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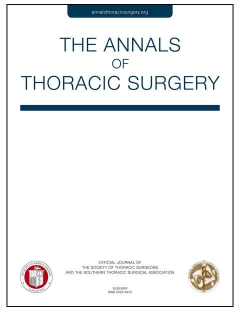

Cardiac Surgery in Patients with Liver Cirrhosis (CASTER) study: early and long-term outcomes

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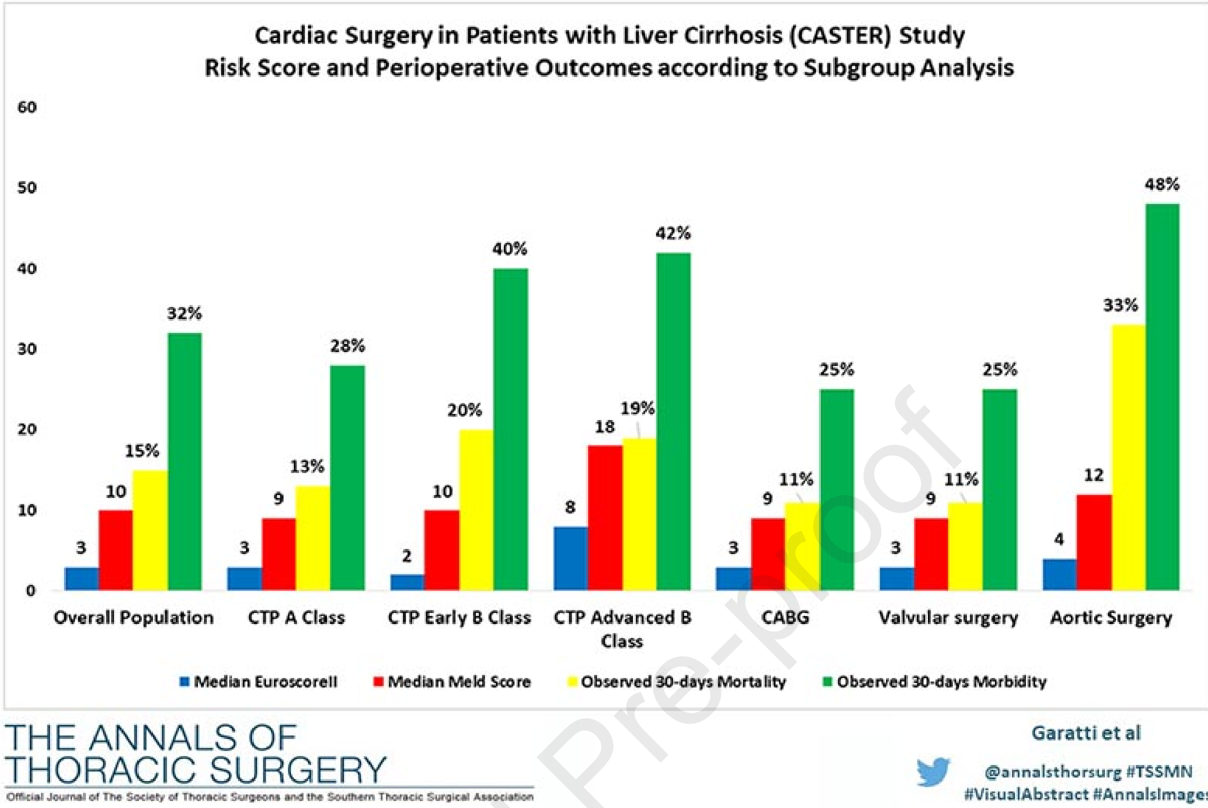
Cardiac Surgery in Patients with Liver Cirrhosis (CASTER) Study
Risk Score and Perioperative Outcomes according to Subgroup Analysis
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Overall Population
CTP A Class
CTP Early B Class
CTP Advanced B Class
CABG
Valvular surgery
Aortic Surgery
Median EuroscoreII
Median Meld Score
Observed 30-days Mortality
Observed 30-days Morbidity
THE ANNALS OF THORACIC SURGERY
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Cardiac Surgery in Patients with Liver Cirrhosis (CASTER) study: early and long-term outcomes

Running Head: Cardiac Surgery in Cirrhotic Patients

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Abstract

Background: patients with liver cirrhosis (LC) undergoing cardiac surgery (CS) face perioperative high mortality and morbidity, but extensive studies on this topic are lacking.

Methods: All adult patients with LC undergoing a CS procedure between 2000-2017 at ten Italian Institutions were included in this retrospective cohort study. LC was classified according to preoperative Child-Turcotte-Pugh (CTP) Score and Model for End-Stage Liver Disease (MELD) score. Early and medium-term outcomes analysis was performed in the overall population and according to CTP classes.

Results: The study population included 144 patients (mean age:66±9 years; male=69%). Ninety-eight, 20 and 26 patients were in CTP class-A, in early (MELD <12) or advanced (MELD >12) CTP class-B respectively. The main LC etiologies were viral (43%) and alcoholic (36%). Liver-related clinical presentation (ascites, esophageal varices and encephalopathy) and laboratory values (EGFR, serum albumin and bilirubin, platelet count) significantly worsened across the CTP-classes(p=.001). CABG or valve surgery (87% bioprosthesis) were performed in 36% and 50% respectively. Postoperative complications (especially AKI, liver complication and LOS) significantly worsened in advanced CTP class-B(p=.001). Notably, observed mortality was 3 or 4-fold higher than the EuroscoreII-predicted mortality, in the overall population, and in the subgroups. At Kaplan-Meier analysis, 1- and 5-years cumulative survival in the overall population was 82±3% and 77±4% respectively. The 5-years survival in CTP class A, early- and advanced-B was 72±5%, 68±11% and 61±10% respectively(p=.238).

Conclusions: CS outcomes in patients with LC are significantly affected in relation to the extent of preoperative liver dysfunction, but in the early CTP classes medium-term survival is acceptable. Further analysis are needed to better estimate the preoperative risk stratification of these patients.

Liver cirrhosis (LC) incidence is growing in the western countries, especially due to a significant increase in alcoholic and metabolic syndrome etiologies(1). The prevalence of LC in patients undergoing cardiac surgery (CS) is reported to be as low as 0.2–0.3%, accounting for over 6000 cases worldwide yearly. However, in recent years, increased longevity has contributed to the increased incidence of cardiovascular disease in cirrhotic patients, so that an increasing number of CS procedures are expected. Despite LC is not included within the most important risk scores(2), it is considered a major preoperative risk factor in CS, depending on the severity of preoperative liver disease(3). Few published studies on this topic concluded that CS is reasonably safe in patients with mild to moderate liver dysfunction(4). However, detailed analysis of the postoperative outcomes in these patients are lacking, and recommendations whether to perform CS remain unclear. The present study aimed to report the early and long-term results of a consecutive multicenter series of patients with LC undergoing CS, to find predictors of outcomes and to assess the relevance of EuroSCORE, CTP class and the MELD score in terms of prediction of surgical morbidity, mortality and medium-term survival.

Material and Methods

Study Design and Inclusion Criteria

The **CA**rdiac **S**urgery in pa**T**ients with liv**ER** cirrhosis (CASTER) study is a retrospective observational cohort study, including all adult patients affected by LC undergoing a CS procedure between January 2000 and December 2017. Exclusion criteria included patients aged<18 years, or patients treated for acute aortic dissection, heart transplant or LVAD implantation.

Patient Cohort and Data Collection

Ten Italian centers participated in the study. All the participant centers are tertiary care hospitals and referral centers for cardiac surgery, and four centers (40%) are University Hospitals. Preoperative, operative, and postoperative data were collected from institutional databases. Follow-up was achieved through direct or telephone interview with survivors, with relatives or with general practitioners. Ethics committee approval was obtained initially from the coordinating center (IRCCS Policlinico San Donato, study code n° 36/INT/2017) and subsequently from each participating site. Surgical procedures, including the use of extracorporeal circulation (ECC) in myocardial revascularization or type of implanted prosthesis were based solely on center or surgeon preference.

Study Outcomes

The outcomes of the study were the following: 1) Primary outcome: 30-days or in-hospital all-cause mortality. 2) Secondary outcomes: a) incidence of major postoperative morbidity and b) long-term freedom from all-cause mortality. Primary and secondary outcomes were defined according to the STS-AATS-EACTS Guidelines for reporting mortality and morbidity after cardiac interventions(5). Postoperative hepatic dysfunction was defined according to the International Study Group of Liver Surgery(6).

Liver Cirrhosis Score definition

The diagnosis of LC was based on clinical history and physical stigmata consistent with findings of abdominal imaging studies(coarsened heterogeneous echo pattern, increased parenchymal echogenicity, and nodularity of the liver surface). The severity of LC was graded according to the Child classification(7) and MELD score(8). Child-Turcotte-Pugh (CTP) score was calculated by using the following variables: severity of hepatic encephalopathy(grade 1-3), ascites(absent, mild, moderate), total bilirubin(mg/dL), serum albumin(gm/dL), and prothrombin time(seconds). CTP classification was defined based on the resulting score(A: 5-6; B: 7-9; C: 10-15). The MELD score was calculated using the formula published by Kamath(8): MELD score = 3.8*$\log_e$(bilirubin [mg/dL]) +11.2*$\log_e$ (international normalized ratio)+ 9.6*$\log_e$(creatinine [mg/dL]) +6.4*(etiology: 0 if cholestatic or alcoholic; 1 otherwise). The combined use of CTP and MELD classification has been recently advocated for enhanced risk stratification of cirrhotic patients undergoing general surgery(9).

Statistical Analysis

Normality distribution of the continuous variables was tested with the Skewness and Kurtosis Test. Results were presented as mean values±SD or median(IQR). Parametric(1-way analysis of variance) and nonparametric(Kruskal-Wallis Test) tests were used for comparison of continuous variables. The Fisher's exact test was used for comparison of categorical variables. A p value <0.05 was considered statistically significant. Potential predictors of 30-days mortality and major morbidity were tested with multivariate logistic regression analysis, using a stepwise logistic regression model. Calibration of the model was assessed with the Hosmer-Lemeshow goodness-of-fit test. The predictive value of risk scores (EuroscoreII, CTP and MELD) on 30-days mortality was evaluated with the ROC curve analysis. Survival curves were calculated starting from the date of surgery. Kaplan-Meier analysis with the Log-Rank test was applied for estimation of medium-term survival across the study groups. Independent predictors of long-term mortality were estimated by means of multivariable Cox regression analysis. Schoenfeld residuals Test was used to check the proportional-hazard assumption for all categorical covariates. Statistical calculations were performed using a computerized statistical program (SPSS Statistics, version 22.0; SPSS Inc, Chicago, Illinois, USA).

Results

The final study population consisted of 144 patients (0.15% of all the CS procedures performed in the study period), all in CTP class A (98 patients) and B (46 patients). Further, patients in CTP class B were dichotomized by MELD scores into early (MELD≤12, 20 patients) and advanced (MELD>12, 26 patients). The MELD score cutoff point of 12 has been selected according to previous studies investigating mortality in patients with LC undergoing CS(10). No patients in CTP Class C were collected in the present series, probably because, due to severe liver dysfunction, they were deem unsuitable for CS.

Temporal trend over the study period

For temporal trend analysis, the study period was divided into six three-year periods(***Figure 1)***. The rate of patients with LC undergoing CS increased 6-fold during the study period, from 0.06% to 0.30% (7 to 45 patients). The preoperative LC severity(p=***.534***) and the CS risk estimation(***p=.336***) were nearly constant over the years. Despite this, in-hospital mortality significantly increased over the study period, starting at 2% in the first years and peaking at 10% in the most recent years(***p=.045***).

Preoperative patients' profile

Preoperative characteristics in the three CTP classes are depicted in ***Table 1***. Overall, the subgroups of patients were comparable as regards the clinical characteristics and cardiac risk factors. We observed a trend towards a worse clinical profile in advanced class B patients, without statistical significance. LC etiology in the overall population was mainly alcoholic (36%) and viral (43%), without significant differences among CTP classes. Preoperative LC severity significantly affected liver-related clinical presentation at admission as symptoms and laboratory values significantly worsened across the three CTP classes (***Table 2***). Median CTP score was 6 in class A and 8 in class B, but median MELD score significantly increased from 9 in class A to 10 and 18 in early and advanced class B respectively(***p=.001***).

Perioperative and postoperative outcomes

Perioperative characteristics are depicted in ***Table 3***. CS procedures included CABG (36%), valvular surgery(50%) and aortic procedures (14%). Interestingly the rate of valve surgery significantly increased in advanced LC (p=***.001***), suggesting an increasing role of valvular-related congestion on more severe liver dysfunction. The ECC was used in 74% of the patients, and a biological valve was implanted in 75% of valvular procedures, without significant differences among the study groups. Postoperative complications rate in the overall population was 32% with a significant increase between CTP classes(***p=.005***). Nearly 70% of the patients were transfused postoperatively(median transfused units=4), without significant differences between CTP classes.

Infections(6%), acute kidney injury(AKI-12%) and hepatic decompensation(15%) were the most common postoperative complications, with a significant increase among CTP classes(p=.001; ***Figure2***). At logistic regression analysis, CTP score(OR=1.34, 95%CI:1.05-1.70, ***p=.016***) preoperative chronic renal failure(OR=2.37, 95%CI:1.06-5.27, ***p=.034***) and preoperative EF(OR=4.32, 95%CI:0.92-0.99, ***p=.006***) resulted independent risk factors for postoperative complications [Hosmer-Lemeshow: chi-square=9.34, p=.32; AUC=0.72(95%CI:0.63-0.81)].

Finally, overall 30-days mortality was 15%(22 patients), without significant differences among the three groups (***Table 4***). However, in CTP Class B patients with very advanced LC (MELD score >18, n° 8 patients) mortality peaked to 37%, even if the small number of observation limited statistical significance (p=.15). The cause of death included hepatic decompensation with multisystem organ failure(8 patients, 36%), renal failure(6 patients, 27%), sepsis(5 patients, 23%) and respiratory failure(3 patients, 14%). Logistic regression analysis identified preoperative bilirubin(OR=1.10, 95%CI:1.01-1.20, ***p=.012***), COPD(OR=2.46, 95%CI:1.91-6.56, ***p=.003***) and aortic procedure(OR=4.32, 95%CI:1.56-8.67, ***p=.001***) as independent risk factors for 30-days mortality[Hosmer-Lemeshow: chi-square=9.03, p=.34; AUC=0.71(95%CI:0.58-0.83)]. Notably, observed mortality was significantly 3 or 4-fold higher than the EuroscoreII and STS score-predicted mortality, in the overall population, as well as in the subgroup analysis based on LC classes and type of surgical procedures (***Figure 3)***. At ROC curve analysis, neither EuroSCORE-II nor CTP and MELD scores provided optimal discrimination in predicting 30-days mortality (***Figure 4***).

Medium-term outcomes

Median follow-up in the overall population was 51(10-88) months, without significant differences among the CTP classes(p=.647). Mid-term survival of the overall population(including 30-days mortality) was 82±3% at 1 year, 77±4% at 5 years and 63±5% at 8 years. The 1-year survival for CTP class A, early B and advanced B was 87±4%, 75±9% and 71±9% respectively. The 5-years survival in the same classes was 72±5%, 68±11% and 61±10%(p=.238; ***Figure 5***). At Cox regression analysis, preoperative serum albumin[HR=0.75(95%CI: 0.69-0.84); p=.005] and perioperative transfusion[HR=2.28(95%CI: 1.43-2.86); p=.001] resulted independent predictors of long-term mortality(***Figure6***).

Comment

Patients with LC undergoing various surgical procedures are at an increased risk of surgery and anesthesia-related complications(11,12). In the present experience, overall 30-days mortality was 15%, ranging between 13%-20% according to preoperative liver dysfunction. This is consistent with the reported perioperative mortality in cirrhotic patients, ranging between 25% and 70% in the most advanced class of liver dysfunction(13). Despite a clear indication in cirrhotic patients is lacking, it is generally accepted that CS can be done safely in patients with CTP class-A and early-B. Moreover, the risk of mortality is higher in patients with CTP class-B with a MELD score >13 and nearly prohibitive in patients with CTP class-C(14). Accordingly, in the present experience, despite perioperative mortality and overall incidence of complications increased constantly among the CTP classes, only patients in CTP advanced class B showed significantly worsen risk profile and clinical outcome compared to the previous classes. Taking this into account, a careful preoperative evaluation in this group of patients is mandatory as clinical preoperative optimization (coagulopathy, ascites and malnutrition) can improve postoperative outcomes(15).

Surgical risk assessment

As previously reported, one of the most striking findings of the present experience is that operative mortality is completely unrelated to the predicted mortality based on CS risk scores. Because mortality in these patients is mainly associated with liver function, liver scores such as the MELD or CTP score have been evaluated to predict post CS mortality, but the results in limited monocentric series are conflicting(16). Other researchers reported that single liver parameters (serum bilirubin, albumin, cholinesterase or platelets count) rather than LC scores are significant determinants of postoperative outcomes(17). In the present experience LC scores didn't prove a significant superiority compared to EuroscoreII in predicting 30-days mortality (**Figure 4**). Furthermore, at multivariable logistic analysis, serum bilirubin proved to be the only liver-related risk factor predicting perioperative mortality. This is consistent with the series from Lin and colleagues(18), who found that serum bilirubin was a strong predictor of early and 5-years mortality post CS. Of course, our analyses could have been underpowered due to the limited sample size. Unfortunately, two recent population-based cohort studies(19,20) including nearly eight thousands patients with LC undergoing CS were unable to collect preoperative liver information, so that the predictive role of CTP/MELD scores on perioperative outcomes could not be assessed.

Perioperative morbidity

Mortality after CS in cirrhotic patients is strictly related to an increased incidence of perioperative complications like infections, renal failure, hepatic decompensation and bleeding. Indeed, postoperative morbidities remain a major issue in this population. Previous studies have documented complication rates ranging from 28% and 69%(21). Similarly, in the present study, postoperative complications ranged between 28% and 43%, depending on preoperative liver dysfunction. The rate of perioperative transfusions in our study was nearly 70%, without significant differences among CTP classes. Several reasons account for a higher requirement of perioperative transfusion in these patients. LC is often accompanied by anemia and thrombocytopenia due to poor nutritional status, splenomegaly and bleeding from varices. Additionally, impaired coagulation may occur in cirrhotic patients since many of the coagulation factors are synthesized by the liver(22). In the present experience blood transfusions were not an independent predictor of early mortality, probably because their net effect was overcame by the weight of liver dysfunction. However, transfusion requirement was an independent predictor of long-term mortality, and this is consistent with the reported literature in CS and in patients with LC(23,24).

AKI, cardiac dysfunction and liver decompensation are interrelated complications, commonly occurring in cirrhotic patients undergoing CS. Advanced LC is often accompanied by various degree of cardiomyopathy, characterized by diastolic dysfunction along with impaired inotropic, and chronotropic incompetence, which can translate in postoperative cardiac impairment (12-21% in the present study). Postoperative cardiac dysfunction results in elevated central venous pressure, which plays a significant role in the pathogenesis of hepatorenal syndrome and AKI(8-23% in our series)(25). Furthermore, physiologic challenges associated with CPB, including hypoperfusion, hemodilution and catecholamine release are poorly tolerated in patients with liver disease(26). Particularly, CPB-related visceral hypoperfusion, can contribute to hepatorenal syndrome, liver decompensation (5-31% in the present study) and bowel ischemia with bacterial translocation and sepsis. It should be noted that the rate of perioperative hepatic and renal complications showed a significant decrease among the study periods. This improvement probably reflects the advances in the perioperative management of these patients achieved during the last decade.

Long-term outcomes

The overall 5-year survival of the study population was 77%, ranging from 72% to 61% among CTP classes. In the present experience, the impact of preoperative liver dysfunction on long-term survival after CS seems less relevant compared to other published experience(27). Of note, this fact can be related to the exclusion of cirrhotic patients with CTP class C, who carry the worse prognosis. On the other hand, our experience suggest that, if patients are able to survive the perioperative period, medium term survival is excellent, at least in CTP early classes, and cirrhotic patients with MELD lower than 12-15 should not be refused CS, advocating long-term dismal prognosis. In our multivariable Cox analysis, we found albumin was an independent predictor of long-term mortality. Lower albumin level is a marker of poor nutritional status in patients with LC, and can help in discriminate patients with minimal hepatic reserve who carry a poor prognosis after CS(28). Furthermore, hypoalbuminemia together with higher perioperative blood transfusion requirements are strongly associated to infection and sepsis, thus resulting in poor early and long-term outcomes after CS(29).

Study Limitation

This was a retrospective observational multicenter study, and patient management was performed according to individual center strategy or protocol, with heterogeneous approaches, therefore making definitive conclusions inapplicable. In designing the study, we did not collect a control group of patients without LC. There are several large population-based studies investigating the independent role of LC on perioperative morbidity and mortality. On the contrary, our aim was to best characterize the cirrhotic patients in order to ascertain the predictive role of liver-related factors on post CS outcomes. A more sophisticated analysis on the subgroups of surgical procedures, as well on the role of ECC is lacking in the present study, and it will be the object of a future research. Finally, our sample size is significantly smaller compared to recent population-based cohort studies. However, despite these latter studies are strengthen by the elevated number of included patients, many specific information regarding liver severity assessment are lacking. Taking into account these limitations, the present study was able to collect precise LC characterization, thus spreading some light on the risk assessment of CS in these patients that deserve further investigations.

Conclusion

In conclusion, the present study confirms that cirrhotic patients undergoing CS experience a significant high perioperative mortality and morbidity. CS outcomes in these patients are unrelated to the predicted outcomes based on the conventional cardiac risk factors and the adjunctive role of liver risk model(CTP and MELD) is debatable. Despite increased perioperative mortality, at least in the early CTP classes medium-term survival is excellent. Further analysis are needed to expand our preliminary observation and to evaluate if the use of more sophisticated liver imaging(i.e. liver stiffness assessment by transient elastography) can better estimate the preoperative risk stratification of these patients

	Total Population	CTP Class A	CTP Class B Early (MELD < 12)	CTP Class B Advanced (MELD>12)	P Value
N° Patients	144	98	20	26	
Mean Age	66±9	66±9	68±8	65±11	.527
Male Gender	100(69%)	74(75%)	10(50%)	16(61%)	***.049***

Table 1: Preoperative characteristic in the overall population and in the CTP classes.

BSA	1.85±0.18	1.9±0.17	1.8±0.18	1.8±0.22	.184
BMI	24(23-27)	25(23-27)	24(23-30)	23(21-26)	.074
Median EF (%)	55(47-60)	56(45-60)	57(55-60)	55(45-62)	.597
Median TAPSE	20(18-21)	22(20-23)	20(19-21)	17(15-19)	***.005***
Pulmonary HPT[§]	69(48%)	43(44%)	9(45%)	17(65%)	***.039***
Clinical Presentation					
Hypertension	88(61%)	57(58%)	15(75%)	16(61%)	.371
Dyslipidemia	46(32%)	29(30%)	4(20%)	13(50%)	.065
Diabetes	63(44%)	43(44%)	8(40%)	12(46%)	.916
Chronic Renal Failure	79(55%)	50(51%)	8(40%)	21(81%)	***.009***
CVA	16(11%)	10(10%)	0(0%)	6(23%)	***.042***
COPD	41(28%)	27(28%)	6(30%)	8(31%)	.937
Previous CS	11(8%)	5(5%)	1(5%)	5(19%)	***.049***
NYHA >II	12(8%)	9(9%)	1(5%)	2(8%)	.821
Preoperative Therapy					
ACE inhibitors	27(19%)	21(21%)	3(15%)	3(12%)	.464
Diuretics	31(21%)	16(16%)	5(25%)	10(38%)	***.023***
Oral Anticoagulant	7(5%)	5(5%)	1(5%)	1(4%)	.965
Statins	10(7%)	8(8%)	1(5%)	1(4%)	.267

§ Pulmonary Hypertension defined as Systolic pulmonary pressure > 45 mmHg

	Total Population	CTP Class A	CTP Class B Early (MELD < 12)	CTP Class B Advanced (MELD>12)	P Value
Cirrhosis Etiology					.627
Alcoholic	48(33%)	32(33%)	6(30%)	10(38%)	
Viral	64(45%)	42(43%)	9(45%)	13(50%)	
Auto-immune	20(14%)	16(16%)	2(10%)	2(8%)	
Cardiogenic	12(8%)	8(8%)	3(15%)	1(4%)	
Ascites	39(27%)	20(20%)	3(15%)	16(61%)	***.001***
Esophageal Varices	58(40%)	35(36%)	8(40%)	15(58%)	.127
Encephalopathy	14(10%)	6(6%)	2(10%)	6(23%)	.058
Laboratory values					
EGFR	63±24	64±23	72±22	53±24	***.019***
Albumin	3.4(2.8-4)	3.7(3.1-4.1)	2.8(2.5-3.6)	2.5(2.3-3.1)	***.001***
Bilirubin	1.2(0.7-2.0)	1.1(0.6.1-7)	1.3(0.8-2.6)	1.9(1.1-3.2)	***.001***
Platelet	134±73	146±80	120±42	98±46	***.007***
INR	1.2(1.1-1.3)	1.1(1.05-1.2)	1.2(1.15-1.4)	1.35(1.2-1.5)	***.021***
Child Score	6(5-7)	6(5-6)	8(7-8)	8(7-9)	***.001***
MELD Score	10(8-15)	9(8-12)	10(8-12)	18(16-20)	***.001***

Table 2: Liver Cirrhosis characteristics in the study population.

Table 3: Operative characteristic in the overall population and in the CTP classes.

	Total Population	CTP Class A	CTP Class B Early (MELD < 12)	CTP Class B Advanced (MELD >12)	P Value
N° Patients	144	98	20	26	
Median Euroscore II	3.1(1.4-7.1)	1.7(1.2-3.1)	3(1.4-6.1)	8.5(2-12)	***.004***
CS Procedure					
CABG	52(36%)	44(45%)	4(20%)	4(15%)	***.001***
OPCABG	*39(75%)*	*31(70%)*	*4(100%)*	*4(100%)*	
Valvular Surgery	72(50%)	40(41%)	13(65%)	19(73%)	***.001***
Valve Replacement	*50(69%)*	*33(83%)*	*6(46%)*	11(58%)	
Valve Repair	*20(28%)*	*6(15%)*	*6(46%)*	8(42%)	
Endocarditis	*2(3%)*	*1(2%)*	*1(8%)*	-	
Aortic Surgery	20(14%)	14(14%)	3(15%)	3(12%)	.256
Bentall/ David	*8(40%)*	*6(43%)*	*2(67%)*	-	
AA Replacement	*12(60%)*	*8(57%)*	*1(33%)*	*3(100%)*	
ECC use	105(74%)	67(68%)	16(80%)	22(84%)	.162
Median ECC time	97(70-127)	98(74-127)	83(66-110)	104(70-186)	.674
Median Clamp time	68(46-92)	71(47-95)	62(46-71)	74(48-136)	.277
Median N° of CABG	2(1-4)	2(2-4)	2(1.5-3.5)	3(2-3)	.997
Biological Valve	54(75%)	31(77%)	11(85%)	16(84%)	.572

Abbreviations: AA= Ascending Aorta; ECC=Extra-Corporeal Circulation; Continuous variable: mean±SD or Median(IQR). Dichotomous variable: n°(%)

Table 4: Perioperative characteristic in the overall population and in the CTP classes

	Total Population	CTP Class A	CTP Class B Early (MELD < 12)	CTP Class B Advanced (MELD >12)	P Value
Inotropic support	61(42%)	41(42%)	6(30%)	14(54%)	.264
IABP Rate	8(6%)	6(6%)	1(5%)	1(4%)	.897
Transfusion Rate	101(70%)	69(70%)	12(60%)	20(77%)	.459
Total Transfused Units	4(0-7)	2(0-5)	3(0-8)	5(2-9)	.581
RBC Units	2(0-4)	1(0-4)	2(0-5)	3(1-6)	.342
FFP Units	1(0-1)	1(0-1)	1(0-1)	1(0-2)	.766
PTL Units	1(0-1)	1(0-2)	1(0-2)	1(0-4)	.717
Median ICU stay (days)	2(1-5)	2(1-5)	2(1-3)	4(2-9)	.154
In-Hospital Mortality	22(15%)	13(13%)	4(20%)	5(19%)	.617
CABG	6(11%)	6(14%)	0(0%)	0(0%)	.343
On-pump CABG	*3(23%)*				
OP-CABG	*3(8%)*				
Valvular Surgery	9(12%)	4(10%)	2(15%)	3(16%)	.773
Aortic Surgery	7(35%)	3(21%)	2(67%)	2(67%)	.151

Abbreviations: FFP=Fresh Frozen Plasma; PTL=Platelets; RBC=Red Blood Cells. Continuous variable: mean±SD or Median (IQR). Dichotomous variable: n° (%)

Figure Legends

Figure 1: Temporal trend of patients with LC submitted to CS procedures.

Figure 2: Perioperative complications rate in the CTP classes.

Figure 3: Comparison between EuroscoreII-predicted and observed 30-days mortality(with 95% CI).

Figure 4: Predictive role of risk factors on 30-days mortality at ROC analysis. A) EuroscoreII; B) CTP score; C) MELD Score; D) Risk Score Comparison.

Figure 5: Long-term cumulative survival according to CTP classes.

Figure 6: Long-term adjusted survival probability according to perioperative transfusion requirement. Cox Regression analysis.

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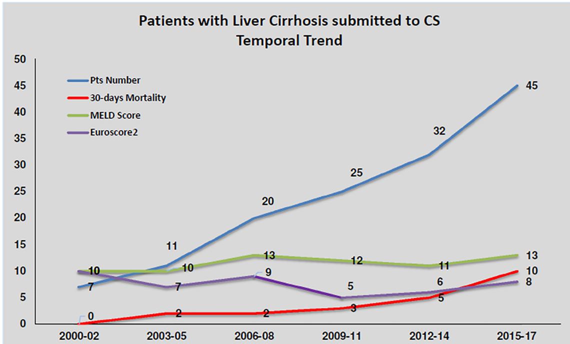
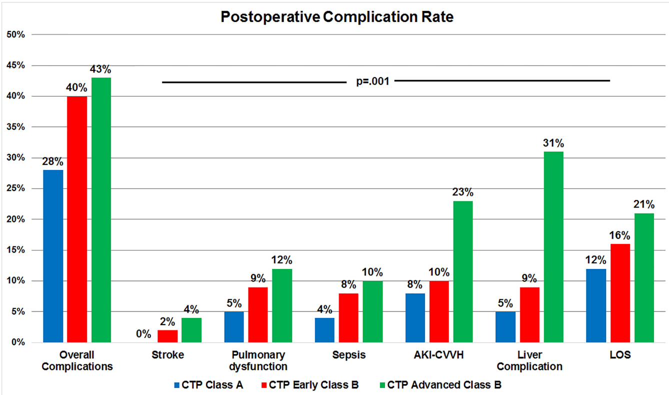
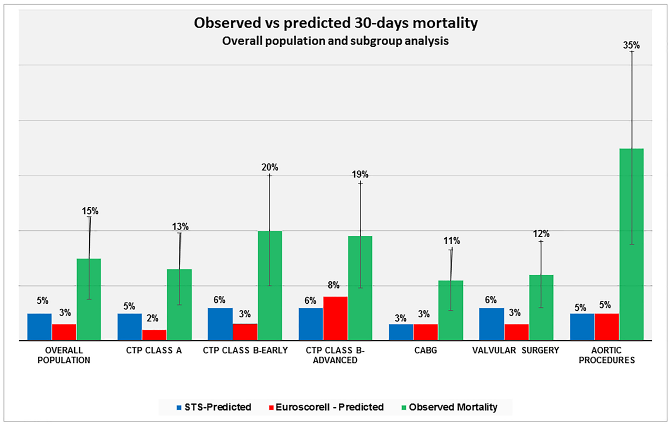
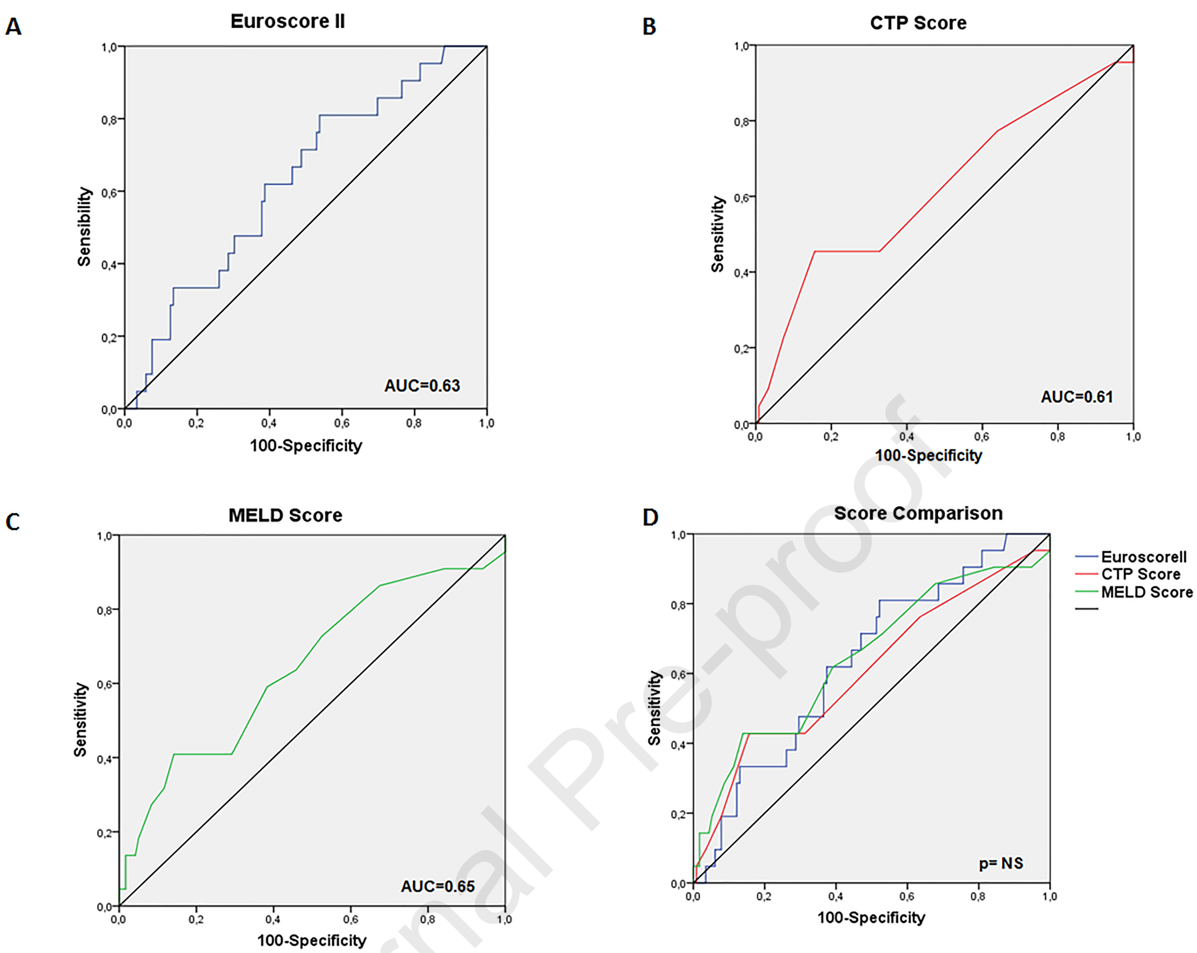


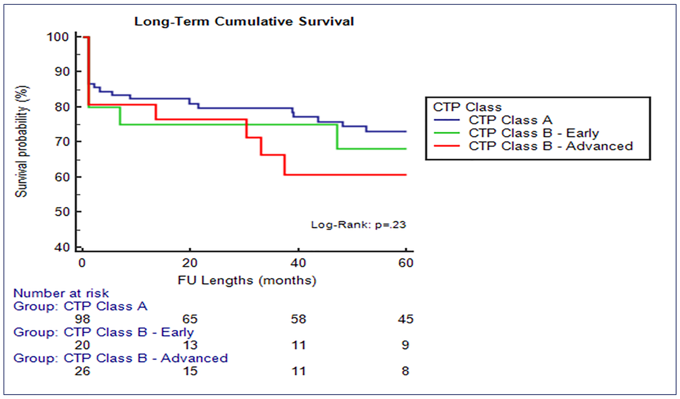
Total CS Procedures	16.469	16.154	15.161	16.138	15.315	14.777	94.014
LC rate (%)	0,06	0,07	0,13	0,15	0,22	0,30	0,15

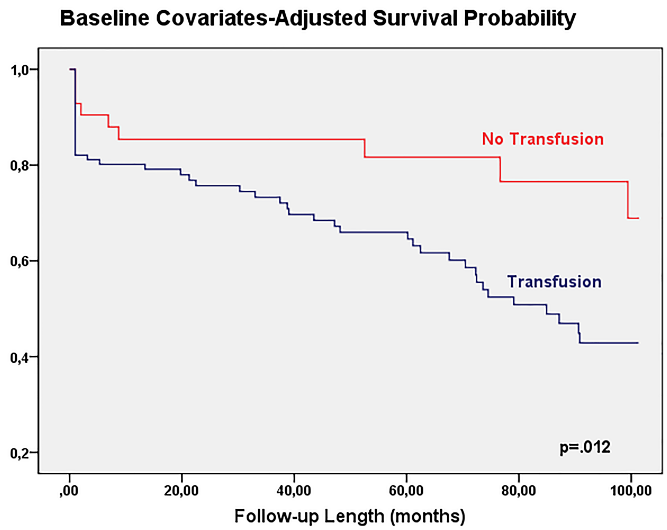


Postoperative Complication Rate
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
p=.001
28%
40%
43%
0%
2%
4%
5%
9%
12%
4%
8%
10%
8%
10%
23%
5%
9%
31%
12%
16%
21%
Overall Complications
Stroke
Pulmonary dysfunction
Sepsis
AKI-CVVH
Liver Complication
LOS
CTP Class A
CTP Early Class B
CTP Advanced Class B


Observed vs predicted 30-days mortality
Overall population and subgroup analysis
35%
20%
19%
15%
13%
11%
12%
5%
3%
5%
2%
6%
3%
6%
8%
3%
3%
6%
3%
5%
5%
OVERALL POPULATION
CTP CLASS A
CTP CLASS B-EARLY
CTP CLASS B-ADVANCED
CABG
VALVULAR SURGERY
AORTIC PROCEDURES
STS-Predicted
Euroscorell - Predicted
Observed Mortality


A
Euroscore II
Sensibility
100-Specificity
AUC=0.63
B
CTP Score
Sensitivity
100-Specificity
AUC=0.61
C
MELD Score
Sensitivity
100-Specificity
AUC=0.65
D
Score Comparison
Sensitivity
100-Specificity
p= NS
EuroscoreII
CTP Score
MELD Score
0,0
0,2
0,4
0,6
0,8
1,0


Long-Term Cumulative Survival
Survival probability (%)
100
90
80
70
60
50
40
0
20
40
60
FU Lengths (months)
Log-Rank: p=.23
CTP Class
CTP Class A
CTP Class B - Early
CTP Class B - Advanced
Number at risk
Group: CTP Class A
98 65 58 45
Group: CTP Class B - Early
20 13 11 9
Group: CTP Class B - Advanced
26 15 11 8


Baseline Covariates-Adjusted Survival Probability
1,0
0,8
0,6
0,4
0,2
No Transfusion
Transfusion
p=.012
,00
20,00
40,00
60,00
80,00
100,00
Follow-up Length (months)