non-E-ARF groups were homogeneous with respect to age, sex, and medical background (abdominal surgery, diabetes, arterial hypertension, and nephropathy).

Table 2 | Comparison of preoperative, intraoperative, and postoperative variables in OLT patients who did or did not develop E-ARF (univariate analysis)

Variable	E-ARF (*N*=57)	Non-E-ARF (*N*=127)	*P*
Preoperative			
Age (year)	48±10	45±14	NS
Sex (male/female)	49 (86)/8 (14)	93 (73)/34 (27)	NS
UNOS status: class 1/2/3	10 (18)/15 (26)/32 (56)	1 (0.8)/17 (14)/107 (86)	<0.01
Prothrombin time (seconds)	7.2±7.9	4.3±4.2	NS
Serum creatinine (mg/dl)	1.16±0.64	0.89±0.21	NS
Serum bilirubin (mg/dl)	6.7±7.6	5±7.5	<0.05
Serum albumin (g/dl)	3.28±0.5	3.69±0.7	<0.001
Urgent retransplant	8 (14)	0 (0)	<0.01
Child–Pugh score: A/B/C	0 (0)/13 (37)/22 (63)	15 (17)/47 (52)/28 (31)	<0.001
Urinary alterations (hematuria and/or proteinuria)	20 (35)	20 (16)	<0.01
Preoperative ARF	12 (21)	3 (2)	<0.001
Intraoperative non-hemodynamics			
RBC transfusions (units)	26±17	16±12	NS
Fresh frozen plasma (units)	24±12	16±10	<0.001
Platelets (units)	12±12	7±8	NS
Cryoprecipitate (units)	18±12	11±12	<0.001
Intraoperative complications	13 (23)	11 (9)	<0.05
Noradrenaline	36 (63)	47 (37)	<0.01
Dobutamine	19 (33)	23 (18)	<0.05
Surgery: standard/VVB/PGB	33 (58)/10 (17)/14 (25)	51 (40)/10 (8)/66 (52)	<0.001
Postoperative			
ICU stay (days)	12.9±7.4	7.2±4.0	NS
Mechanical ventilation (days)	6.6±6.3	2.5±2.7	<0.01
RBC transfusions (units)	4.5±4.4	1.8±2.3	NS
Fresh frozen plasma (units)	10.1±6.9	6.6±4.7	NS
Platelets (units)	16.1±15.1	9±12.3	<0.001
Dobutamine (days)	2.7±2.7	0.7±1.5	NS
Dopamine (days)	5.4±1.9	3.2±2.2	<0.001
Cyclosporine level (ng/ml)	272±106	253±94	NS
Graft dysfunction (II–III–IV)	24 (42)	20 (16)	<0.001
Bacterial infection	23 (40)	28 (22)	<0.05
Acute rejection	8 (14)	50 (39)	<0.001

The values are number and (%) of patients.
The results of quantitative data are expressed as mean±s.d.
E-ARF, early acute renal failure; ICU, intensive care unit; OLT, orthotopic liver transplantation; NS, not significant; PGB, piggy back; RBC, red blood cells; UNOS, united network for organ sharing; VVB, venovenous bypass.

The univariate study of the main preoperative variables is shown in Table 2. Patients with E-ARF more frequently presented urgent retransplant indication ($P<0.01$), Child–Pugh score C ($P<0.001$), united network for organ sharing status 1 and 2 ($P<0.001$), higher levels of S-bilirubin ($P<0.05$), lower levels of S-albumin ($P<0.001$), a higher rate of urinary changes (proteinuria and/or hematuria) ($P<0.01$), and a higher rate of preoperative ARF ($P<0.001$) than patients without E-ARF.

The univariate analysis of non-hemodynamic intraoperative variables showed that in patients with E-ARF the number of units of all blood products infused was greater, but only reached statistic significance in those of fresh frozen plasma ($P<0.001$) and cryoprecipitate ($P<0.001$). We registered 27 intraoperative incidences in 24 patients: 11 fibrinolysis, seven portal vein thrombosis, three air embolisms, three hepatic artery thrombosis, one gastrointestinal hemorrhage, one anaphylactic shock, and one ventricular fibrillation. Patients with E-ARF had a higher rate of intraoperative complications ($P<0.05$) and a greater need of support with dobutamine ($P<0.05$) and noradrenaline ($P<0.01$). The standard surgical technique were used more frequently than 'Piggy-back' technique (PGB) in patients with E-ARF ($P<0.001$) (Table 2).

Patients with E-ARF had lower systolic arterial pressure in the anhepatic ($P<0.01$) and post-anhepatic phases ($P<0.05$), lower mean arterial pressure (MAP) in the anhepatic and post-anhepatic phases ($P<0.05$), higher pulmonary capillary wedge pressure in the pre-anhepatic phase ($P<0.05$), and a lower cardiac index in the post-anhepatic phase ($P<0.01$) than patients without E-ARF (Table 3).

In the postoperative period, patients with E-ARF needed artificial ventilation for a longer period ($P<0.01$), a higher number of platelet units infused ($P<0.001$), dopamine support for a greater number of days ($P<0.001$), and presented liver graft dysfunction ($P<0.001$) and bacterial infections ($P<0.05$) with greater frequency than patients without E-ARF. The incidence of acute rejection was significantly less in the E-ARF group (Table 2).

Risk factors for E-ARF

In the multivariate analysis, four independent risk factors for E-ARF were found: preoperative ARF (odds ratio (OR) = 10.2, $P=0.025$), preoperative S-albumin (OR = 0.3, $P=0.001$), duration of treatment with dopamine (OR = 1.6, $P=0.001$), and grade II–IV dysfunction of the liver graft (OR = 5.6, $P=0.002$). The cut-off point used for the quantitative variables was the value of the median in the E-ARF group: 3.2 g/dl for the S-albumin and 6 days for the dopamine treatment duration (Table 4).

All the patients with preoperative-ARF had an S-Cr level of above 1.5 mg/dl. In Table 5, we show the characteristics of

Table 4 | Results of risk factors of E-ARF and L-ARF in multivariate analysis

Variable	OR (95% CI)	P
E-ARF		
Serum albumin <3.2 g/dl	0.3 (0.2–0.4)	=0.001
Preoperative ARF	10 (1.3–78)	=0.025
Treatment with dopamine >6 days	1.6 (1.3–2.1)	=0.001
Graft dysfunction II–IV vs I	5.6 (1.8–17)	=0.002
L-ARF		
Surgical re-operation	3.1 (1.2–7.8)	=0.013
Bacterial infection	2.9 (1.2–7.0)	=0.017

ARF, acute renal failure; CI, confidence interval; E-ARF, early acute renal failure; L-ARF, late acute renal failure; OR, odds ratio; S-Cr, serum creatinine.

Table 3 | Hemodynamic results in OLT with E-ARF and non-E-ARF

Variable	Moment	E-ARF	Non E-ARF	P
SAP (mmHg)	A	116±28	112±19	NS
	B	105±21	116±21	<0.01
	C	122±35	135±30	<0.05
MAP (mmHg)	A	79±17	79±13	NS
	B	78±16	84±14	<0.05
	C	84±24	92±21	<0.05
PCWP (mmHg)	A	13±4	12±3	<0.05
	B	10±4	9±4	NS
	C	17±5	17±5	NS
CI (l/min/m^2)	A	5±2	4.9±1.7	NS
	B	4.2±1.9	4.7±2.2	NS
	C	6±1.8	7±2.1	<0.01
SVRI (din seg/cm^5/m^2)	A	1.290±690	1.232±451	NS
	B	1.578±789	1.511±625	NS
	C	844±390	848±339	NS

The results of quantitative data are expressed as mean±s.d.
CI, cardiac index; MAP, mean arterial pressure; NS, not significant; OLT, orthotopic liver transplantation; PCWP, pulmonary capillary wedge pressure; SAP, systolic arterial pressure; SVRI, systemic vascular resistance index.
Moment A, after anesthesia induction; Moment B, 5 min at the start of anhepatic phase; Moment C 5 min at the start of post-anhepatic phase.

Table 5 | Clinical characteristics and evolution of the patients with preoperative ARF

Case number	Etiology of ARF	Indication of OLT	UNOS status	Intraoprative RRT	S-Cr (mg/dl)	E-ARF (RRT, days)	L-ARF (RRT, days)	Outcome 30th day
1	HRS/AHF	u-RT	1	Yes	3.3	Yes (8 d)	—	Dead
2	HRS/AHF	u-RT	1	Yes	2.2	Yes (3 d)	Non	Alive
3	HRS/AHF	u-RT	1	Non	2	Yes (3 d)	Yes (4 d)	Dead
4	HRS/AHF	FH	1	Yes	4.1	Yes (10 d)	Non	Alive
5	HRS/AHF	u-RT	1	Yes	1.5	Yes (6 d)	Non	Dead
6	HRS/AHF	u-RT	1	Yes	2.5	Yes (7 d)	—	Dead
7	HRS/AHF	u-RT	1	Yes	2.1	Yes (4 d)	Non	Alive
8	IS-N	e-RT	3	Non	1.5	Non	Non	Alive
9	HRS/AHF	u-RT	1	Yes	1.6	Yes (1 d)	Non	Alive
10	IS-N	e-RT	2	Non	1.7	Yes (0)	Yes (0)	Alive
11	HRS class I	LC	2	Yes	1.9	Yes (8 d)	—	Loss of the graft
12	IS-N	e-RT	2	Non	1.8	Non	Yes (0)	Dead
13	MF-ARF	e-RT	2	Yes	1.7	Yes (0)	Yes (0)	Dead
14	HRS/AHF	u-RT	1	Yes	2	Yes (6 d)	Yes (2 d)	Dead
15	PRE-ARF	LC	3	Non	1.7	Non	Yes (0)	Alive

ARF, acute renal failure; e-RT, elective retransplant; FH, fulminant hepatitis; HRS/AHF, hepatorenal syndrome/acute hepatic failure; IS-N, immunosuppressant nephotoxicity; LC, liver cirrhosis; MF-ARF, multifactorial acute renal failure; OLT, orthotopic liver transplantation; PRE-ARF, prerenal acute renal failure; RRT, renal replacement therapy; S-Cr, serum creatinine; u-RT, urgent retransplant; UNOS, united network for organ sharing. UNOS status: 1, ICU; 2, hospital; 3, home.

these patients: 15 patients presented preoperative ARF, the most frequent etiology being hepatorenal syndrome ($n = 10$); urgent retransplant was the most frequent indication of OLT ($n = 8$); nine patients were admitted to the intensive care unit before OLT; 10 needed intraoperative RRT; 12 developed E-ARF; 10 needed early-postoperative RRT; six developed L-ARF; and finally, seven died in the first month post-OLT.

Univariate analysis for L-ARF

In all, 178 OLT were analyzed for the L-ARF statistical study. The variables found to have statistical significance in the univariate analysis are shown in Table 6. The postoperative variables are significant. The patients in the L-ARF group presented mechanical ventilation for a longer period of time ($P < 0.05$), more units of concentrate of platelets infused ($P < 0.05$), and a higher rate of surgical re-operations ($P < 0.001$) and of bacterial infections ($P < 0.001$) than the patients without L-ARF.

Risk factors for L-ARF

In the logistic regression analysis, two independent risk factors for L-ARF were found: surgical re-operation (OR = 3.1 and $P = 0.013$) and bacterial infection (OR = 2.9 and $P = 0.017$) (Table 4).

Of the 44 patients who required re-operation, 39% were due to intra-abdominal bleeding, 25% due to biliary fistulas, 14% due to intra-abdominal abscesses, and 22% due to other causes. The 45% of the re-operations were performed during the first week and the 55% between the second and fourth weeks after OLT.

There were 51 episodes of bacterial infection, distributed between bacteremia (47%), intraabdominal infection (28%), pulmonary infection (20%), and other causes (one cervical abscess, one endocarditis, and one cellulitis) (5%). Bacterial infection has been produced by microorganisms that are typically nosocomial. Of these, 24% occurred during the first week, and the 76% between the second and fourth weeks after OLT.

DISCUSSION

The global rate of postoperative ARF in our series was comparatively lower than in others who used the same criteria for ARF.[1,2] The lower doses of cyclosporine used, the beginning of the cyclosporine treatment after surgery, the fact that aminoglucoside antibiotics were avoided, and the fact that in almost half of the patients the technique of PGB was employed are factors which may have helped to reduce this rate.[9]

In this study, we have tried to identify the etiology of ARF by using clinical and hemodynamic data and normal laboratory tests of the blood and urine. We think that the etiological diagnosis of postoperative ARF in OLT is possible, although the real cause may be difficult to establish due to the large number of diverse factors. Our findings suggest that there are differences in the etiology of E-ARF and L-ARF. In the early postoperative period, prerenal and ischemic acute tubular necrosis are the principal causes of ARF, which is in agreement with previous publications by McCauley *et al.*[2] and Ishitani *et al.*[5] The zero incidence of cyclosporine nephrotoxicity etiology in the E-ARF group can be accounted for because the treatment with cyclosporine was started 12 h after OLT and with smaller doses than in other series.[1] However, the fact that cyclosporine played some etiological role in the 14 episodes of multifactorial E-ARF cannot be discounted. On the other hand, in the late postoperative period multifactorial ARF is the most common etiology, although cyclosporine nephrotoxicity and sepsis-associated ARF are also meaningful.

Risk factors for E-ARF

In our series, we found that preoperative ARF is an independent risk factor for E-ARF. In other studies, either

Table 6 | Comparison of preoperative, intraoperative and postoperative variables in OLT patients who did or did not develop L-ARF (univariate analysis)

Period	Variable	L-ARF (*n*=34)	Non L-ARF (*n*=144)	*P*
Preoperative	Elective retransplant	7 (21)	9 (6)	<0.05
	Preoperative ARF	6 (18)	7 (5)	<0.05
Intraoperative	Platelets (units)	11.3±8.1	7.7±10	<0.01
	Operative incidents	8 (24.2)	14 (10.1)	<0.05
Postoperative	Mechanical ventilation (days)	5±5.9	3.2±4.1	<0.05
	Platelets (units)	16±14	9.8±13	<0.05
	Surgical re-operation	18 (53)	24 (17)	<0.001
	Bacterial infection	19 (56)	29 (20)	<0.001

The values are number and (%) of patients.
The results of quantitative data are expressed as mean±s.d.
L-ARF, late acute renal failure; OLT, orthotopic liver transplantation.

S-Cr >1 mg/dl[8,10] or >1.5 mg/dl[3] before OLT were factors predicting postoperative RRT. Our patients with preoperative ARF had a worse united network for organ sharing status, a higher rate of re-transplants, a higher rate of severe ARF, and a greater postoperative mortality. Lafayette *et al.*[10] and Baliga *et al.*[11] report a worse united network for organ sharing status, greater need for postoperative RRT, and lower survival rate in patients with preoperative renal dysfunction. Moreover, the high mortality in this group of patients is in agreement with the findings of previous studies.[12,13] Patients with hepatorenal syndrome have a lower post-transplant survival rate,[12] especially when it is associated with fulminant liver failure.[13] The important prognosis of the preoperative renal function has been taken up by the model for end-stage liver disease score to give priority in the waiting list for OLT.[14,15] At present, the mechanism by which preoperative ARF worsens the prognosis of liver transplants is not known. It has been suggested that renal insufficiency is an indicator of the severity of the underlying disease,[10] and that it is associated with a higher rate of intraoperative haemorrhage,[16] postoperative infection,[10] and primary dysfunction of the graft.[17]

A decrease in preoperative S-albumin is a prognostic factor in patients with cirrhosis of the liver[18] and in those who undergo major surgical operations.[19] In liver transplantation, various studies show that preoperative hypoproteinemia[3] and hypoalbuminemia[20] are associated with a greater incidence of postoperative ARF. Patients with advanced liver disease have a greater incidence of ARF after OLT.[11] Likewise, Gonwa *et al.*[4] found a higher Child–Pugh score in patients who need postoperative dialysis. In our study, there was a greater incidence of ARF in Child–Pugh stage C cirrhotic patients, but in the multivariate study of the individual components of this classification only hypoalbuminemia was an independent risk factor. As far as we know, this is a new finding in liver transplantation. When interpreting this finding, it should be taken into consideration that the population studied is not composed exclusively of patients with liver cirrhosis. Thus, the Child–Pugh clinical variables (ascitis and encephalopathy) have only been recorded in cirrhotic patients, whereas the biochemical variables (albumin, bilirubin, and the prothrombin time) have been considered in all the patients studied. From a physiopathological point of view, hypoalbuminemia may increase the likelihood of ARF, since it modifies Starling's forces in the systemic capillaries, reduces the glomerular filtration,[21] and alters the pharmacokinetics of potentially nephrotoxic drugs.[22]

Changes in the hemodynamic parameters during surgery have an effect on the development of E-ARF, as shown by the results of univariate analysis. Patients with E-ARF had a lower systolic arterial pressure and MAP during the anhepatic and post-anhepatic phases, and lower cardiac index during the post-anhepatic phase. These data suggest that the patients with E-ARF have more problems withstanding the OLT hemodynamic changes, although we cannot state categorically that they suffer cardiac failure. Grande *et al.*[20] found a lower MAP during anesthesia induction and during the anhepatic phase in patients with postoperative ARF, although only MAP (70 mmHg) during anesthesia induction was an independent risk factor. Bilbao *et al.*[3] found a more frequent use of vasoactive drugs in patients who required RRT after OLT. In our series, the patients with E-ARF also had a greater need for infused blood products and adrenergic agonist drugs during and after OLT than patients without E-ARF. However, it was the duration of the treatment with dopamine during the postoperative period which showed an independent correlation with E-ARF. We believe that a more prolonged use of dopamine in patients with E-ARF, in our study, indicates the patients with greater hemodynamic instability and thus more susceptibility to suffering ARF.

Dysfunction of the liver graft (grades II–IV) is another important variable that independently correlates with E-ARF. Bilbao *et al.*[3] found severe dysfunction (III–IV) of the liver graft to be a predictive factor of the need for postoperative dialysis. In our case, moderate dysfunction (grade II, AST >1000 U/l) also is associated with postoperative E-ARF. Both chronic and acute liver dysfunction produces different types of renal disease, in particular the hepatorenal syndrome.[23] On the other hand, the exact mechanisms that

cause primary dysfunction of the liver graft are unknown, although ischemia–reperfusion appears to play an important role.[17] We may conclude that there is an independent relation between liver dysfunction and ARF after OLT. Our results enable us to affirm that any measure which improves maintenance of the donor, perfusion of the liver graft, and its conservation will result in better initial functioning of the liver transplant and an improvement in the postoperative renal function.

Risk factors for L-ARF

In our experience, once the first week after OLT has elapsed the rate of ARF decreases, while the etiology and risk factors of ARF also change. In L-ARF, preoperative and intraoperative variables lose importance as prognostic factors for ARF. In L-ARF it is the postoperative variables that become more important and moreover are different from those found in E-ARF. The only independent risk factors for L-ARF that have been found are bacterial infection and surgical re-operation.

Most bacterial infections occur in the first 2 months post-OLT; they are produced by microorganisms that are typically nosocomial, and are the main cause of death during this period. Septic shock is a main cause of ARF, and has been shown to be an independent risk factor for acquired ARF in a hospital setting.[24] In OLT, patients who need postoperative RRT have infections more frequently.[3] Likewise, major surgery infection has been identified also as an independent risk factor in the need for dialysis during the first month after OLT.[25] From a physiopathological point of view, sepsis causes systemic arterial vasodilation and intra-renal vasoconstriction, and also facilitates the harmful action of other injuries on the kidneys.[26,27]

In the study by Bilbao *et al.*,[3] patients who needed RRT post-OLT were more frequently re-operated on. In our series, re-operation was, in addition, an independent risk factor for L-ARF. Re-operation implies another aggression on the delicate physiological equilibrium of a patient convalescing of OLT. Anesthesia and the surgery itself lead to hemodynamic and hormonal changes that are conducive to postoperative ARF.[28]

Experimental evidence exists which indicates that the occlusion of the inferior cava vein produces ischemic ARF.[29] However, the PGB, which is widely used in Europe,[30] is linked to a lower incidence of ARF post-OLT, according to some authors.[9,31] One of the aims of our study was to analyze whether the change from the standard technique (with or without venovenous bypass) to the PGB altered the incidence of ARF after OLT. The result of the univariate analysis enables us to assert that the PGB significantly reduces the rate of postoperative E-ARF. However, the surgical variable in the analysis of logistical regression loses predictive power and does not appear as an independent risk factor.

The results of our study enable us to conclude that the risk factors for postoperative ARF in OLT vary according to the time elapsed since surgery. The development of E-ARF is influenced by preoperative factors such as acute renal insufficiency and hypoalbuminemia, as well as postoperative factors such as poor function of the liver graft and treatment with a vasoactive drug (dopamine). However, in the late postoperative period, preoperative variables become less important as prognostic factors for L-ARF, and other postoperative variables (surgical re-operation and bacterial infection), which are different from those in the early period, affect the outcome.

MATERIALS AND METHODS

We have retrospectively studied the clinical records of 200 consecutive OLT performed between 1991 and 1997. We have chosen this period of time so that we can compare OLT performed using the standard technique (without or with venovenous bypass) to OLT carried out using PGB (inferior vena cava preservation), while other conditions, such as the surgical team and immunosuppressive therapy, were similar. This enabled us to evaluate the influence of the surgical technique on postoperative ARF. Since 1997 all OLT have been performed using the PGB, and both the surgical team and the immunosuppression guidelines have varied.

We excluded 16 OLT: eight because of patient death and eight because of premature failure of the liver graft within the first 72 h after OLT. Of the patients who died, five were operated on using the standard technique and three using PGB. The causes of death were hypovolemic shock due to postoperative bleeding ($n=4$), multiorgan failure ($n=3$), and ventricular fibrillation ($n=1$). Of the eight OLT with premature failure of the liver graft, six were operated on using the standard technique and two using PGB. The causes of the graft failure were primary non-function ($n=6$), arterial thrombosis ($n=1$), and suprahepatic vein thrombosis ($n=1$).

We have divided the postoperative into early (first week post-OLT) and late (second to fourth week post-OLT), and we have studied the episodes of ARF in each case and then classified them as E-ARF and L-ARF, accordingly. There were 184 patients in the early postoperative period, and 178 in the late period (due to the death of six patients in the early postoperative period).

The demographic data of the patients are shown in Table 7.

Postoperative ARF was defined as a 50% or greater increase in postoperative S-Cr compared to pretransplant values.[32,33] The etiological categories of ARF were as follows:[2,32]

Prerenal azotemia was diagnosed in patients with evidence of hypovolemia or hypotension in whom the S-Cr returned to base values after the volemia or hypotension had been corrected. In addition, urinalysis had to have a high osmolality and a low Na^+ excretion. Although the term ARF would not be used to apply to these patients by most authors, a significant rise in S-Cr is often called ARF.[2]

Ischemic acute tubular necrosis was diagnosed when severe and prolonged hypovolemia or hypotension was observed. The S-Cr, which had initially risen sufficiently to satisfy the criteria of ARF, did not decline after treating volume depletion or hypotension. Urinalysis was consistent with acute tubular necrosis (at least low osmolality and high Na^+ excretion).

Cyclosporine nephrotoxicity was the only etiology for ARF if the rise in level of S-Cr coincided with high levels of cyclosporine and then dropped to base level after a reduction in the cyclosporine dosage in the absence of any other corrective measures.

We have defined ARF associated with sepsis as nitrogen retention temporarily linked to a septic episode. Sepsis was diagnosed in an

Table 7 | Characteristics and demographic data of OLT

Total OLT	184
Mean age	46±13 years
Sex (male, female)	142 M, 42 F
Indications for OLT	
Liver cirrhosis	125 (68%)
Alcoholic cirrhosis	50
Viral cirrhosis	33
Alcohol and viral cirrhosis	17
Biliary cirrhosis	11
Wilson's disease	6
Cryptogenic cirrhosis	8
Elective retransplant	17 (9%)
Familial amyloidosis polyneuropathy	16 (9%)
Urgent retransplant	8 (4%)
Fulminant hepatitis	5 (3%)
Liver malignancies	13 (7%)
Child–Pugh score	
A	15 (12%)
B	60 (48%)
C	50 (40%)
UNOS status	
Class 1 (ICU)	11 (6%)
Class 2 (hospital)	33 (18%)
Class 3 (home)	140 (76%)
Surgical technique	
Standard without VVB	84 (46%)
Standard with VVB	20 (11%)
Piggy-back	80 (44%)
Immunosuppression	
PRED+AZA+CsA	147 (80%)
PRED+AZA+OKT3	37 (20%)

The values are number and (%) of patients.
AZA, azathioprine; CsA, cyclosporine; F, female; ICU, intensive care unit; M, male; OLT, orthotopic liver transplantation; PRED, prednisone; UNOS, united network for organ sharing; VVB, venovenous bypass.

appropriate clinical setting when at least one of the following conditions was present: documented bacteriemia, a known focus infection, immunosuppression with neutropenia, and at least two of the following findings had been documented at the same time: $T^a < 36^\circ C$ or $> 38^\circ C$, hyperventilation, unexplained sudden fall in blood pressure, and leukocytosis to more than 15 000.[34]

Multifactorial-ARF was defined as episodes of ARF in which two or more causes that precede are identified, but when it is not possible to choose between one or the other as the principal cause.

Hepatorenal syndrome was considered when all the major criteria of the International Ascites Club were fulfilled.[35]

We have used the continuous arterio-venous hemofiltration (femoral artery to jugular vein) as the intraoperative RRT. This makes hemofiltration also possible in the anhepatic phase of the standard technique. Also, we have used the intermittent hemodialysis in the postoperative period.

During the surgical operation, furosemide 1 mg/kg/h was administered when the diuresis dropped to below 1 ml/kg/h. The essential hemodynamic objective was to maintain a MAP equal or superior to 70 mmHg. In order to achieve this, and only after ensuring that the cardiac preload was sufficient, dobutamine was used when systolic dysfunction existed and noradrenaline was used when the systemic vascular resistance index was low and the systolic function and the cardiac preload were normal.

We collected the following data on potential risk factors for ARF:

Preoperative variables recipient: age, sex, pretransplantation comorbidity (arterial hypertension, diabetes mellitus, nephropathy, and abdominal surgery), indication for transplant, etiology, and clinical presentation of the cirrhosis, Child–Pugh stage, united network for organ sharing status, serum bilirubin, serum albumin, prothrombin time, S-urea, S-Cr, urinary alterations (proteinuria and/or hematuria), and some donor's data (age, sex, cause of death, blood group, and number of days in the intensive care unit). Preoperative ARF was defined as a 50% or greater increase in S-Cr compared to baseline values.

Intraoperative variables: the hemodynamic variables systolic arterial pressure, MAP, pulmonary capillary wedge pressure, cardiac index, and systemic vascular resistance index were measured at three different times during the operation. The non-hemodynamic variables were surgical technique, number of blood products infused (platelet and red blood cells, fresh frozen plasma, and cryoprecipitates), need for dobutamine and noradrenaline, and intraoperative complications.

Postoperative variables: duration of stay in the intensive care unit, time on mechanic ventilation, liver graft dysfunction according to Greigg *et al.*,[36] need for dobutamine and dopamine in the first week, blood products infused in the first week, episodes of acute rejection, re-operations, and bacterial infections. In the post-operative period, dopamine was used as a vasoactive drug at a dose of 2–3 μg/kg/min in patients with refractory hypotension and a risk of renal hypoperfusion, rarely noradrenaline.

The dose of cyclosporin was 4–5 mg/kg/day. The first dose was given 12 h after surgery and subsequently adjusted according to trough levels of 250–350 ng/ml.

Statistical analysis was performed comparing the groups of patients with E-ARF and L-ARF to those with no ARF. Mann Whitney's *U*-test or Student's *t*-test was used (depending on the normality conditions) to compare the means of quantitative variables, while Pearson's χ^2 or Fisher's exact test was used for qualitative data. Those variables which showed statistical significance ($P < 0.05$) in the univariate analysis and which were relevant were then subjected to multivariate analysis, by means of a logistic regression model, in order to estimate the effect of their interdependence. The cut-off point used for the quantitative data was the median in the E-ARF group.

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