# Novel Composite Endpoint for Assessing Outcomes in Liver Transplantation: Arterial and Biliary Complication–Free Survival

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# Novel Composite Endpoint for Assessing Outcomes in Liver Transplantation: Arterial and Biliary Complication–Free Survival

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**Transplant and patient survival are the validated endpoints to assess the success of liver transplantation (LT). This study evaluates arterial and biliary complication–free survival (ABCFS) as a new metric. ABC, considered as an event, was an arterial or biliary complication of Dindo-Clavien grade ≥III complication dated at the interventional, endoscopic, or surgical treatment required to correct it. ABCFS was defined as the time from the date of LT to the dates of first ABC, death, relisting, or last follow-up (transplant survival is time from LT to repeat LT or death). Following primary whole LT (n = 532), 106 ABCs occurred and 99 (93%) occurred during the first year after LT. An ABC occurring during the first year after LT (overall rate 19%) was an independent factor associated with transplant survival (hazard ratio [HR], 3.17; $P < 0.001$) and patient survival (HR, 2.7; $P = 0.002$) in univariate and multivariate analyses. This result was confirmed after extension of the cohort to split-liver graft, donation after circulatory death, or re-LT (n = 658). Data from 2 external cohorts of primary whole LTs (n = 249 and 229, respectively) confirmed that the first-year ABC was an independent prognostic factor for transplant survival but not for patient survival. ABCFS was correlated with transplant and patient survival ($\rho = 0.85$ [95% CI, 0.78-0.90] and 0.81 [95% CI, 0.71-0.88], respectively). Preoperative factors known to influence 5-year transplant survival influenced ABCFS after 1 year of follow-up. The 1-year ABCFS was indicative of 5-year transplant survival. ABCFS is a reproducible metric to evaluate the results of LT after 1 year of follow-up and could serve as a new endpoint in clinical trials.**

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Patient and transplant survival are currently the only well-validated endpoints to assess the success of liver transplantation (LT). They have been used in research and quality reporting to evaluate the results of LT and to compare transplant center performance.[1,2] Because 5-year graft and patient survival following LT have continuously improved, reaching more than 80% and 90%, respectively, for many patients with end-stage liver disease,[3,4] the rates of events such as repeat LT (re-LT) or death are now lower. Hence, long-term survival is no longer a satisfactory primary endpoint to evaluate the success of LT. Although the survival rate after LT remains

*Abbreviations: ABC, arterial or biliary complication (as event); ABCFS, arterial or biliary complication–free survival; ALF, acute liver failure; BAR, balance of risk; CI, confidence interval; CT, computerized tomography; DCD, donation after circulatory death;*

robust, a large number of patients would today be needed to demonstrate positive effects on transplant or patient survival with this criterion. Other metrics including their refinements focus on donor quality,[5] donor–recipient matching,[6,7] or graft recovery.[8-12] A recent publication measured symptomatic nonanastomotic biliary strictures at 6 months after LT as the endpoint.[13] The sum of postoperative complications may be calculated by the comprehensive complication index.[14]

In parallel, to match need and graft offers, many centers have been transplanting "higher-risk" liver grafts, including living donation, donation after circulatory arrest, fatty livers, split-liver grafts, domino grafts, and grafts from donors who are hepatitis C virus or hepatitis B virus positive, in LT candidates who are sicker. The issue thus arises of how to assess these strategies in terms of mid-term and long-term survival.[15]

The concept of surrogacy has been widely studied in oncology. Progression-free survival and disease-free survival are among the best studied, validated, and generally accepted surrogate endpoints for overall survival in solid cancer.[16,17] Clearly, such surrogates are needed in the fields of LT as described by Richards et al.[15] We developed a composite time-dependent metric named arterial and biliary complication–free survival (ABCFS).[18] ABCFS took into account (1) arterial or biliary complications, which remain high during the first year after LT,[14] are specific to the LT, and later result in several hospital readmissions[19]; (2) re-LT; and (3) death. The aim of this study was to validate ABCFS as a new metric to evaluate results in LT.

*EAD, early allograft dysfunction; ERCP, endoscopic retrograde cholangiopancreatography; ET-DRI, Euro-transplant donor risk index; HMN, Henri Mondor Hospital; HR, hazard ratio; HTK, histidine tryptophan ketoglutarate; HUB, Hospital Universitari de Bellvitge; ICU, intensive care unit; IGL-1, Institute Georges Lopez-1; IQR, interquartile range; KMP%, Kaplan-Meier curve probability percentage at 12 months; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRCP, magnetic resonance cholangiopancreatography; $P_{cl}$, P value of the test of the class compared with the reference class (robust Wald test); PSL, Pitié-Salpêtrière Hospital; re-LT, repeat liver transplantation; SCOT 15, solution of conservation for organ transplantation; UW, University of Wisconsin.*

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# Patients and Methods

## STUDY DESIGN

The aim of the study was to evaluate whether a composite endpoint, namely ABCFS for patients who have undergone LT, may be considered as an acceptable indicator for transplant survival. For this to be so, 2 conditions must be met. The first is that ABCFS and transplant survivals are well correlated. The second is external validation of these results in another cohort of patients who received transplants. The study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of Pitié-Salpêtrière Hospital (PSL). No informed consent was needed because the data from all of the centers were anonymized.

## PATIENTS

The first cohort (PSL cohort) included all consecutive adult patients who had undergone primary brain-dead, deceased donor, liver-only transplantation between January 2008 and December 2017 at a single French LT center (PSL, Paris, France). This PSL cohort was used to develop the statistical analysis (Fig. 1). The statistical analysis was extended to split-liver grafts, re-LT, domino, and types 2 and 3 donation after circulatory death (DCD) to validate results. We note that every DCD had normothermic regional perfusion. The external validation cohorts included all patients from 2 European LT centers who had undergone primary transplantation from brain-dead deceased donors between 2011 and 2015 (Henri Mondor Hospital [HMN], Créteil, France, and Hospital Universitari de Bellvitge [HUB], Barcelona, Spain). These 2 cohorts were used to validate the composite endpoint.

Patients with multiorgan transplantations were excluded from the analysis. All of the patients who died intraoperatively were also excluded from the analysis because they were not exposed to postoperative

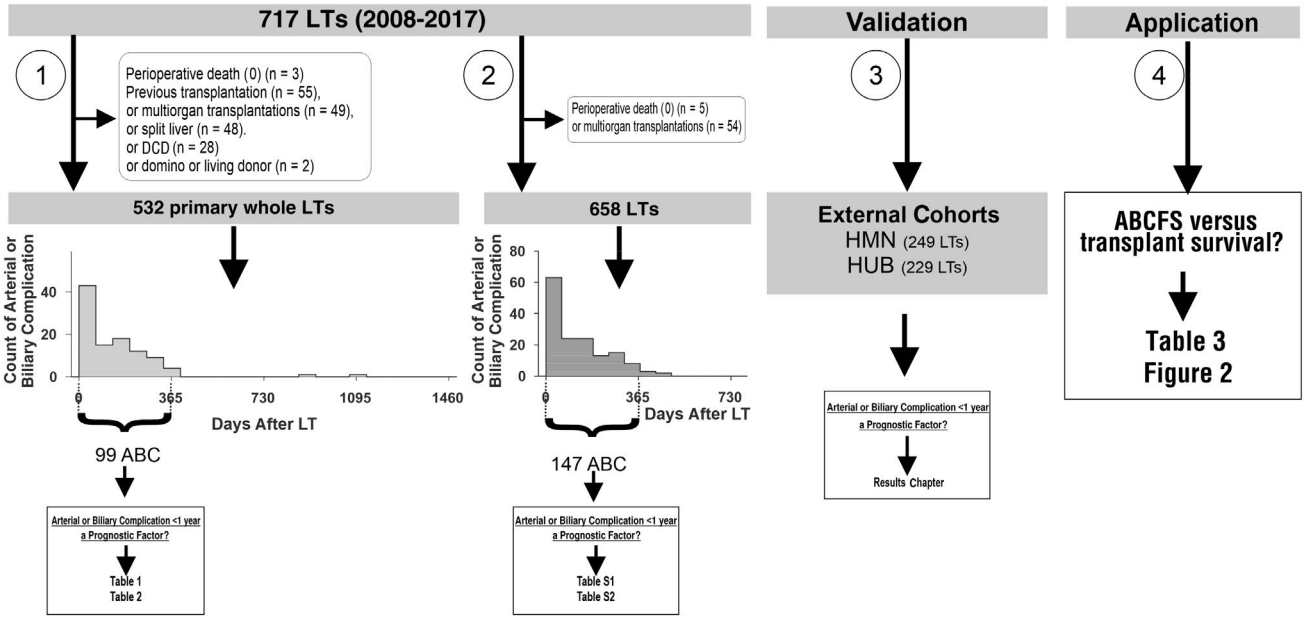


**FIG. 1.** Scheme describing the step-by-step statistical analysis. Arterial or biliary complication during the first year after LT was tested as a prognostic factor of transplant survival in a homogeneous cohort of LT (step 1), in an extended cohort (step 2), and in 2 external cohorts (step 3). Consequently, ABCFS could be compared with the transplant survival (step 4). Every LT from DCD (types 2 and 3) included normothermic regional circulation.

complications. No organs from executed prisoners were used. Urgent LTs were included.

## DATA SOURCE

Data used for the first cohort were obtained from the prospectively maintained database SCD/PromeTHée, registered at the Commission Nationale Informatique et Libertés (no. 1929196). This database was prospectively maintained by liver surgeons, hepatologists, and LT coordination nurses. Supplementary data, when needed, were retrieved from the prospective French national database CRISTAL (managed by the French Regulatory Agency for Transplantation). Hospital lengths of stay were extracted from the management hospital database (P.R.). These data are available on request from the corresponding author (E.S.). Data used for the second cohort were obtained from each center's prospectively maintained database. These data are available on request from the 2 senior authors (L.L. and D.A.).

## OUTCOME DEFINITIONS

Postoperative complications included all postoperative medical and surgical complications, graded according to the Dindo-Clavien classification.[20] Severe complications were defined as Dindo-Clavien class III complications. Primary nonfunction was defined as early graft failure leading to either recipient death within the first 7 days or re-LT in the absence of any vascular complications.[21] Early allograft dysfunction (EAD) was defined according to the definition of Olthoff et al.[8] Acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[22]

## DEFINITION OF ARTERIAL AND BILIARY COMPLICATIONS

An arterial or biliary complication (ABC) was considered as an event defined by the following 2 parameters: (1) any arterial or biliary complication (arterial, between the aorta and the small arteries of the graft; biliary, between the biliary canaliculi and the intestinal stream; ie, Y loop included) of class ≥III according to the Dindo-Clavien classification[20]; and (2) the date of the interventional, endoscopic, or surgical treatment performed to correct this complication and so prevent graft loss by re-LT or death of the patient (Table 1). Failure of the treatment or iatrogenic consequences were taken into account (Table 1). Some patients had multiple ABCs

**TABLE 1. Examples and Counterexamples of ABC**

| Diagnosis | Therapeutic Act | Dindo-Clavien | Arterial or Biliary Disorder | Risk of Graft Loss or Patient Death | ABC | Comment |
|---|---|---|---|---|---|---|
| *Simple or linear examples* | | | | | | |
| Arterial stenosis described by sonography or CT scanner | Angiography immediately followed by angioplasty or stent | IIIa | Yes | Yes | Yes | High risk of arterial thrombosis and consequently of graft loss |
| Abnormal blood liver test leading to the diagnosis of biliary stenosis on sonographic exam | ERCP and endoscopic retrograde stenting | IIIb | Yes | Yes | Yes | High risk of chronic cholestatic disease and consequently of graft loss |
| Choleperitoneum after T-tube removal | Percutaneous or coelioscopic or surgical drainage | IIIb | Yes | Yes | Yes | Biliary complication (leakage) severe enough (localized abcess or diffused peritonitis) to decide an interventional treatment because of the risk of patient death |
| Stone in the main bile duct | ERCP | IIIb | Yes | Yes | Yes | Risk of chronic cholestatic disease or septicemia, graft loss, and patient death |
| Disseminated cholangiopathy | Relisting | IVa | Yes | Yes | Yes | Were other treatments or invasive procedures attempted before deciding the relisting? If yes, the date of arterial or biliary complication was the date of this treatment |
| Complex or nonlinear examples | | | | | | |
| False aneurysm described by sonography or CT scanner | Angiography: absence of aneurysm but large anastomotic area | IIIa | No | No | No | Absence of arterial disorder; no risk of graft loss |
| Arterial stenosis or thrombosis on CT scanner | Antiplatelet agent | II | Yes | Yes | No | Long-term survival after arterial thrombosis is possible |
| Ischemic cholangiopathy or liver abscess following arterial thrombosis | Relisting but without re-LT several months later | IVa | Yes | Yes | Yes | Complication was severe enough to decide relisting; the time elapsed from relisting to re-LT does not affect ABCFS |
| Presence of bile in the abdominal drain few days following LT | No treatment; observation | I | Yes | No | No | Absence of therapeutic act; risk of graft loss nonpredictable; absence of treatment means that the risk of graft loss was estimated as negligible |
| Choleperitoneum after T-tube removal | Analgesic, antibiotic, parenteral nutrition | II | Yes | Yes | No | Biliary complication not severe enough (class II) to be an arterial or biliary complication |
| Absence of anomaly on the retrograde cholangiography with sphincterotomy. Acute pancreatic following ERCP | Multiple organ failure | IVa | Yes | Yes | Yes | A wrong diagnosis of biliary anomaly may lead to a real complication with a risk of patient death; a sphincterotomy is a biliary anomaly; failure of the treatment or iatrogenic consequences are taken into account in arterial or biliary complication definition |

**TABLE 2. Examples of ABCs in Patients With Disseminated Cholangiopathy**

| Example | Time to Complication (days) | Short Description of the Complication, Its Treatment, and Dindo-Clavien Class (Grades I to V) | ABC | Complication Type: Arterial or Biliary | Biliary Complication Type |
|---|---|---|---|---|---|
| Patient 1 | 49 | Hemobilia, false aneurysm on CT scan → stent (IIIb) | Yes (first chronological ABC) | Arterial | |
| | 699 | Liver abscess + arterial thrombosis → percutaneous drainage (IIIb) | Yes | Biliary | Disseminated cholangiopathy |
| Patient 2 | 66 | Arterial stenosis → angioplasty (IIIb) | Yes (first chronological ABC) | Arterial | |
| | 508 | Arterial thrombosis → angiography → medical treatment (II) | No | Arterial | |
| | 623 | MRCP: ischemic cholangiopathy → medical treatment (II) | No | Biliary | Disseminated cholangiopathy |
| Patient 3 | 1981 | Liver abcess → percutaneous drainage (IIIb) | Yes (first chronological ABC) | Biliary | Disseminated cholangiopathy |
| | 2004 | Arterial thrombosis → relisting (IVa) | Yes | Arterial | |
| Patient 4 | 133 | Biliary anastomotic stricture → endoscopic stenting (IIIb) | Yes (first chronological ABC) | Biliary | Anastomotic stricture |
| | 153 | ERCP → distal cholangiopathy → endoscopic stenting (IIIb) | Yes | Biliary | Disseminated cholangiopathy |
| | 200 | Cachexia → relisting → death before re-LT (V) | Yes | Biliary | Disseminated cholangiopathy |
| Patient 5 | 187 | Biliary anastomotic stricture → ERCP: failure of the stenting (IIIb) | Yes (first chronological ABC) | Biliary | Supra-anastomotic stricture |
| | 194 | ERCP: supra-anastomotic stricture → stent (IIIb) | Yes | Biliary | Supra-anastomotic stricture |
| | 247 | ERCP: supra-anastomotic stricture → stent (IIIb) | Yes | Biliary | Disseminated cholangiopathy |
| | 305 | ERCP: diffuse cholangiopathy → relisting (IVa) | Yes | Biliary | Disseminated cholangiopathy |
| Patient 6, LT no. 2 | 163 | Angiocholitis + multiple organ failure → medical treatment in ICU (II) | No | Biliary | Disseminated cholangiopathy |
| | 164 | Angioscanner → angiography (IIIb) → arterial stenosis → medical treatment | Yes (first chronological ABC) | Arterial | Disseminated cholangiopathy |
| | 181 | Angiocholitis → percutaneous drainage then angiography → angioplasty (IIIb) | Yes | Biliary | Disseminated cholangiopathy |
| | 190 | Angiocholitis → multiple organ failure → death (V) | Yes | Biliary | Disseminated cholangiopathy |
| Patient 7 | 256 | Arterial stenosis → angioplasty (IIIb) | Yes (first chronological ABC) | Arterial | |
| | 1023 | Biliary stones + anastomotic stricture → hepatico-jejunostomy (IIIb) | Yes | Biliary | Anastomotic stricture |
| | 1269 | Angiocholitis → cholangiopathy → relisting (IVa) | Yes | Biliary | Disseminated cholangiopathy |
| Patient 8, type 2 DCD | 126 | Anastomotic stricture → surgical repair (IIIb) | Yes (first chronological ABC) | Biliary | Anastomotic stricture |
| | 173 | Ischemic cholangiopathy → relisting (not performed 8 years later) (IVa) | Yes | Biliary | Disseminated cholangiopathy |
| | 1407 | Predominance of left biliary tree injury → left hepatectomy (IIIb) | Yes | Biliary | Disseminated cholangiopathy/ supra-anastomotic stricture |

(Table 2). For statistical analysis, only the first chronological posttransplant ABC was retained. Subsequent complications were recorded but not used for the statistical analysis (Table 2; Supporting Fig. 1).

ABCFS was defined as the time from transplantation to the date of ABC treatment (ie, interventional endoscopic or surgical), death from any causes, relisting date, or last follow-up. In the case of re-LT, the date of relisting on the waiting list was retained and not the date of re-LT (Tables 1 and 2).

Patient survival was defined as the time from transplantation to the date of death or last follow-up. Transplant survival was the time from transplantation to the date of death, re-LT, or last follow-up.[15]

## PERIOPERATIVE MANAGEMENT AND FOLLOW-UP

Peritransplant follow-up was homogeneous across centers and included at least a daily liver function test assessment and Doppler ultrasonography until postoperative day 7. Long-term follow-up included liver function tests and Doppler ultrasonography every week for 1 month, every 3 months for the first 12 months, and thereafter every 6 months.

## STATISTICAL ANALYSIS

Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as medians (25%-75% interquartile range [IQR]). The chi-square test or 2-sided Fisher's exact test was used for qualitative variables, and the Student *t* test or Mann-Whitney U test was used for quantitative variables. Survival rates were estimated by the Kaplan-Meier curve method and compared using the log-rank test. As the variable ABC during the 12 months following transplantation (first-year ABC) was time dependent, we used the robust score test in the Cox proportional hazards model. Multivariate analysis was performed with a Cox proportional hazards model and tested with the robust score test in ascending steps with a *P* value at 5%.

Correlation factor (ρ) was obtained by the method of Schemper et al.[23] Survival rates and correlations included every arterial or biliary complication, graft loss, or death within 60 months.

All variables with $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SigmaStat version 12.0 (Systat Software Inc., Erkrath, Germany) and R program version 3.3.3 software (R Foundation for Statistical Computing, Vienna, Austria).

# Results

## OVERVIEW OF THE FIRST COHORT

Of 717 consecutive LTs performed in 662 patients, 185 did not meet the inclusion criteria. The PSL cohort thus included 532 patients who had undergone primary brain-dead, deceased donor LT using whole liver grafts. The characteristics of recipients and donors are detailed in Supporting Table 1. The flowchart and step-by-step analysis are shown in Fig. 1.

## MORBIDITY

The overall morbidity rate was 41%, and the severe morbidity rate (Dindo-Clavien grade ≥III) was 35%. Almost half of the complications (44%) occurred within the first 3 months, but 3 months after LT, most of the complications were classified as Dindo-Clavien class III, and ABC was the most frequent cause of Dindo-Clavien grade ≥III complications (Supporting Fig. 1B).

## ABC

Overall, a total of 260 ABCs occurred in 106 patients. The mean count of ABCs per patient was 2.3 ± 1.5 (67% had ≤2 ABCs, 24% had between 3 and 4 ABCs, 6% between 5 and 6 ABCs, and 3% of patients had >6 ABCs). The vast majority of patients (93%) experienced the first ABC within the first 12 months after LT (global rate of ABC at 12 months = 18.6%). The median time before occurrence of the first ABC was 116 (IQR, 34-242) days. The median time before occurrence of the first biliary complication was longer than that for the first arterial complication (132 [IQR, 41-26] days versus 54 [IQR, 30-144] days; $P = 0.01$). Details of the 99 ABC occurring during the first 12 months after LT are shown in Supporting Table 2.

## IMPACT OF FIRST-YEAR ABC ON TRANSPLANT AND PATIENT SURVIVAL AND HOSPITAL LENGTH OF STAY

The effect of the first-year ABC (n = 99) on transplant and patient survival was tested in univariate and multivariate analyses (Tables 3 and 4). Model for End-Stage Liver Disease (MELD) score, balance

of risk (BAR) score, tumor on explant, cold ischemia time, EAD, and ABC influenced transplant and patient survival significantly. The same factors influenced patient survival except for cold ischemia time. For ABC, the hazard ratio (HR) for transplant survival was 3.17 (95% confidence interval [CI], 2.00-5.04; $P < 0.001$) and 2.70 (95% CI, 1.65-4.41; $P < 0.001$) for patient survival. In the multivariate analysis, first-year ABC HR was the highest compared with other HRs of factors associated with the survival, that is, MELD score, EAD, or tumor on explant (Tables 3 and 4). Including split-liver graft, re-LT, and normothermic regional perfusion DCD, an ABC occurring before 1 year after LT was significantly associated with a graft loss in univariate and multivariate analyses. Again, ABC had the highest HR compared with other factors associated with the transplant survival (HR, 2.12; $P < 0.001$; Supporting Table 3). First-year ABC was significantly associated with patient survival, but HR was not the highest compared with other factors (HR, 1.65; Supporting Table 4).

To estimate the impact on a patient's life, we recorded total hospital length of stay during the first year after LT for patients with a follow-up of more than 12 months. In the absence of ABC, total length of stay was 29 (IQR, 20-49) days versus 45 (IQR, 32-77) days in the presence of ABC ($P < 0.001$).

## ABCFS, TRANSPLANT SURVIVAL, AND PATIENT SURVIVAL

In the PSL cohort, the 1-year, 3-year, and 5-year transplant survival rates were 89%, 80%, and 74%, respectively, and the 1-year, 3-year, and 5-year patient survival rates were 90%, 82%, and 78% (Fig. 2, PSL). The 1-year, 3-year, and 5-year ABCFS rates were 72%, 67%, and 61%, respectively (Fig. 2, PSL).

There was a strong correlation between transplant survival and ABCFS ($\rho = 0.85$ [95% CI, 0.78-0.90] and between patient survival and ABCFS ($\rho = 0.81$ [95% CI, 0.71-0.88]). We compared the probability of survival at 1 year following LT using transplant survival or ABCFS. With ABCFS, significant differences were observed for age of donor (aged ≤65 or >65 years), preservation solution (UW, SCOT 15, IGL-1, histidine tryptophan ketoglutarate [HTK]), Euro-transplant donor risk index (ET-DRI; ≤1.5 or >1.5), EAD and BAR score, although transplant survival showed differences for EAD and BAR score only (Table 5).

## VALIDATION OF THE ABCFS IN THE EXTERNAL COHORTS

We compared the PSL cohort to 2 external cohorts from HMN and HUB. Donors of the PSL cohort were younger ($P < 0.001$) with lower ET-DRIs ($P < 0.001$) than those of the HMN cohort. Recipients had higher MELD scores ($P < 0.001$) and lower 3-month mortality ($P = 0.02$) and re-LT rates ($P = 0.001$; Table 6). The overall rate of ABC at 12 months was similar between the PSL and HMN cohorts (23% versus 17%).

Donors of the PSL cohort had lower ET-DRIs ($P < 0.001$) than those of the HUB cohort. Recipients were more frequently hospitalized in the intensive care unit (ICU) at the time of LT ($P < 0.001$) with higher BAR ($P < 0.001$) and MELD scores ($P < 0.001$) and lower 3-month re-LT rates ($P = 0.02$; Table 6). The overall rate of ABC at 12 months was similar between the PSL and HUB cohorts (18.6% versus 16.6%).

For graft or patient survival, the transplant center had no effect (interaction test not shown). First-year ABC was associated with transplant survival in all 3 cohorts (HMN: HR, 2.41 [95% CI, 1.23-4.70; $P = 0.036$]; HUB: HR, 4.89 [95% CI, 2.41-9.92; $P = 0.001$]; PSL: HR, 3.17 [95% CI, 1.10-5.04; $P < 0.001$]). However, 1-year ABC was associated with patient survival in the PSL cohort only (HMN: HR, 1.01 [95% CI, 0.42-2.86; $P = 0.85$]; HUB: HR, 1.16 [95% CI, 0.48-2.8; $P = 0.76$]; PSL: HR, 2.7 [95% CI, 1.65-4.41; $P = 0.002$]).

In the HMN cohort, the 1-year, 3-year, and 5-year transplant survival rates were 87%, 84%, and 81%, respectively, and the 1-year, 3-year, and 5-year patient survival rates were 95%, 92%, and 88%, respectively (Fig. 2 ,HMN). The 1-year, 3-year, and 5-year ABCFS rates were 73%, 71%, and 67% (Fig. 2, HMN).

In the HUB cohort, the 1-year, 3-year, and 5-year transplant survival rates were 86%, 80%, and 75%, respectively, and the 1-year, 3-year, and 5-year patient survival rates were 90%, 85%, and 82%, respectively (Fig. 2, HUB). The 1-year, 3-year, and 5-year ABCFS rates were 73%, 69%, and 66%, respectively (Fig. 2, HUB). Interestingly, we observed that the 1-year ABCFS rate was close to the 5-year transplant survival rate in all 3 cohorts.

# Discussion

The definition of a successful transplantation should be not only whether a patient will live for a long time

**TABLE 3. Factors Associated With Transplant Survival (532 Primary Whole LTs)**

| | | Univariate Analysis | | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|---|---|
| Covariate | Class | HR | 95% CI | $P_{cl}$ Value | *P* Value† | HR | 95% CI | *P* Value‡ |
| Donor | | | | | | | | |
| Sex | Female | 1.00 | | | 0.87 | | | |
| | Male | 0.97 | 0.67-1.41 | 0.87 | | | | |
| Age, years | ≤65 | 1.00 | | | 0.12 | | | |
| | >65 | 1.37 | 0.94-1.99 | 0.11 | | | | |
| BMI, kg/m² | ≤25 | 1.00 | | | 0.31 | | | |
| | [25;30] | 1.14 | 0.75-1.73 | 0.54 | | | | |
| | >30 | 1.58 | 0.93-2.69 | 0.09 | | | | |
| ET-DRI | ≤1.5 | 1.00 | | | 0.08 | | | |
| | >1.5 | 1.40 | 0.95-2.05 | 0.086 | | | | |
| Preservation solution | Celsior | 1.00 | | | 0.56 | | | |
| | HTK | 1.58 | 0.72-3.47 | 0.25 | | | | |
| | IGL-1 | 1.06 | 0.51-2.2 | 0.89 | | | | |
| | SCOT 15 | 1.42 | 0.73-2.76 | 0.31 | | | | |
| | UW | 1.08 | 0.46-2.53 | 0.85 | | | | |
| Recipient | | | | | | | | |
| Sex | Female | 1.00 | | | 0.35 | | | |
| | Male | 1.25 | 0.76-2.04 | 0.38 | | | | |
| Age, years | ≤65 | 1.00 | | | 0.68 | | | |
| | >65 | 0.90 | 0.54-1.5 | 0.70 | | | | |
| BMI, kg/m² | ≤25 | 1.00 | | | 0.44 | | | |
| | [25;30] | 1.31 | 0.87-1.98 | 0.20 | | | | |
| | >30 | 1.06 | 0.62-1.81 | 0.82 | | | | |
| Status at LT | Home | 1.00 | | | 0.38 | | | |
| | Hospital or ICU | 1.19 | 0.81-1.75 | 0.37 | | | | |
| MELD | ≤35 | 1.00 | | | 0.01 | 1.00 | | 0.03 |
| | >35 | 1.97 | 1.25-3.11 | 0.003 | | 1.92 | 1.15-3.2 | |
| BAR score | ≤18 | 1.00 | | | 0.01 | | | |
| | >18 | 2.65 | 1.49-4.73 | 0.001 | | | | |
| Tumor on explant | No | 1.00 | | | 0.03 | 1.00 | | 0.002 |
| | Yes | 1.57 | 1.06-2.31 | 0.02 | | 1.94 | 1.29-2.93 | |
| Intraoperative data | | | | | | | | |
| Cold ischemia time | ≤9 hours | 1.00 | | | 0.048 | | | |
| | >9 hours | 1.70 | 1.07-2.68 | 0.02 | | | | |
| Biliary drainage | No | 1.00 | | | 0.96 | | | |
| | Yes | 1.01 | 0.65-1.57 | 0.96 | | | | |
| Postoperative data | | | | | | | | |
| ABC at 1 year* | No | 1.00 | | | <0.001 | 1.00 | | <0.001 |
| | Yes | 3.17 | 2-5.04 | <0.001 | | 3.04 | 1.89-4.89 | |
| EAD | No | 1.00 | | | <0.001 | 1.00 | | 0.003 |
| | Yes | 2.02 | 1.36-3 | <0.001 | | 1.88 | 1.24-2.85 | |
| Acute kidney injury | No | 1.00 | | | 0.62 | | | |
| | Yes | 1.11 | 0.73-1.69 | 0.62 | | | | |

*Taking into account the time to onset of the complication.
†*P* value of the test of the prognostic role of the variable (robust score test).
‡*P* value of the test of the prognostic role of the variable (robust score test) adjusted on the other covariates.

**TABLE 4. Factors Associated With Patient Survival (532 Primary Whole LTs)**

| | | Univariate Analysis | | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|---|---|
| Covariate | Class | HR | 95% CI | $P_{cl}$ Value | *P* Value† | HR | 95% CI | *P* Value‡ |
| Donor | | | | | | | | |
| Sex | Female | 1.00 | | | 0.74 | | | |
| | Male | 0.93 | 0.63-1.39 | 0.73 | | | | |
| Age, years | ≤65 | 1.00 | | | 0.07 | | | |
| | >65 | 1.47 | 0.98-2.2 | 0.06 | | | | |
| BMI, kg/m² | ≤25 | 1.00 | | | 0.23 | | | |
| | [25;30] | 1.13 | 0.72-1.77 | 0.60 | | | | |
| | >30 | 1.73 | 0.99-3.02 | 0.05 | | | | |
| ET-DRI | ≤1.5 | 1.00 | | | 0.39 | | | |
| | >1.5 | 1.19 | 0.8-1.79 | 0.39 | | | | |
| Preservation solution | Celsior | 1.00 | | | 0.41 | | | |
| | HTK | 1.67 | 0.74-3.75 | 0.22 | | | | |
| | IGL-1 | 0.95 | 0.43-2.07 | 0.89 | | | | |
| | SCOT 15 | 1.41 | 0.7-2.83 | 0.34 | | | | |
| | UW | 1.08 | 0.45-2.61 | 0.86 | | | | |
| Recipient | | | | | | | | |
| Sex | Female | 1.00 | | | 0.63 | | | |
| | Male | 1.13 | 0.68-1.87 | 0.64 | | | | |
| Age, years | ≤65 | 1.00 | | | 0.78 | | | |
| | >65 | 1.08 | 0.64-1.8 | 0.77 | | | | |
| BMI, kg/m² | ≤25 | 1.00 | | | 0.77 | | | |
| | [25;30] | 1.18 | 0.75-1.83 | 0.47 | | | | |
| | >30 | 1.03 | 0.59-1.81 | 0.92 | | | | |
| Status on the waiting list | Home | 1.00 | | | 0.19 | | | |
| | Hospital or ICU | 1.32 | 0.88-1.98 | 0.17 | | | | |
| MELD | ≤35 | 1.00 | | | 0.01 | 1.00 | | 0.01 |
| | >35 | 2.05 | 1.28-3.28 | 0.003 | | 2.17 | 1.28-3.7 | |
| BAR score | ≤18 | 1.00 | | | 0.007 | | | |
| | >18 | 3.08 | 1.73-5.49 | <0.001 | | | | |
| Tumor on explant | No | 1.00 | | | 0.01 | 1.00 | | <0.001 |
| | Yes | 1.75 | 1.16-2.66 | 0.008 | | 2.2 | 1.42-3.41 | |
| Intraoperative data | | | | | | | | |
| Cold ischemia time | ≤9 hours | 1.00 | | | 0.20 | | | |
| | >9 hours | 1.44 | 0.87-2.39 | 0.16 | | | | |
| Biliary drainage | No | 1.00 | | | 0.75 | | | |
| | Yes | 1.08 | 0.68-1.7 | 0.74 | | | | |
| Postoperative data | | | | | | | | |
| ABC at 1 year* | No | 1.00 | | | 0.002 | 1.00 | | 0.003 |
| | Yes | 2.70 | 1.65-4.41 | <0.001 | | 2.59 | 1.57-4.27 | |
| EAD | No | 1.00 | | | 0.01 | 1.00 | | 0.04 |
| | Yes | 1.72 | 1.13-2.6 | 0.01 | | 1.57 | 1.01-2.44 | |
| Acute kidney injury | No | 1.00 | | | 0.93 | | | |
| | Yes | 1.02 | 0.65-1.6 | 0.93 | | | | |

*Taking into account the time to onset of the complication.
†*P* value of the test of the prognostic role of the variable (robust score test).
‡*P* value of the test of the prognostic role of the variable (robust score test) adjusted on the other covariates.

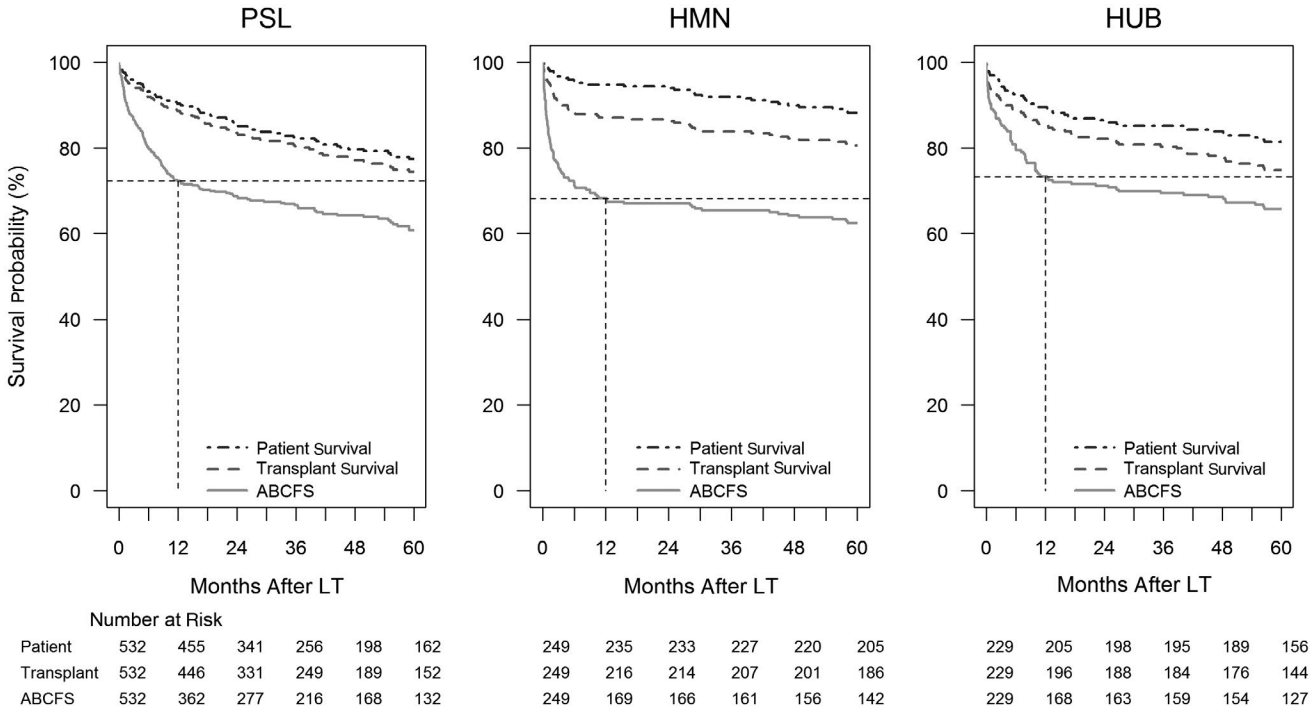


**FIG. 2.** Survival curves in the 3 cohorts: PSL, 2008 to 2017; HMN, 2011 to 2015; HUB, 2011 to 2015.

but also what the patient's quality of life will be during that time,[15] which is largely complication related.

In the setting of LT, posttransplant morbidity, mostly attributed to arterial and biliary complications, remains high during the first year after LT.[14] It results in multiple interventions and requires several hospital readmissions.[19] Here we show that following an ABC during the first year after LT, the risk of graft loss was around 2 to 3 times at each time point higher than in the absence of an ABC (following an ABC, the risk of graft loss was multiplied by the HR). This was observed in 3 independent cohorts with different policies and management. An ABC was thus a strong time-dependent prognostic variable, which we introduced as an event to calculate a composite survival probability, ABCFS. We found that ABCFS correlated to the transplant and patient survival and that 1-year ABCFS was indicative of 5-year transplant survival (Fig. 2). By capturing more events, ABCFS improved the statistical power of the test and was able to identify more variables of interest than transplant survival. The discriminative effect was illustrated for the age of the donor, the preservation solution, and the ET-DRI (Table 5). Our results were in line with those of other studies using transplant survival as an endpoint and needing large numbers of patients (n = 48,261 LTs for the series by Houben et al.,[24] n = 42,869 LTs for Adam et al.,[3] n = 5939 LTs for Braat et al.[5]). ABCFS could therefore serve as a clinically relevant endpoint. In DCD LT, for example, ischemic cholangiopathy increased morbidity and mortality, resulting from either ischemic cholangiopathy-related complications (requiring multiple radiological, interventional, or surgical interventions), re-LT, or both. Many efforts, such as machine perfusion[25-27] and normothermic regional perfusion,[28] have been tested in an attempt to improve results and decrease ischemic cholangiopathy. Evaluating the effect of perfusion machines with 1-year ABCFS as an endpoint rather than transplant survival could be a direct application of our method.

For example, how many LTs would be needed to observe a difference between 2 LT groups with HRs of 1.5 and 195 expected events (α risk = 5%; power = 80%; events = ABC + re-LT + death)? To obtain a result after 1 year, the population needed will be 828 LTs using ABCFS and 2032 LTs using transplant survival. To obtain results after 5 years, the population needed will be 480 LTs using ABCFS and 898 LTs using transplant survival. Provided that several studies confirm our results, the ABCFS would be a statistical

**TABLE 5. Comparison of ABCFS or Transplant Survival for Perioperative Factors**

| | | Transplant Survival | | | ABCFS | | |
|---|---|---|---|---|---|---|---|
| Variable | n | Dead or Re-LT | KMP% (95% CI) | HR (95% CI) | Death or Re-LT or ABC | KMP% (95% CI) | HR (95% CI) |
| Cohort | 532 | 60 | 89 (86-91) | | 146 | 72 (69-76) | |
| BAR score | | | | $P < 0.001$ | | | $P = 0.001$ |
| ≤18 | 496 | 48 | 90 (88-93) | 1 | 128 | 74 (70-78) | 1 |
| >18 | 36 | 12 | 67 (53-84) | 3.92 (2.19-6.35) | 18 | 50 (36-69) | 2.17 (1.49-3.18) |
| EAD* | | | | $P < 0.001$ | | | $P = 0.047$ |
| No | 270 | 29 | 92 (89-95) | 1 | 94 | 74 (70-79) | 1 |
| Yes | 159 | 31 | 80 (75-87) | 2.66 (1.77-4.01) | 52 | 67 (60-75) | 1.38 (1.04-1.78) |
| Preservation solution | | | | $P = 0.80$ | | | $P = 0.01$ |
| Celsior | 63 | 7 | 89 (81-97) | 1 | 15 | 76 (66-87) | 1 |
| HTK | 88 | 12 | 96 (79-94) | 1.24 (0.62-3.15) | 36 | 59 (59-70) | 2.0 (1.33-3.26) |
| IGL-1 | 130 | 11 | 92 (87-96) | 0.77 (0.36-1.79) | 35 | 73 (66-81) | 1.21 (0.78-2.00) |
| SCOT 15 | 199 | 23 | 88 (84-93) | 1.06 (0.59-2.55) | 50 | 75 (69-81) | 1.12 (10.75-1.80) |
| UW | 51 | 6 | 88 (80-98) | 1.02 (0.31-2.66) | 9 | 82 (73-94) | 0.70 (0.32-1.19) |
| Donor age, years | | | | $P = 0.17$ | | | $P = 0.007$ |
| ≤65 | 329 | 32 | 90 (87-94) | 1 | 76 | 77 (72-81) | 1 |
| >65 | 203 | 28 | 86 (81-91) | 1.43 (0.94-2.14) | 70 | 65 (59-72) | 1.56 (1.22-1.95) |
| ET-DRI | | | | $P = 0.14$ | | | $P = 0.03$ |
| ≤1.5 | 251 | 23 | 91 (87-94) | 1 | 58 | 77 (72-82) | 1 |
| >1.5 | 281 | 37 | 87 (83-91) | 1.50 (0.98-2.19) | 88 | 68 (63-74) | 1.45 (1.14-1.89) |
| Main indication for LT | | | | $P = 0.93$ | | | $P = 0.43$ |
| Other | 43 | 5 | 88 (79-99) | 1 | 15 | 65 (52-81) | 1 |
| Cancer | 179 | 18 | 90 (86-94) | 0.82 (0.42-2.15) | 48 | 73 (67-80) | 0.70 (0.46-1.15) |
| Cirrhosis | 291 | 35 | 88 (84-92) | 0.97 (0.51-2.77) | 80 | 72 (67-78) | 0.70 (0.48-0.85) |
| Acute hepatitis | 19 | 2 | 90 (77-100) | 0.85 (0.00-2.81) | 3 | 84 (69-100) | 0.38 (0.00-0.85) |

*A total of 3 patients were excluded for transplant survival <24 hours.

tool such as disease-free survival or the disease-free progression in oncology. This type of tool is currently lacking in LT clinical research.[15]

The ABCFS curve described an inflection point at 1 year (Fig. 2). As shown by the distribution frequency of ABC (Fig. 1), the 1-year ABCFS took into account more than 90% of all ABCs. After the first year, most events were re-LTs or deaths, and the slopes of ABCFS and transplant survival curves were almost parallel (Fig. 2). The 1-year ABCFS was therefore indicative of the transplant survival 5 or 6 years later. The first-year cutoff was chosen for the following 2 reasons: (1) a statistical reason because the effect was time dependent and the earlier the ABC, the stronger the effect on transplant survival (not shown), and (2) a follow-up of 1 year is clinically relevant.

The "first-year ABC" was analyzed as a nominal variable (yes/no). We observed that "first-year ABC" was prognostic for the transplant survival in every group tested, but not for patient survival. This last result was not surprising because patient survival could be influenced by the re-LT rate.

At the root of the ABCFS is the definition used for ABC, which prompts several comments:

1. We considered the treatment of the complication rather than the diagnosis because the date of treatment was more precise than the date of diagnosis.
2. Arterial and biliary complications are specific to the LT process, and any such complications may lead to a graft loss. Furthermore, arterial and biliary complications may be combined during the follow-up.[29]

**TABLE 6. Summary Data of the 3 Cohorts**

| Variable | PSL Cohort, 2008-2017 (n = 532) | HMN Cohort, 2011-2015 (n = 249) | *P* Value* | HUB Cohort, 2011-2015 (n = 229) | *P* Value† |
|---|---|---|---|---|---|
| Donor age | 59 (44-70) | 65 (48-76) | 0.002 | 58 (47-70) | 0.94 |
| Donor female sex | 232 (44) | 131 (53) | 0.02 | 101 (44) | 0.90 |
| ET-DRI | 1.5 (1.3-1.8) | 1.8 (1.7-2.0) | <0.001 | 1.7 (1.4-2.0) | <0.001 |
| BAR score | 8 (4-13) | 7 (3-13) | 0.68 | 5 (3-8) | <0.001 |
| Recipient female sex | 112 (21) | 65 (26) | 0.12 | 56 (25) | 0.30 |
| Recipient age | 57 (49-63) | 56 (49-62) | 0.13 | 57 (51-63) | 0.38 |
| Hospitalized in ICU at LT | 130 (24) | 58 (23) | 0.73 | 0 (0) | <0.001 |
| MELD score | 18 (10-31) | 17 (9-28) | 0.02 | 15 (9-21) | <0.001 |
| Indications | | | <0.001 | | 0.003 |
| Decompensated cirrhosis | 304 (57) | 103 (41) | | 114 (50) | |
| Cancer | 179 (33) | 121 (48) | | 94 (41) | |
| ALF | 19 (4) | 0 (0) | | 0 (0) | |
| Cholestatic liver diseases | 10 (2) | 15 (6) | | 5 (2) | |
| Other | 20 (4) | 10 (4) | | 16 (7) | |
| Mortality at 3 months | 24 (5) | 22 (9) | 0.02 | 13 (6) | 0.49 |
| Re-LT at 3 months | 8 (2) | 14 (6) | 0.001 | 10 (4) | 0.02 |
| ABC at 12 months | 99 (18) | 59 (24) | 0.10 | 38 (17) | 0.51 |
| Arterial | 39 (7) | 25 (10) | 0.20 | 12 (5) | 0.29 |
| Biliary | 68 (13) | 43 (17) | 0.10 | 28 (12) | 0.83 |
| Follow-up, years | 2.9 (1.4-5.8) | 6.2 (5.2-7.3) | <0.001 | 6.0 (4.6-7.4) | <0.001 |

NOTE: Continuous variables are expressed as median (IQR). Categorical variables are expressed as number (percentage).
*PSL cohort versus HMN cohort.
†PSL cohort versus HUB cohort.

3. Portal vein or caval complications occur but rarely lead to a specific treatment of Dindo-Clavien class ≥III (PSL series: 2%, 10/532 LTs).
4. Our definition did not capture clinically silent hepatic artery occlusion or biliary strictures. However, if asymptomatic, long-term transplant survival may be observed.[30]
5. ABC is accessible by a computerized request from the financial database of the health care department, even retrospectively.
6. Treatment implies additional cost, and often a readmission, as our results confirm.

Finally, ABCFS was correlated to transplant and patient survival, and the 1-year ABCFS was indicative of 5-year transplant survival (Fig. 2). Although "a correlate does not a surrogate make,"[15] subject to future validations by randomized trials or retrospective studies from large cohorts, our results suggest that ABCFS is a metric that could become a surrogate in LT.

In conclusion, this study has several limitations, and our results will need to be confirmed in further work. This was a retrospective study with all its inherent limitations. Despite external validation, biases cannot be ruled out. ABCFS must be validated in an international registry, such as the European Liver Transplant Registry. From the 5-year survival results from these registries, it would be interesting to see whether small cohorts observed similar 1-year results with the ABCFS method. A future way of standard outcome evaluation could be a computerized extraction of therapeutic acts following LT with semiautomatic ABCFS calculation (complex or nonlinear ABC [Table 1] should be checked by a clinician).

However, taken together, our results argue for considering ABCFS as a valid and useful primary endpoint for future studies assessing the outcomes of LT.

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