

Liver transplantation for Budd–Chiari syndrome: A European study on 248 patients from 51 centres[☆]

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Background/Aims: The results of liver transplantation for Budd–Chiari syndrome (BCS) are poorly known and the role and timing of the procedure are still controversial. The aim of this study was to investigate the results of transplantation for BCS, focusing on overall outcome, on prognostic factors and on the impact of the underlying disease.

Methods: An enquiry on 248 patients representing 84% of the patients transplanted for BCS in the European Liver Transplantation Registry between 1988 and 1999.

Results: Of the 248 patients, 70.4% were female and 29.6% male. The mean age was 35.7 years. The overall actuarial survival was 76% at 1 year, 71% at 5 years and 68% at 10 years. 77% of deaths occurred in the first 3 months: 47% were due to infection and multiple organ failure, and 18% to graft failure or hepatic artery thrombosis. Late mortality (> 1 year) occurred in nine patients, due to BCS recurrence in four of them. The only pre-transplant predictors of mortality on multivariate analysis (Cox) were impaired renal function and a history of a shunt.

Conclusions: Liver transplantation for BCS is an effective treatment, irrespective of the underlying cause, and should be considered before renal failure occurs.

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1. Introduction

Budd-Chiari syndrome (BCS) is a clinical condition caused by obstruction of the venous outflow of the liver. The pathogenesis of BCS is complex: usually, an acquired thrombotic stimulus associates with a genetic clotting abnormality to produce occlusion of the hepatic veins [1,2]. Several treatments are available for the different stages and clinical manifestations of the disease, and the role of orthotopic liver transplantation (LT) has been controversial since it was performed for the first time in 1974 [3]. While LT was rapidly identified as the only chance to survive the fulminant form of the disease or the terminal stage of chronic progressive form of BCS, studies from pioneering centres concluded that, in most patients and irrespective of the underlying disease, LT should be offered only after more conventional therapy, such as anticoagulation, diuretics or porto-systemic shunts, had failed [4–7]. However, the above-mentioned series spanned long periods of time and included patients operated at the beginning of the liver transplantation era, with mortality and morbidity figures higher than currently expected in a young patient population.

The aim of the present study was to report an updated picture of LT for BCS, focusing on outcome, on preoperative prognostic factors, on the impact of the underlying disease, and on the effects of postoperative anticoagulation on morbidity and disease recurrence.

2. Patients and methods

To identify the current outcome of LT for BCS the Committee of the European liver transplantation association (ELTA) decided to start a BCS project. The data collected in the European liver transplantation registry (ELTR) served as a basis. A questionnaire was sent to all European centres known to have transplanted BCS patients between 1988 and 1999. The centres participated on a voluntary basis (Appendix A).

The questionnaire, intentionally limited to three pages to encourage completion, contained 121 items (Appendix B).

According to the ELTR, from January 1st, 1988 to December 31st, 1999, 295 LT for BCS were performed in 66 centres. Completed questionnaires were obtained for 248 patients from 51 centres (compliance: 77% of centres known to have performed LT for BCS, corresponding to 84% of all procedures performed during the period), no patients were lost to follow-up in the centres that responded, and all questionnaires were retrieved.

The number of questionnaires ranged from 1 to 40 in each centre. Six centres contributed each more than 10 patients, for a total of 115 patients and 133 patients came from the remaining 45 centres.

Major items (Patient and graft survival, liver function, renal function, anticoagulation, recurrence of BCS) were available for all patients, and were cross-checked with ELTR data for accuracy and consistency.

Patients were classified in prognostic categories based on prothrombin time, bilirubin, encephalopathy and ascites as described by Murad et al. [8]. All four items were available for 151 patients (61% of the 248 patients of the study population—missing data on mainly due to the prothrombin time before anticoagulation at diagnosis, rather than at transplantation). These patients did not differ from the 229 patients with three values available (92% of the study population) and from the whole population as for the main factors related to severity (creatinine, bilirubin).

3. Statistical methods

Analysis was performed with the SPSS statistical software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were provided as mean \pm SD. The cumulative survival probability was estimated by the method described by Kaplan and Meier. Factors influencing survival (covariates) were assessed by univariate analysis comparing the subgroups (strata) using the log-rank test. A multivariate analysis was performed with a Cox proportional-hazards model on all 248 patients, based on the factors that were significant by univariate analysis. This model, proposed by Cox, is a multiple regression model for analysis of censored survival data. A model with the backward elimination method was used to select the variables. For each variable, the regression coefficient and its significance were given. For each significant variable, a relative risk was estimated [9]. *P*-values < 0.05 were considered statistically significant.

4. Results

Pre-LT characteristics of the 248 patients are summarized in Table 1.

A cause of BCS had been looked for in all patients, and the main factors are summarized in Table 2. No patient had protein S deficiency.

Liver transplantation was performed electively in 55%, as an emergency in 21%, and the urgency status was unknown in 24% of the patients (this concerned the early cases in the series when the urgency status was still undefined).

Histology was obtained before transplantation by percutaneous liver biopsy in 95 patients, during an operation in 43 patients and by the transjugular approach in six patients. As six patients had both a percutaneous and an operative liver biopsy, 138 patients (56%) had liver histology before LT. Overall, details concerning the histological diagnosis were available for 184 patients (74%). Cirrhosis was present in 36 patients (20%), fibrosis and congestion in 29 (16%), extensive hepatocellular necrosis and sinusoid dilatation in 53 (29%), congestion alone was the main histological sign in 57 (31%) and hyperplastic liver nodules and sinusoid dilatation in eight patients (4%). Hepatocellular carcinoma in the explanted liver was found in three patients: one patient had cirrhosis, a second extensive fibrosis, and nodular hyperplasia was the prominent sign in the third patient. These three patients were alive at the end of the study.

Pre-LT treatment included anticoagulants in 58% of the patients (heparin 35%, coumarins in 36%, both treatments in 16% and others 3%), and diuretics in 68%. A surgical porto systemic shunt (SPSS) had been performed in 20% of the patients, a transjugular intrahepatic porto systemic shunt (TIPS) in 4%, a percutaneous angioplasty in 5%. An intravascular lysis had been done in four patients (streptokinase/urokinase or actilysis) and prostacyclin had

Table 1
Pre-OLT clinical characteristics of patients transplanted for BCS

		Patients	%
Age (years)	35.7 ± 11.5		
Sex ratio	Female	175	70.4
	Male	73	29.6
	Total	248	
Clinical presentation	Ascites	236	95
	Wasting	126	51
	Encephalopathy	84	34
	Prior variceal bleeding	72	29
	Jaundice	44	18
	Fulminant hepatic failure	47	19
AST pre-OLT (IU/L)	306 ± 825		
ALT pre-OLT (IU/L)	257 ± 629		
PT (%)	47.9 ± 20.4		
Bilirubin (µmol/L)	77 ± 116		
Renal function pre-OLT	Normal (creatinine ≤ 120 µmol/L)	161	70
	Mildly impaired (creatinine > 120 and ≤ 160 µmol/L)	29	12.6
	Severely impaired (creatinine ≥ 160 µmol/L)	29	12.6
	Dialysis	11	4.8
	Total	230	
Vein thrombosis pre-OLT	Portal vein	47	19
	Vena cava	40	16
	Other	25	10
	Total	112	
Treatment pre-OLT	Anti-vitamin K	77	31
	Heparin	67	27
	Both anticoagulants	25	10
	Surgical porto-systemic shunt	49	20
	Transjugular intrahepatic shunt	11	4.4
	Percutaneous Angioplasty	13	5.2
Delay from onset of symptoms to OLT (days)	670 ± 1156		
Delay from onset of symptoms to diagnosis (days)	222.9 ± 628		

been given in 1 case. LT was performed within 2 weeks of a shunt procedure (SPSS or TIPS) in 14 patients and within 1 month in 17 patients. In addition to occlusion of the hepatic veins, pre-LT portal vein thrombosis was present in 19% of the cases, thrombosis of the inferior vena cava in 16%, and thrombosis of other veins in 10% (inferior mesenteric vein, splenic vein, internal jugular vein, femoral vein) (Table 1).

At transplantation, the mean score described by Murad [8] was 1.86 (± 0.8) for the 151 patients in whom all variables were available (Class III, with a poor outcome, is defined by a score of 1.5 or higher): 69 in class III (47%), 76 in class II (51%) and six in class I (2%). Of the 229 patients with at least three items (92% of the series), 69 were in class III (46%), 76 in class II (50%) and nine in class I (4%) (the missing item lowering the score of the patient). The mean Murad score was 1.77 for the 48 patients with a SPSS, and 1.78 for the 10 patients receiving TIPS, and did not differ from the mean score of the remaining patients (1.96).

After a median follow-up of 48 months (SD 42 months), a total of 67 deaths (27% of the patients) were observed in this study; 33 during the first month (49%) and nine between 1 and 8 years (13%) (Fig. 1). The main causes of early deaths were sepsis and multiple organ failure (47%). Other causes were graft dysfunction or hepatic artery thrombosis (HAT) (19%), venous thrombosis (12%), cardiac complications (9%), brain damage (5%) and others (8%). Mortality

was high in patients whose transplantation was performed shortly after a SPSS or a TIPS procedure (9/14 patients within 2 weeks and 11/17 patients within 1 month: $P < 0.001$).

Thirty-seven patients were retransplanted (15%), four of them twice: 14 during the first post-transplant week for primary non-function in 13 and for HAT in one patient, 15 between the second and the 52 week due to HAT (six patients), portal vein thrombosis (three patients) and other causes (six patients), eight patients after the first year post-transplant due to chronic rejection in three, HAT in three and two for other causes. Eleven of the 37 patients

Table 2
Aetiology of Budd-Chiari syndrome

	Patients	%
Myeloproliferative syndrome	111	45
Oral contraceptives	27	11
Protein C deficiency	15	6
Factor V Leiden	10	4
Anti-phospholipid syndrome	7	3
Pregnancy or post-partum	7	3
AT III deficiency	5	2
Paroxysmal nocturnal hemoglobinuria	5	2
Others	22	9
Not determined	72	29

Total > 100% (10% of patients with two or more causes).

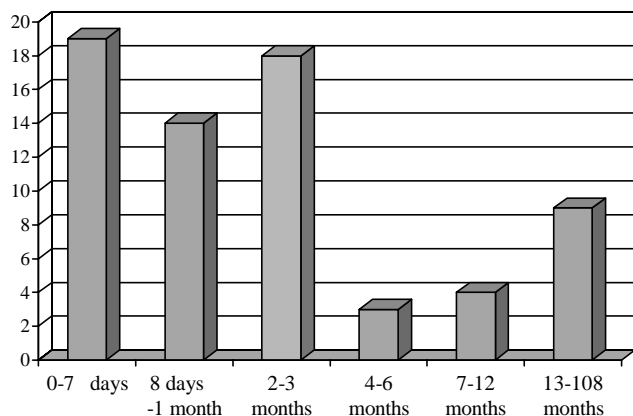


Fig. 1. Distribution of mortality after transplantation according to the date of death (67/248 patients).

retransplanted died in the first 3 months after retransplantation (37%).

For the entire series, the mean survival was 48.6 ± 42.5 months. Actuarial survival was 75.6% at 1 year, 71.4% at 5 years, and 68.0% at 10 years (Fig. 2). According to the classification of Murad [8], the 5-year survival rate was 76% in class II (115 patients) and 71% in class III (105 patients), and did not differ significantly between the two groups ($P=0.83$). Among the causes of death there were recurrence of BCS (despite anticoagulation) in four patients, one patient died of leukaemia with a myelofibrosis 7 years after LT, two deaths were unrelated to BCS (ovarian cancer at 42 months and sepsis due to recurrent cholangitis at 57 months) and the cause of two sudden deaths at home could not be ascertained. Among the nine patients dying after 1 year, seven had a myeloproliferative disease.

Two hundred patients out of 235 (85%) received anticoagulants whereas 10 patients (4%) did not. The information was missing for 11%, the majority represented by the 13 patients who died within the first postoperative day. All remaining patients received life-long anticoagulant treatment, except 10 patients in whom the cause of the BCS

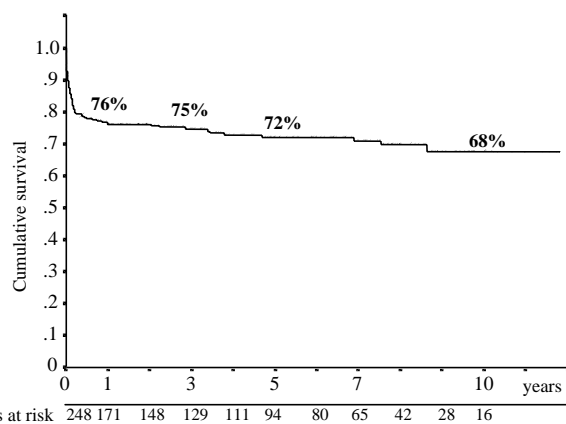


Fig. 2. Survival of the 248 patients transplanted for BCS in the study (Kaplan–Meier).

Table 3
Recurrence of vein thrombosis after OLT ($n=27$)

	Patients	%
Portal vein thrombosis	17	7
Hepatic vein thrombosis	6	2.4
Vena cava thrombosis	5	2
Others	6	2.4
Mortality after recurrence	11	40.7

Five patients had thrombosis at two or more sites.

was protein C or antithrombin III deficiency considered to have been cured by LT. Of 197 patients living longer than 3 months, 162 patients had coumarins, 18 patients had other treatments (heparin, aspirin, etc.), 10 patients had no anticoagulant treatment, and for seven patients the information was not available. Despite anticoagulants, venous thrombosis (any site) recurred in 27 patients (11%). Five patients had thrombosis at multiple sites (Table 3). Among the six patients in whom BCS recurred, one patient was successfully retransplanted (at 4 months), one was successfully treated by TIPS, and four patients died (24, 34, 56 and 104 months after LT). Of the 27 patients who had venous thrombosis after LT, 11 died (mortality 41%).

Haemorrhage attributed to anticoagulants was observed in 27 patients (11%). Two patients with intracranial bleeding died and the mortality attributed to anticoagulants was 1% (Table 4).

To assess the factors influencing survival, univariate analysis of the variables reported in Table 5 was performed. Creatinine, bilirubin, presence of SPSS/TIPS were found to influence survival and impacted on early mortality. The survival according to renal function is indicated in the Fig. 3.

Multivariate analysis showed that only pre-LT renal function and the presence of SPSS/TIPS had an independent prognostic value (Table 6).

Data of the long-term renal function after LT were available for 138 of the 151 1-year survivors (91%) at the time of the study. A normal renal function (creatinine below $120 \mu\text{mol/L}$) was documented in 75% of the patients, a mild impairment (creatinine between 120 and $160 \mu\text{mol/L}$) in 17% and a severe impairment (creatinine higher than $160 \mu\text{mol/L}$) in 8%.

Table 4
Complications of anticoagulant therapy after OLT ($n=27$)

	Patients	%
Intraperitoneal bleeding	16	7
Gastrointestinal bleeding	9	3.6
Central nervous system bleeding	2	0.8
Mortality due to bleeding	2	7.4 ^a

^a Two patients with intracranial bleeding.

Table 5
Results of univariate analysis

Factor	Values	Patients	5-year survival (%)	P
Renal function	Normal (creatinine $\leq 120 \mu\text{Mol/l}$)	161	77	0.0004
	Mildly impaired (creatinine $\leq 160 \mu\text{Mol/l}$)	29	66	
	Severely impaired (creatinine $\geq 160 \mu\text{Mol/L}$) or dialysis	40	50	
	Total	230		
Surgical shunt/TIPS	Absent	191	70	0.0174
	Present	57	58	
	Total	248		
Bilirubin	$\leq 50 \mu\text{mol/L}$	128	75	0.037
	$> 50 \mu\text{mol/L}$	96	62	
	Total	224		
Delay between diagnosis and OLT	≤ 7 days	23	52	Ns (0.073)
	> 7 days and ≤ 500 days	131	74	
	> 500 days	73	63	
	Total	227		
Underlying disease	Myeloproliferative disease	111	45	Ns (0.50)
	Not determined	72	29	
	Others	65	26	
	Total	248		
Urgency status (ELTR)	Yes	50	27	Ns (0.47)
	No	136	73	
	Total	186		
Serum ALT	$\leq 150 \text{ UI/L}$	179	75.5	Ns (0.22)
	$> 150 \text{ UI/L}$	58	24.5	
	Total	237		
Age	≤ 50 years	222	89.5	Ns (0.78)
	> 50 years	26	10.5	
	Total	248		

Emergency status: transplantation performed as an emergency according to ELTR data; TIPS, transjugular porto-systemic shunt.

5. Discussion

This study illustrates the status of LT for BCS in Europe during 12 years. The results show that, while LT in BCS was a demanding procedure, and early mortality was high, long-term outcome was excellent, whatever the underlying aetiology of the disease, with 5 and 10 years survival figures similar to liver transplantation for more common indications [10].

The population of the study, although limited to the 51 centres that answered the questionnaire and to 84% of the patients transplanted for BCS during the period of the investigation, was representative of general population suffering from BCS, as shown by a similar distribution of genders, underlying aetiologies and prevalence of cirrhosis as in other studies reporting on BCS patients treated without a liver transplant [8,11,12]. The relatively high mortality in the series concerned mainly early deaths, reflecting the complexity of LT for BCS, often performed on patients after previous medical and surgical treatments. Univariate analysis showed that a high bilirubin, a previous shunt procedure, and renal failure were significantly associated with increased mortality, and the two latter factors were confirmed on multivariate analysis. Nearly, 40% of early deaths occurred among patients who had a creatinine higher

than $160 \mu\text{mol/L}$ at the time of LT, while patients with a normal renal function did well, with a survival of 77% at 10 years. Conversely, the need of being transplanted as an emergency for the fulminant form of the disease was not a significant risk factor. The results on early outcome in our series expand on the results of previous investigations, limited by the relative rarity of BCS. [13,14].

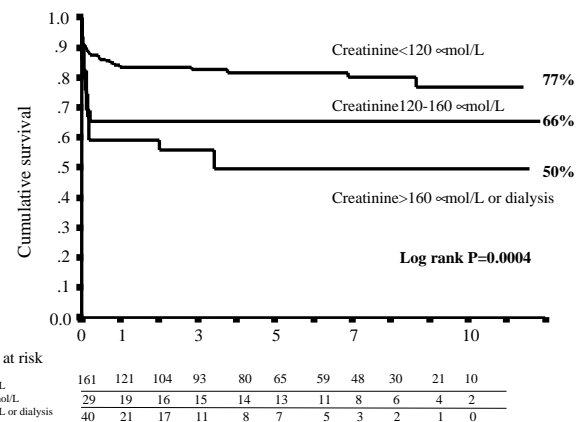


Fig. 3. Survival of patients according to renal function at transplantation: normal (serum creatinine $\leq 120 \mu\text{Mol/L}$), mildly impaired (serum creatinine $\leq 160 \mu\text{Mol/L}$), severely impaired (serum creatinine $> 160 \mu\text{Mol/L}$ or dialysis).

Table 6
Results of multivariate analysis (Cox model) *n* = 215

Factor	Patients at risk	<i>P</i>	Relative risk (95% CI)
Renal failure	154/27/34	0.002	3 (1.6–5.7)
Surgical shunt/ TIPS	162/53	0.005	2.2 (1.2–3.99)

TIPS, transjugular porto-systemic shunt.

Among the 248 patients of the study, late mortality was low. Only nine patients died after 1 year. Seven of these had a myeloproliferative disorder and five died of causes related to it (four BCS recurrences and one acute leukaemia). Although our study failed to show the impact of the underlying disease on outcome, a longer follow-up may have revealed a difference between patients with or without a myeloproliferative syndrome. Myeloproliferative disorders such as polycythaemia rubra vera are slow diseases with a rate of leukaemic transformation of 10% at 15 years and 25% at 25 years, and a nearly normal 10-year life expectancy [15]. Our study, however, shows that the slow course of myeloproliferative syndromes is not appreciably affected by transplantation, and that LT can be offered to these patients in spite of the possible negative effect in the long term. [16].

BCS recurring in a transplanted liver was described in 1983 (a 21-year-old woman who, at 1 year, discontinued anticoagulants before a biopsy) [17], and there is a consensus that anticoagulants are mandatory immediately after LT, except for patients for whom the underlying disease is cured by transplantation [18–20]. Among the 10 patients not submitted to anticoagulant treatment in the long term, a 35 year-old patient with BCS thought to be related to oral contraceptives had coumarin therapy stopped after several months. The patient suffered a pulmonary embolism 1 year post OLT, and antiphospholipid antibodies were found. Coumarin was re-instituted with an uneventful course in the past 7 years. This case exemplifies that several causes of BCS may coexist and if there is any doubt, anticoagulant treatment should be maintained after OLT. In our population, the thrombotic tendency manifested after LT in several veins (mainly portal, hepatic and caval veins), despite an apparently close monitoring of anticoagulant treatment. The balance of the adverse events was strongly in favour of anticoagulation, with a relatively low risk of death from haemorrhagic complications (two deaths in 27 patients, 7%), as opposed to a high mortality when thrombosis recurred (11 deaths in 27 patients, 41%).

One of the main issues in BCS is the indication and timing of LT as opposed to medical, radiological or surgical treatment, and how far these options should be pursued [8,21–30]. Because all the patients were transplanted (i.e. represented failures of more conservative treatments), our study can offer only indirect arguments to the discussion. Two points, however, came out strongly enough to be

considered in the balance. The first is that the overall outcome of LT was good, especially in terms of late results, and compared favourably to the results of conservative treatments reported in other studies, in particular for patients with severely impaired liver function. In this respect our study validates Murad's classification to determine when LT should be undertaken: the outcome of the 105 class III patients in the present series was better than the outcome of the 55 patients in class III of Murad's study treated without transplantation (5-year survival 71% in our study vs 42% in Murad's series) [8]. The periods of time considered in the two studies are similar (1988–1999 in the present study and 1984–2001 in Murad's study). The second point concerns survival once transplantation is performed: renal function was the most important prognostic factor of LT (while pre-transplant Murad's score was not a predictor of outcome after transplantation), suggesting that alternatives to LT should not be pursued up to the stage of renal impairment.

For patients with less severe disease—class II patients—the outcome of the two series was similar (5-year survival 76% in our study vs 74% in Murad's) showing that porto-systemic shunts or other conservative treatments offer results equivalent to LT and may be the therapies of choice in selected patients.

For this reason, and because of the specificities of our population (i.e. the shunt must have failed for our patients to come to transplantation), we warn against interpreting the increased mortality associated with a previous SPSS or TIPS in our investigation as an argument to abandon shunts as treatment options for BCS. In recent studies, TIPS was very efficient in the short term, when successfully inserted [27–29]. However, TIPS dysfunction and re-interventions were frequent, including, ultimately, liver transplantation in 10–40% of the patients [27–29]. High revision probability (47% at 1 year), transplantation and mortality (15%) figures are reported even in the most experienced centres [30]. PTFE covered stents seem to have a higher patency rate (67% at 1 year) and may be more successful in the long-term [27]. While a previous shunt procedure may complicate the operation [21], is probably dangerous for the acute form of the disease [25], and LT performed shortly after a shunt (i.e. most likely rescue transplantation) was associated to a high mortality in our study, porto-systemic shunts can offer durable remission or cure in selected patients [21–23]. It has been suggested that elective LT should be preferred to shunts when patients with the BCS have a cirrhotic liver [3,4], and our study might have shown that the results of a subsequent transplant were particularly poor in patients who had received shunt in the presence of cirrhosis. However, this information is difficult to obtain even in a prospective investigation, as the histological picture in BCS can vary markedly within the same liver. The issue of the best treatment in the individual patient should remain open.

In conclusion, this European series of 248 patients shows that LT is an effective treatment for BCS—regardless of the underlying disease—despite the complexity of the

procedure, and its relatively high early mortality. On multivariate analysis, renal failure before LT was the strongest predictor of survival, and this result should encourage considering liver transplantation early, when more conservative options are not successful, in particular when poor prognostic factors for survival without transplantation can be identified.

Acknowledgements

All contributors to the project are acknowledged in Appendix A.

Appendix A. Fifty one centres have participated to the ELTA project 'LT FOR BUDD-CHIARI: EUROPEAN STUDY 1988–1999'

- BARCELONA—Hospital Clínic I Provincial de Barcelona (Prof. Luis GRANDE); C.S.U. Bellvitge (Prof. Joan FIGUERAS, Dr Antonio RAFECAS).
- BELGRADE—KBC 'Zvezdara' (Prof. DAPCEVIC).
- BERGAMO—Ospedali Riuniti di Bergamo (Prof. Bruno GRIDELLI, Dr Marco SPADA).
- BERLIN—Charité—Humboldt Univ.-Virchow-Klinikum (Prof. Peter NEUHAUS, Dr M. STOCKMANN).
- BERN—Inselspital—Universitätsklinik Bern (Prof. M. BÜCHLER, Dr Ch. SEILER).
- BESANCON—C.H.U. Besançon (Prof. Georges MANTION).
- BIRMINGHAM—The Queen Elizabeth Hospital (Prof. Paul McMASTER, Miss Bridget GUNSON).
- BOLOGNA—S. Orsola Hospital (Prof. A. MAZZIOTTI, Dr Gian Luca GRAZI).
- BRUSSELS—Cliniques Universitaires Saint-Luc (Prof. J. OTTE, Prof. Jan LERUT).
- BUDAPEST—Semmelweis Medical University (Prof. Ferenc PERNER, Dr I. FEHERKASI).
- CAEN—C.H.U. Caen (Prof. Philippe SEGOL).
- CAMBRIDGE—Addenbrooke's Hospital (Prof. Peter FRIEND, Dr R.-K. PRASEEDOM).
- CLICHY—Hôpital BEAUJON (Prof. Jacques BELGHITI).
- COIMBRA—Hospitais da Universidade (Prof. A. LINHARES FURTADO, Prof. Rui PERDIGOTO).
- COPENHAGEN—University Hospital Copenhagen (Prof. Preben KIRKEGAARD, Dr André WETTERGREN).
- EDINBURGH—Royal Infirmary of Edinburgh (Prof. James GARDEN, Ms Rosanne BATE).
- EL PALMAR (Murcia)—Hospital Universitario « Virgen de la Arrixaca » (Prof. Francisco SÁNCHEZ BUENO).
- ERLANGEN—Chirurgische Klinik der Univ. Erlangen-Nürnberg (Prof. W. HOHENBERGER, Dr Rudolf OTT).
- GENEVE—University Hospital Geneva (Prof. Philippe MOREL, Dr Emiliano GIOSTRA).
- GÖTEBORG—Sahlgrenska Univ. Hospital/University of Göteborg (Prof. Styrbjörn FRIMAN).
- GÖTTINGEN—Georg-August-Universität Göttingen (Prof. Burckhardt RINGE).
- HAMBURG—Universitätskrankenhaus Eppendorf (Prof. Xavier ROGIERS, Dr D. BRÖRING).
- HANNOVER—Medizinische Hochschule Hannover (Prof. Jürgen KLEMPNAUER, Dr Thomas BECKER).
- HEIDELBERG—Universitätsklinikum Heidelberg (Prof. E. KLAR, Dr Gunther WEISS).
- HELSINKI—Univ. of Helsinki/Transplant. and Liver Surgery (Prof. Krister HÖCKERSTEDT).
- HUDDINGE—Huddinge University Hospital (Prof. B. ERICZON, Mr Thomas JOHANSSON).
- INNSBRUCK—C.U.K Innsbruck/Universitätsklinik für Chirurgie (Prof. Raimund MARGREITER, Dr Ruth LADURNER).
- LEIPZIG—Universitätsklinikum Leipzig (Prof. J. HAUSS).
- LIEGE—CHU Liège (Prof. M. MEURISSE, Dr P. HONORE).
- LONDON—King's College Hospital (Prof. John O'GRADY, Prof Nigel HEATON); Royal Free Hospital (Prof. A.K. BURROUGHS, Mr K. ROLLES).
- LYON—Hôpital Edouard Herriot (Prof. Olivier BOILLLOT, Dr Jérôme DUMORTIER).
- MADRID—Hospital Universitario « 12 de Octubre » (Prof. E. MORENO GONZÁLEZ, Prof. C. LOINAZ-SEGUROLA; Clínica Puerta de Hierro (Prof. J. ARDAIZ SAN MARTIN, Dr C. BARRIOS PEINADO).
- MARSEILLE—Hôpital de la Conception, Marseille (Prof. Yves Patrice LE TREUT, Dr Xavier HANNA).
- MILANO—Ospedale Maggiore di Milano (Prof. Luigi Rainero FASSATI, Dr Umberto MAGGI).
- NICE—C.H.U. Nice/Hôpital de l'Archet II (Prof. Jean GUGENHEIM).
- OSLO—The National Hospital, RIKSHOSPITALE (Prof. O. SOREIDE, Dr Kristian BJORO).
- PADOVA—Clinica Chirurgica III/University Hospital of Padova (Prof. Giorgio Enrico GERUNDA, Dr Roberto MERENDA).
- PAMPLONA—Clinica Universitaria—Universidad de Navarra (Prof. J. IGNACIO HERRERO).
- PARIS—Hôpital COCHIN (Prof. Didier HOUSSIN, Dr Jean-Marc THILLOIS); Hôpital Saint-Antoine (Prof. P. BALLADUR, Pr. O. CHAZOUILLE); Hôpital Henri Mondor (Créteil) (Prof. Daniel CHERQUI).
- ROTTERDAM—University Hospital Rotterdam (Prof. SW. SCHALM, S. de RAVE).
- SANTANDER—Hospital Universitario « Marques de Valdecilla » (Prof. Luis Antonio HERRERA).
- STRASBOURG—Hôpital de Hautepierre (Prof. Daniel JAECK, Prof. Philippe WOLF).

- TOULOUSE—C.H.U. Toulouse (Rangueil) (Prof. Gilles FOURTANIER).
- VILLEJUIF—Hôpital Paul Brousse (Prof. Henri BISMUTH, Dr Vincent KARAM).
- WIEN—Universitätsklinik AKH Wien (Prof. F. MUEHLBACHER, Dr S. RASUOL-ROCK-ENSCHAUB).
- WURZBURG—Chirurgische Univ. Würzburg (Prof. W. TIMMERMANN).

Appendix B. The questionnaire

The items of the questionnaire can be summarized as follows: age, sex, dates of transplantation, of retransplantation, of death, and of the last outpatient visit, patient's current activities, cause of death or retransplantation.

Questions on the clinical presentation at onset of the disease included: interval from clinical symptoms to diagnosis of BCS, presence of ascites, wasting or encephalopathy, history of bleeding, and history of fulminant hepatitis-like presentation.

Questions on the histology before LT included a description of the diagnosis, presence of cirrhosis and the method by which histology was obtained: (percutaneous, transjugular, or surgical liver biopsy during LT).

List of underlying disease included myeloproliferative syndromes, anti-thrombin III-, protein C- or protein S-deficiency, presence of a membranous web, treatment with oral contraceptives, other or not determined causes.

Questions on pre-LT treatment concerned the use of anticoagulants (anti-vitamin K, heparin), diuretics, surgical porto-systemic shunts (SPSS), trans jugular porto systemic shunts (TIPS), percutaneous angioplasty, or others. The timing of the pre-LT treatment was also included.

Tests of the liver function (AST, ALT, albumin, bilirubin, prothrombin time) were given pre-LT, in the early period (<3 months), at the first year after LT and in the long term. At the same time marks, renal function was defined as normal (creatinine less than 120 $\mu\text{mol/L}$), mildly impaired (creatinine 120–160 $\mu\text{mol/L}$), severely impaired (creatinine more than 160 $\mu\text{mol/L}$), or patient on dialysis.

In case of a post-LT liver biopsy, the date and the results were asked.

Question on vein thrombosis included the site (hepatic veins, portal vein, vena cava or others), and where and when the thrombosis recurred after LT, during the early period (<3 months), the first year or in the long term and whether with or without anticoagulants, the type of anticoagulants. The time and pattern of disease recurrence were also asked.

The post-LT complications were defined as: variceal hemorrhage, intra-abdominal bleeding, other bleeding, infection, acute or chronic rejection, surgical complications (artery, biliary tract, portal vein or others) and others.

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