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Title Page

The learning curve for piggyback liver transplantation: identifying factors challenging surgery.

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Abstract

Background: This study aimed to quantify the learning curve of PBLT and to identify factors that impact the operative time and blood transfusion during the learning curve.

Methods: A retrospective review was performed on consecutive cases of patients' first PBLTs that were performed by a single surgeon. The learning curve for the operative time was evaluated using the cumulative sum (CUSUM) method.

Results: There were 181 consecutive first-time PBLTs. The median operative time was 345 minutes (range: 180-745 minutes) with a median transfusion rate of 4 packed red blood cell units (range: 2-23 units). The CUSUM learning curve identified three phases: an initial phase (1-70 PBLTs), a plateau phase (71-101 PBLTs), and a stable phase (102-181 PBLTs). Over the three phases, there were significant decreases in the median duration of the surgery (388.8 vs. 344.8 vs. 326.9 minutes; p=0.004, p=0.0004, p=<0.0001) and the number of red blood cell units transfused (6.00 vs. 3.90 vs. 3.71; p=0.02, p=0.79; p=0.0006). Multivariable analysis identified that the following factors impacted the operative time: surgeon experience (p = 0.00006), previous upper abdominal surgery (p = 0.01), portocaval shunt fashioning (p = 0.0003**), early portal section (p = 0.00001)**, multiple arterial graft reconstruction (p = 0.03), and the length of the retrohepatic inferior vena covered by segment 1 (p = 0.0006). Independent risk factors for increased blood loss were surgeon experience (p = 0.0001), previous upper abdominal surgery (p = 0.002), the retrohepatic inferior vena cava encirclement by segment 1 (p = 0.0001), severe portal hypertension (p = 0.01), **early portal section (p=0.001)**and low prothrombin time (p = 0.00001).

Conclusions: Easily identifiable factors related to recipients (segment 1 morphology, previous upper abdominal surgery, severe portal hypertension) and to surgeon (operative experience, portocaval shunt fashioning, early portal section and multiple arterial reconstructions) impact

operative time and blood losses during the learning curve of PBLT. These factors can be used for grading the difficulties of LT to tailor the surgical strategy.

Keywords: liver transplantation; piggyback; anthropometrics; cirrhosis; morphology; blood loss; operative time.

Introduction

Liver transplantation (LT) is now a "standard of care" surgical procedure that provides a cure for selected patients with acute and chronic liver failure or certain liver tumors. The surgical technique of orthotopic LT using brain-dead liver donors was standardized by Starzl et al. more than 30 years ago(1). A technique that involves the preservation of the recipient's inferior vena cava (IVC) was first described in the early 1990s and has progressively replaced the "standard" resection of the native retrohepatic IVC with a need for veno-venous bypass(2).

The IVC preservation has led to the possibility of implanting liver grafts with various types of "piggyback" (PB) venous anastomosis(3-6), which has obvious advantages in terms of hemodynamic stability and shorter implantation time(5). While considered as a relatively straightforward procedure, LT involves variable degrees of difficulties related to native liver hepatectomy and graft implantation. Both of these phases can be technically challenging because of patients' conditions and anthropometrics, liver morphology, presence and degree of portal hypertension, the recipient and donor's vascular anatomy, and the surgeon's experience (7-15).

Greater experience with a given operation should usually lead to improved results in terms of direct quality metrics including operative time, need for transfusion, and morbidity (16). The identification of factors impacting these quality metrics can be particularly useful in scoring the difficulties of a surgical procedure and quantifying its mastery by surgeons. There are scare reports on the exact impact of different factors related to recipients of LT and the experience of surgeons on these metrics(7, 13). This is mainly related to the high variability of indications for LT(12), the

heterogeneity of surgical approaches adopted for LT(17, 18), the variable degree of experience among surgeons(7), and the lack of a uniform dataset in this regard. Thus, we examined a cohort of consecutive patients undergoing a PBLT for the first time by the same surgeon with the goal of determining 1) whether a learning curve effect can be identified and 2) the factors that impact the overall operative time and blood transfusion.

Patients and Methods

Data Collection

This retrospective cohort study was conducted at the Hepato-Pancreato-Biliary Surgery and Liver Transplantation Centre of the University of Strasbourg, France. **Data were obtained from all patients undergoing a PB-LT for the first time from a single surgeon (P.A.) between June 1, 2014, and December 30, 2019. Previous surgeon experience included 3 year fellowship in abdominal and HPB surgery including liver procurement (70 cases), first-assistance in liver transplantation (80 cases) and doing part of liver transplant (25 cases).** The exclusion criteria were early or late liver retransplantation (n=14) and cases lacking radiological data (n=15).

The data collected included demographics, preoperative laboratory data and operative variables such as operative time, presence and need for red blood cell (RBC) unit transfusion, reoperation rate, and 90-day morbidity and mortality rates. Details about the indications, model for end-stage liver disease (MELD) score, and biological values were recorded. Operative time was defined as the time from skin incision to skin closure. The lengths of cold ischemia and the weights of liver grafts and recipient livers were systematically recorded. The clinical, operative and survival data were collected prospectively in a dedicated database and then analyzed retrospectively. **Radiological data were retrospectively gathered by analysis of preoperative CT-scans on a dedicated Philips Intellispace portal console (Koninklijke Philips NV, Amsterdam, The Netherlands). All LTs were performed by the same surgeon from skin incision to skin closure.**

Assistant during LT were usually surgical fellows and senior residents who varied through the entire experience. Anesthesia team consisted of senior anesthesiologist with long-time experience in HPB and transplant anesthesia but junior faculties were also introduced gradually over the period study.

Study Definitions

Morbidity was classified and graded according to the Dindo-Clavien classification(19). Biliary complications included early and late leaks or stenosis. Arterial, caval, and portal complications included early and late stenosis and thrombosis. Significant blood transfusion was defined as RBC transfusion ≥ 6 units as described elsewhere(20). **Postreperfusion syndrome occurring after portal unclamping was defined as a decrease in the mean arterial pressure of more than 30% of the value observed in the anhepatic phase, for more than 1 minute during the first 5 minutes after reperfusion of the graft.(21).** Previous upper abdominal surgery definition included: partial liver resection, splenectomy, open cholecystectomy, gastric and/or duodenal surgery, right or transverse colectomy.

The anthropometrics of the recipient included body weight, body height, body mass index (BMI), intra-abdominal fat (IAF), outer abdominal fat (OAF), and modified sagittal abdominal diameter (M-SAD) (22, 23) (**Figure 1**). IAF was defined as the greatest distance between the kidney and the abdominal wall measured at the level of the renal veins. OAF was defined as the thickest abdominal wall distance at the level of the umbilicus. M-SAD was defined as the deepest distance between the abdominal wall and the origin of the celiac trunk. These three measures were recorded from preoperative computed tomography (CT) scans of the LT patients.

The liver morphology data included the type of segment 1 (complete or partial encirclement of the IVC)(10), liver conformation (atrophic, normal, or hypertrophic livers), and the length of the IVC covered by segment 1 (L-IVC). L-IVC was defined at the longest distance between the confluence of hepatic veins into the IVC and the lowest extremity of the segment 1 recorded in the

sagittal reconstruction of the CT scan (**Figure 2**). The largest anterior-posterior measurement in axial images of the spleen was used to define the presence of splenomegaly (greater than 10.5 cm).

The presence and the type of spontaneous porto-systemic shunts (umbilical, gastric, transjugular intrahepatic portosystemic, splenorenal, and others) were recorded from preoperative CT scans. Clinically evident portal hypertension was defined as the presence of esophageal varices, ascites, or an association of thrombopenia (<100,000/mm^3) and splenomegaly. Severe portal hypertension was defined by the presence of esophageal varices/spontaneous shunts, splenomegaly, thrombopenia, and ascites (24).

Surgical Techniques

All LTs were performed using the PB technique through a bilateral subcostal incision with a midline extension. The hepatic arteries and bile ducts were highly transected into the hepatic pedicle. A temporary portocaval direct or passive mesenterico-saphenous shunt was created after portal section when hemodynamically efficacious spontaneous shunts were absent (25, 26). **Briefly, a portocaval shunt was systematically created in patients with no portal hypertension. In presence of portal hypertension preoperative CT-scans of recipients were systematically reviewed before LT to look for spontaneous shunts. Patients having umbilical, transjugular intrahepatic portosystemic shunts which are usually transected early during hepatectomy received either a portocaval shunt or a passive mesentericosaphenous shunt. Patients with spontaneous distal shunts (i.e. large left splenorenal) received no portal derivation except if bowel edema was perceived after portal clamping. At the beginning of the experience, a variable phase of liver dissection (liver mobilization, initial dissection of the liver from IVC) was performed under a divided hepatic artery and an undivided portal vein with portosystemic shunts being performed once portal vein was clamped. Gradually, the hepatectomy technique was changed toward the sequence: incision -section of artery and portal vein-portosystemic shunt creation if needed-liver mobilization-dissection of the**

retrohepatic IVC. In order to evaluate the efficacy of this technique over the period study we therefore defined an early portal section as a section of the portal vein within 1:30 hours from the skin incision. The approach to the retrohepatic IVC was performed in two ways. A retroperitoneal approach going from the left to the right in patients with segment 1 not completely encircling the IVC(27). A retroperitoneal approach going from the right-to-the left instead was used when complete encirclement of the IVC by segment 1 was present(28). During IVC dissection multiples small accessory hepatic veins were controlled by not-absorbable 5/0 stiches. Caval anastomoses were constructed according to the three-vein techniques(29). The IVC of the graft was anastomosed end-to-side to a common neo-ostium made by bringing together the three hepatic veins' ostia using 4/0 sutures. The portal anastomoses were end-to-end and made using 6/0 sutures.

Liver grafts were perfused at the end of the portal vein anastomosis. Arterial anastomosis was performed under 3.5× magnification with loops using 7/0 or 8/0 sutures. The length of the graft artery left in situ was trimmed to the local anatomy while avoiding discrepancies in caliber as much as possible. The recipient site of the arterial anastomosis was preferentially made at the bifurcation between the common hepatic artery and the gastroduodenal artery. A direct end-to-end choledoco-choledocal anastomosis was usually performed, but a transanastomotic T-tube was not used systematically. Patients received systematic postoperative CT scans between 5 and 15 days postoperatively to assess vascular complications, and echocolor Doppler was performed daily. In cases of renal failure, CT scans were performed when the renal function was recovered.

During LTs anesthesia team tended to have low central pressure during hepatectomy in order to reduce bleeding during caval dissection whenever possible. Systematic use of thromboelastogram was introduced at the beginning of the year 2018 for monitoring blood coagulation disorders. Extended donor criteria were defined according to the European Association for Study of Liver Disease, such as age ≥65 years, ICU stay with

ventilation >7 days, BMI >30, serum sodium >165 mmol/L, transaminases (alanine aminotransferase [ALT)] >105 U/L, aspartate aminotransferase [AST] >90 U/L), and serum bilirubin >3 mg/dl(30).

Statistical Analysis

The results for continuous data are expressed as the mean ± standard deviation or median and range as appropriate, whereas categorical variables are presented as numbers and percentages. Differences between groups were assessed by the chi-squared or Fisher's exact test for categorical variables as appropriate. In cases of continuous variables, the Wilcoxon rank sum test or the student *t*-test were used as appropriate. **Patient survivals estimated were calculated according the Kaplan–Meier method, and differences were assessed by the log-rank test.**

Two analyses were performed. In the first analysis, the cumulative sum (CUSUM) method was used for quantitative analysis of the learning curve. This method was used for operative time, and blood loss (need for transfusion of ≥ 6 RBC units). First, the cases were ordered chronologically and listed on a chart left from right. The line ascended for every patient who was operated on within a certain operating time and descended for every patient whose operative time was longer than a cut-off. For each patient included in the analysis, the real time to complete the operation minus the expected time to complete the procedure was used.

The CUSUM of the first patient was considered as the difference between the operative time for the first patients and the mean operative time for all patients. CUSUM of the second patient was considered as CUSUSM of the previous patient plus the difference between the operating time of the second patient and the mean operating time. This process was continued until CUSUM of the last patient was calculated as zero. Univariable and multivariable analysis was performed for factors that were predictive of longer operative time and blood losses (≥ 6 RBC) using logistic regression. The second adjusted CUSUM analysis was performed by adjusting for these factors. All

analyses were conducted using the following python modules (Python version 3.7.5): statsmodel 0.11.0 (https://www.statsmodels.org/) .

Results

During the period study, 210 consecutive LTs were performed by a single surgeon after having completed a hepato-pancreatico-biliary surgery fellowship. Based on the selection criteria, 181 LT cases were included. The median age of subjects was 57 years (range: 19-70 years), and the ratio of men to women ratio was 2.01 (121:60). All patients had cirrhosis but 9 patients who had fulminant liver failure (**Table 1**). Twenty patients had previous upper abdominal surgery.

The median MELD score was 23 (range: 6-40), and roughly 37% of the patients had a MELD score greater than 30. The morphologic characteristics of the recipients included a median BMI of 26 kg/m^2 (range: 16-45 kg/m^2), a median IAF value of 10 mm (range: 0.1-38 mm), a median OAF value of 19 mm (range: 4-62 mm), and a median M-SAD value of 144 mm (range: 76-247 mm). Liver atrophy was present in 45.3% of the recipients, and 43% (n=78 recipients) had retrohepatic IVC encirclement by segment 1. The median length of the retrohepatic IVC covered by segment 1 was 78.7 mm (range: 35.3-150.2 mm). A length greater than 8 cm was present in 74 patients (40.8%).

Splenomegaly and portosystemic shunts were present in 45.8% and 76.8% of the recipients, respectively (**Table 2**). Ascites and severe portal hypertension were present in 83(45.8%) and 59(32.5%) patients, respectively. The median operative time was 345 minutes (range: 180-745 minutes; mean 353±76 minutes), and the median cold ischemia time was 413 minutes (range: 172-731 minutes). Grafts with extended criteria were used in 123 patients (68%). The transfusion rate was 81% (n=141) with a median transfusion rate of 4 packed RBC units (range: 2-23 RBC units; mean 4.6±3.9 RBC units). While 34(18.7%) patients had no transfusion, 58 had ≥ 6 RBC units

transfused (41%) (**Table 3**). Perioperative continuous renal replacement therapy was used in 40 patients (22, 10%).

An early portal section (≤ 1.5 hours from skin incision) was performed in 101 LTs (55.8%). A temporary passive (n=63) or active portocaval shunt (n=68) was constructed during 131 LTs (71.8%), and postreperfusion syndrome occurred in 68 patients (37.5%). Multiple graft arteries were reconstructed in 38 (21%) LTs, 3 patients (1.66%) had postoperative arterial thrombosis, 5 patients had arterial stenosis (2.7%), 1 patient had portal thrombosis, and 1 patient had caval stenosis and 21 early and/or late biliary complications (11.6%). There were 28 patients who needed reoperation (15%), and 6 deaths were recorded during the first 90 postoperative days. Three patients underwent liver re-transplantation for: late hepatic artery thrombosis (1) and chronic rejection (2).

Learning Curve of PBLT

The raw operative time was plotted in chronological order with the corresponding adjusted CUSUM learning curve (**Figure 3**). This curve was seen to consist of three phases: an initial phase (1-70 PBLTs), a plateau phase (71-101 PBLTs), and a stable phase (102-181 PBLTs). **Table 4** shows a comparison of the three phases according to various parameters. No differences were detected across the three phases in terms of age, MELD score, biological values, and BMI.

The median duration of surgery (388.8 vs. 344.8 vs. 326.9 minutes; p=0.004, p=0.0004, p=<0.0001) and cold ischemia time (482.1 vs. 434 vs. 375 minutes; p=0.03, p=0.0005, p=<0.0001) decreased significantly across the three phases, despite having similar rates of previous upper abdominal surgery (8.7% vs. 16% vs. 11%; p>0.05), and obesity (30% vs. 26% vs. 22.2%; p>0.05). **There were no differences in the rate of ECD grafts transplanted over the three periods (62% vs. 66% vs. 73%; p=0.82, p=0.48, p=0.16).** There was a significant reduction in the amount of IAF over the three phases (12.6 vs. 14.7 vs. 10.4 mm; p=0.17, p=0.005, p=0.04), but the sagittal abdominal diameters were comparable (146.9 vs. 146.0 vs. 139.5 mm; p>0.05). While liver explant

weight was similar across the three phases, more patients had complete IVC encirclement by segment 1 in the initial phase (61% vs. 36% vs. 50%; p=0.02, p=1.00, p=0.13), as well as a longer segment of the IVC covered by segment 1 (83.4 vs. 86.7 vs. 75.9 mm; p=0.47, p=0.006, p=0.02) and a greater rate of IVC covered by segment 1 > 8cm (64% vs. 50% vs. 20%; p=0.25, p=0.13, p=<0.0001). Subgroup analysis indicated that complete IVC encirclement by segment 1 was also associated with a longer length of the IVC covered by segment 1 (p=0.0008) and was more frequent in men than women (49% vs. 34%; p=0.06), but it was not associated with higher rates of liver atrophy, obesity, and severe portal hypertension (p>0.05). **Subgroup analysis showed that obese patients (n=47) had higher OAF(27.9 ±13.9 vs 17.9±7.9;p<0.0001) and IAF (14.8±8.4 vs 10.9 ±6.2; p=0.001) and M-SAD (160.1 ±28.1 vs 137.2±25.1; p<0.0001) but similar morphometric liver characteristics (atrophy, segment of the IVC covered by segment 1, IVC encirclement by segment 1). In obese patients LTs took longer (380 vs 344 minutes; p=0.006), were characterized by higher RBC units transfused (5.5±4.9 vs 4.3±3.5;p=0.002) and decreased rate of early portal section (36% vs 62%; p=0.002). Moreover, patients with previous upper abdominal surgery had also longer operative time (413±102 vs.346±69; p=0.01), increased requirement for RBC units transfusions (6±5.07 vs. 4.4±3.07; p=0.05) and decreased rate of early portal section (30% vs 60%; p=0.01).**

There were no differences in the surgical approach used during the three phases except for a higher rate of transitory portocaval shunts during the early phase (81% vs. 46% vs. 72.8%; p=0.0007, p=0.01, p=0.24) and a progressive higher rate of early portal section over the time (35% vs. 43% vs. 77%; p=0.50, p=0.001, p<0.0001). As expected, temporary portocaval shunts were used less in patients with splenorenal shunts (64% (n=7) vs. 36% (n=4); p=0.01).

There was a statistically significant decrease in blood losses over the three phases, as demonstrated by the reduced number of RBC units transfused (6.00 vs. 3.90 vs. 3.71; p=0.02, p=0.79; p=0.0006), the increase in the rate of LT without transfusion (12% vs. 13% vs. 25.2%;

p=1.00, p=0.20, p=0.04), and the decrease in the rate of ≥6 RBC units transfused (55.5% vs. 23% vs. 30%; p=0.09, p=0.60, p=0.005). There were no differences in mortality, reoperation, biliary, and arterial complications over the three phases (p>0.05).

Overall, 1, 3, 5 year patients survival were 93%, 90%, 86%. Across the three phases there were no differences in 1 year patient survival (96% vs.92% vs.96%; p=0.37, p=0.25; p=0.93) nor in re-transplantation rates (2.8% vs0% vs1.2%; p=1.00, p=1.00; p=0.59).

The multivariable analysis identified the following as independent risk factors of longer operative time: surgeon experience (OR = 0.99; 95% CI = 1.00–1.01; p = 0.00006), previous abdominal surgery (OR = 1.97; 95% CI = 1.32–2.96; p = 0.01), early portal section (OR = 0.42; 95% CI = 0.30-0.57; p = 0.00001), portocaval shunt fashioning (OR = 1.68; 95% CI = 1.26–2.23; p = 0.0003), multiple arterial graft reconstruction (OR = 1.39; 95% CI = 1.02–1.91; p = 0.03), and length of the retrohepatic IVC (OR = 1.01; 95% CI = 1.00–1.01; p = 0.0006) (**Table 5**). The independent risk factors for increased blood loss (>6 RBC units transfused) were surgeon experience (OR = 0.98; 95% CI = 0.97–0.99; p = 0.0001), previous abdominal surgery (OR = 17.33; 95% CI = 2.73–110.2; p = 0.002), complete vena cava encircled by segment 1 (OR = 4.47; 95% CI = 1.34-14.86; p = 0.0001), severe portal hypertension (OR = 5.28; 95% CI = 1.45–19.2; p = 0.01), early portal section (OR = 0.09; 95% CI = 0.02-0.41; p = 0.001) prothrombin time (OR = 0.92; 95% CI = 0.90-0.95; p = 0.00001).

Discussion

The present study identified factors related to recipients (segment 1 morphology, previous abdominal surgery, severe portal hypertension) and the surgeon (surgeon experience, portocaval shunt fashioning, early portal section and multiple arterial reconstructions) that pose challenges in terms of operative time and blood losses during the learning curve of PB-LT. According to the CUSUM plot, three phases could be identified to assess the learning curve effect. Despite similar

characteristics of patients in terms of anthropometrics and severity of their liver disease, the operative time and blood loss improved over these phases.

To the best of our knowledge (7, 13), this is the first study to quantify this learning curve cut-off in seventy consecutive LTs to reach proficiency in terms of operative time and blood loss. The surgeon's experience was identified as an independent risk factor that impacts operative time and blood loss. The identification of the cut-off and recognizing surgeon experience as prognostic factor could be useful for training, organization of surgical teams, and credentialing. The identification of factors that predict prolonged operative time and difficulties could help to improve the results of LT. Recognizing the most difficult cases could help transplant centers to tailor operative timing and the operating surgeon based on the case's complexity. This could consequently lead to a significant reduction in operative time, blood losses, ischemia time, and graft loss.

Not surprisingly, the recipients' characteristics have a major impact on the operative time and blood loss in LT. Previous upper abdominal surgery was identified as an independent risk factor for increased operative time and blood loss. This is certainly related to the difficulties of entering the abdominal cavity in the presence of dense adhesions with portal hypertension, which increased notably the overall blood losses and the time to achieve portal section. We confirmed the findings of three previous studies(7, 13, 14) that showed that previous abdominal surgery increases hepatectomy time and bleeding with a consequent reduction in overall survival in the long term.

We also identified that the morphology of the dorsal sector of the liver contributes to increasing the complexity of LT. Liver dysmorphia characterized by variable degrees of total liver volume, atrophy, and hypertrophy of the dorsal sector of the liver is a common finding in cirrhotic patients. About 50% of our recipients had complete encirclement of the retrophepatic IVC by segment 1, which is similar to what was reported in other series (10, 11). This circumferential hypertrophy of the dorsal sector is also accompanied by a variable amount of coverage of the retrohepatic IVC by segment 1. Both of these phenomena, which are closely related, significantly

increased the operative time and blood loss in the present study. These findings are in accordance with two previous studies(10, 11), which showed that hypertrophy of segment 1 is associated with increased rates of IVC injuries and blood loss. Both the degree of encirclement of the IVC and the length of the IVC covered by the dorsal sector of the liver can be easily identified in preoperative CT scans as contributing to scoring the difficulties of LT preoperatively. Indeed, one can imagine that in some cases of advanced hypertrophy of segment 1, the classical resection of the native retrohepatic IVC instead of a PB technique could be planned to reduce the time and blood loss.

At this regard surgical approach to the retrohepatic IVC during PBLT such as methods of venous reconstruction still change according to different centers as demonstrated by multicenter surveys (17, 18). While some authors reported reduced operative time and blood loss using a side-to-side cavo-cavostomy instead of PB technique (31) others reported opposing results(32). The dissection of the segment 1 from the retrohepatic IVC, achieved by different approaches (3, 27-29), represents probably the most time-consuming part of the PB hepatectomy technique. Morphology of the segment 1 impacts the duration and the difficulties of this phase such as confirmed in the present study. In the technique of side-to-side cavo-cavostomy the hepatic veins can be sectioned earlier during the hepatectomy, and this could theoretically accelerate the hepatectomy time by improving the exposure of the IVC from a side-view. A randomized controlled study, stratifying on surgeon, disease and patients' factors, could provide a possible answer to identify the most efficacious technique of hepatectomy and venous reconstruction for PB LT.

A recent Eurotransplant cohort study(9) demonstrated that prolonged implantation time linearly contributes to graft loss, with each 10-minutes increase in implantation time being equivalent to one hour of cold ischemia time. We also identified that multiple arterial reconstruction increases the total operative time. This is certainly related to the fact that at our center, replaced arteries are always reconstructed after first unclamping the arterial axis directly in the recipient. A direct

reconstruction by a senior surgeon on the back table could certainly reduce the operating time, although some authors discourage this(15).

Fashioning a transitory portocaval shunt was associated with prolonged operative time in our study. The fashioning of these shunts could add more time to the entire procedure (15 to 25 minutes), but in our opinion, several advantages must be acknowledged besides those already demonstrated in terms of blood loss and renal function(33, 34). Early portal section followed by shunt creation can in fact improve the dissection of the retrohepatic IVC while avoiding bowel edema and reduced working space. In the current study, the overall operative time significantly improved despite a similar rate of shunt fashioning between the initial and stable phases (p=0.24).

Blood loss has a major impact on the long-term survival of LT recipients. Rana et al.(13) found that previous major abdominal surgery, warm ischemia time, previous surgery, and hepatectomy time are correlated with increased blood loss. The current study found that severe portal hypertension (varices/shunts and splenomegaly and thrombopenia) and low prothrombin time were independent risk factors along with previous abdominal surgery for increased blood loss. Platelet count and prothrombin time have previously been identified as risk factors for increased bleeding by other studies(20) and were similar over the three phases identified by the CUSUM analysis. Nevertheless, the transfusion rate and amount of RBC units transfused significantly improved, showing that surgeon experience can play a determinate role in difficult cases. Again, the factors identified could be used to score LT difficulties preoperatively to tailor the surgeon's strategy. **Continuous experience in PBLT contributed to the gradual improvement in its performance as showed by decreased operative and blood loss. The gain in experience was also associated to changes in operative technique. In fact the approach used for total hepatectomy was gradually changed over the time toward an immediate liver devascularization as indicated by the rate of "early portal section". This early portal section, in our opinion, reduces blood losses and improves the access to the retrohepatic IVC speeding**

up the entire procedure. The time needed to achieve this early portal section reflects also the difficulties to reach the portal vein which is the deepest element into the hepatic pedicle. This time can be influenced by patients (anthropometrics (M-ASD), obesity, and previous surgery), disease (degree of portal hypertension, blood coagulation disorder, presence of portal thrombosis) and surgeon (experience) factors.

The results of challenging procedures such LTs performed in critical-ill patients should be considered always as a "team-work" result. The impact of anesthesia management during LTs had undoubtedly a greater weight such as preoperative reanimation and postoperative care given from our intensive care units. The current analysis could not capture and quantify the exact impact of all these factors.

The current study has several limitations that deserve commentary. First, all of our LTs were performed according to the three-vein PB technique, in which the dissection of the IVC can be somewhat different from those seen in other techniques (two veins, side-to-side, and end-to-side).The results of this study should be confirmed in other studies using these techniques. Second, cumulatively analyzing the hepatectomy and the reconstructive time could have hidden some factors related to one of the two phases. However, the factors that we identified were similar to those identified in previous studies (7, 13). **Third, LTs were performed by a senior surgeon assisted by different fellows and senior residents changing over almost 6 years. These changes had probably an impact on operative time which was difficult to quantify but more important at the beginning of experience.**

Conclusions

Easily identifiable factors related to recipients (segment 1 morphology, previous upper abdominal surgery, severe portal hypertension) and the surgeon (operative experience, portocaval shunt fashioning, early portal section and multiple arterial reconstructions) impact operative time and

blood losses during the learning curve of PB-LT. These factors can be used for grading the difficulties of LT to tailor the surgical strategy.

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Conflict of Interest/Disclosure

None.

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Figure Legends

Figure 1. Radiologic representation of anthropometric measures used. Anthropometrics of the recipient included intra-abdominal fat (IAF), outer abdominal fat (OAF), and modified sagittal abdominal diameter (M-SAD).

Figure 2. Radiologic representation of segment 1 morphology with complete encircling of the IVC. The length of the IVC covered by segment 1 (L-IVC) was defined at the longest distance between the confluence of hepatic veins in the IVC and the lowest extremity of segment 1 recorded on the sagittal reconstruction of the CT scan

Figure 3. Evolution of operating time in hours plotted against cases of LTs performed (blue curve). Cumulative sum (CUSUM) plotted against number of patients; the red dotted curve represents the curve of best-fit for the plot.

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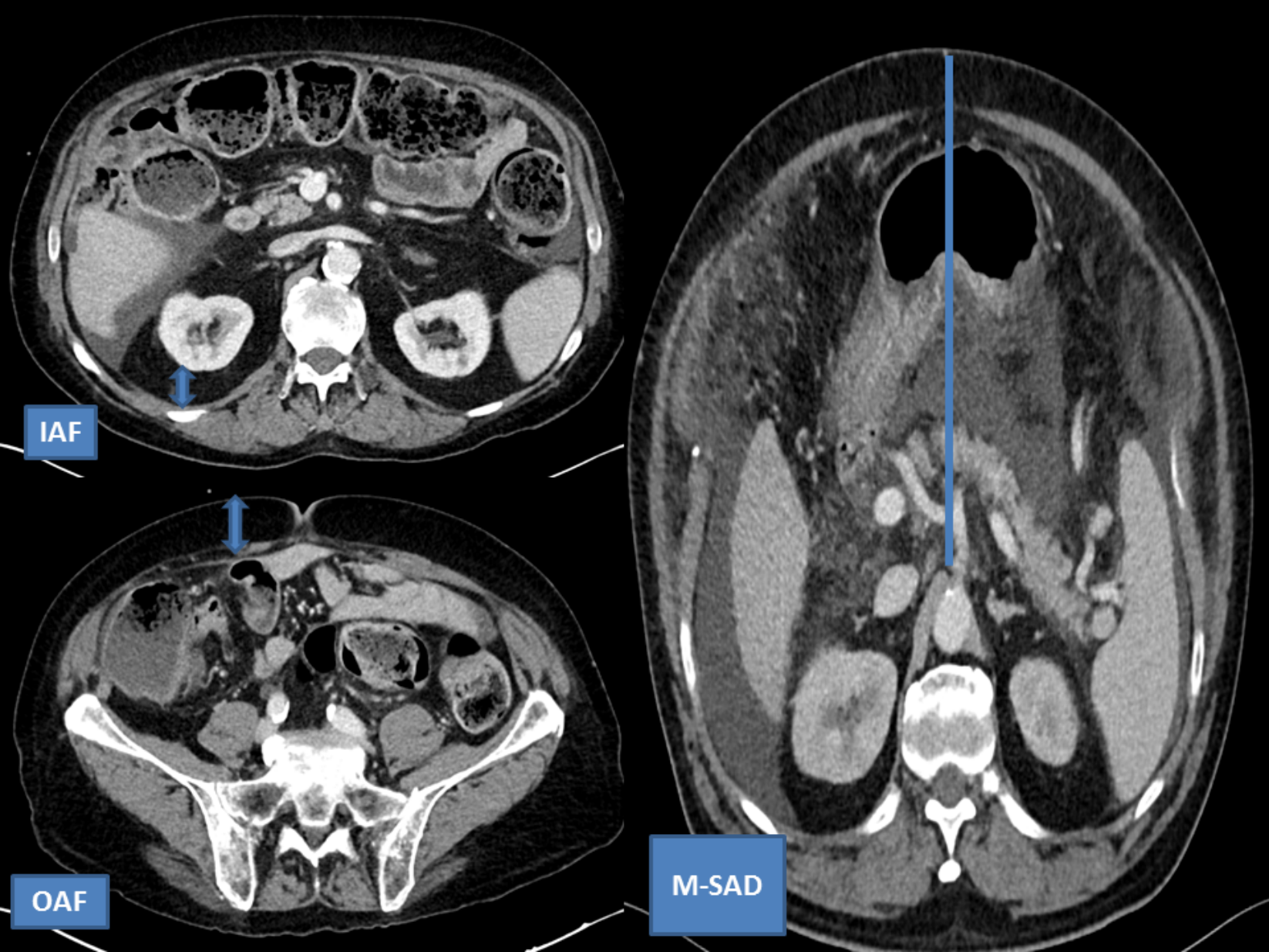
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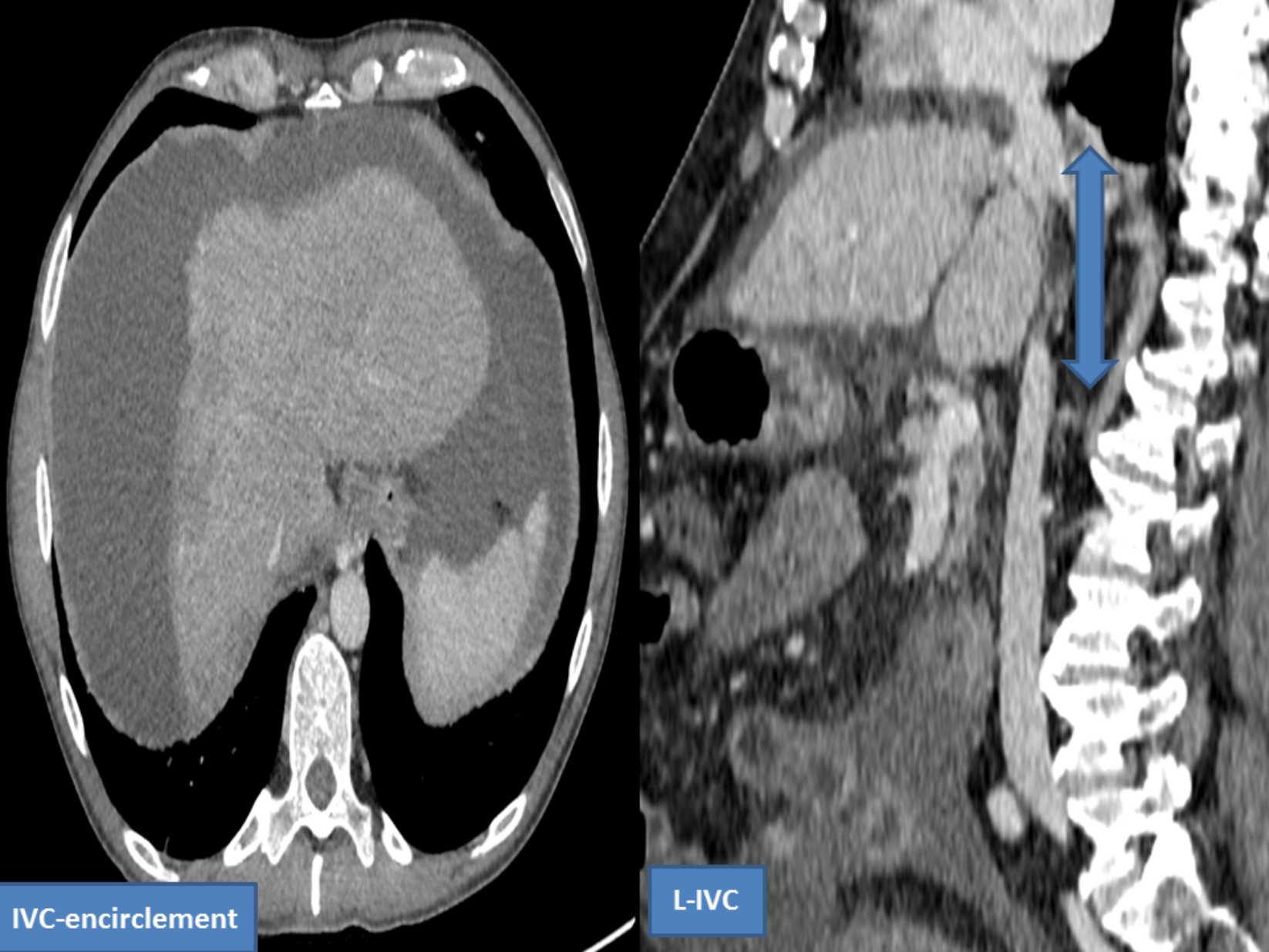
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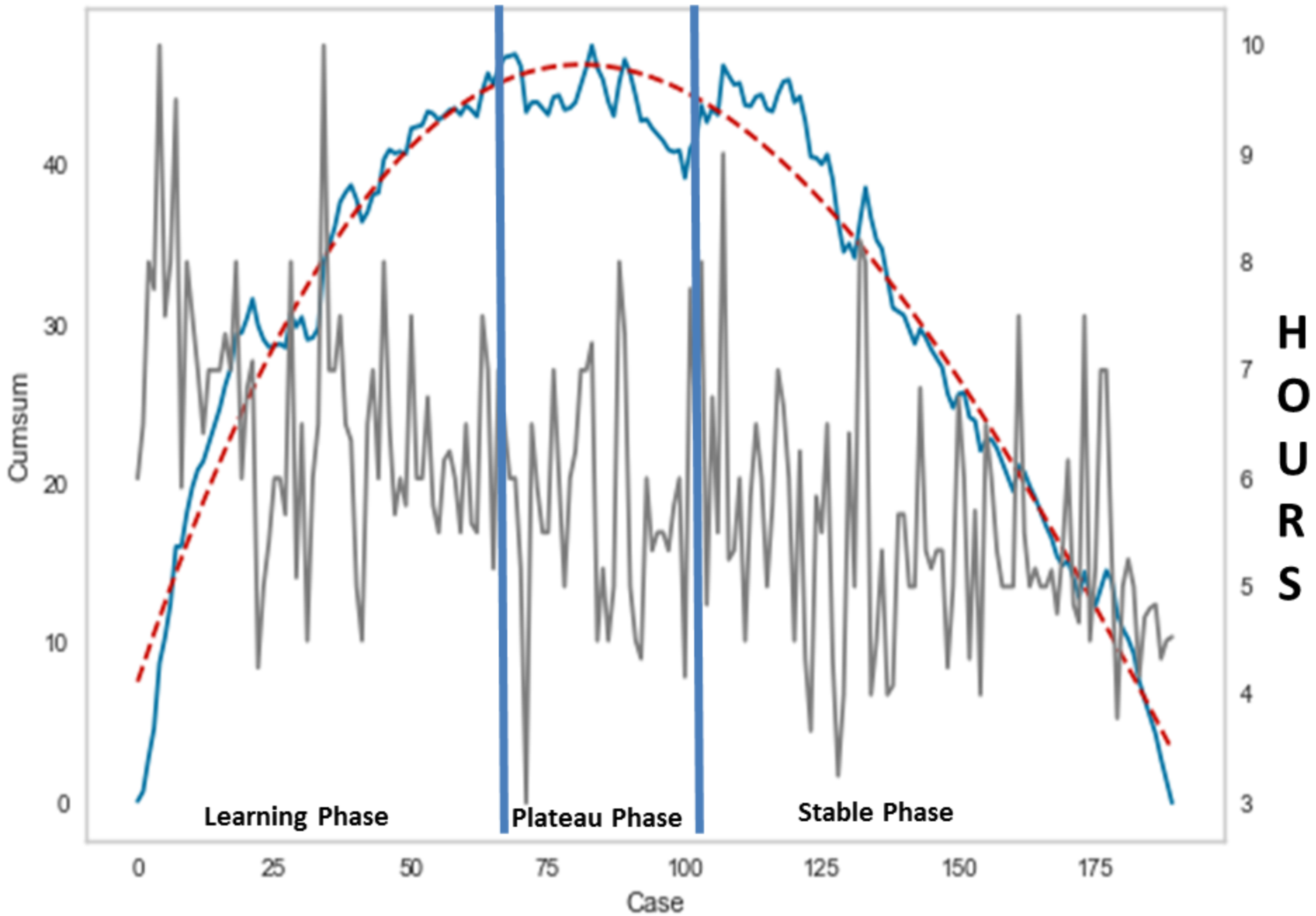
Cumsum
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Learning Phase
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175

Table 1 : Demographic and clinical data

Age, median (range)	57(19-70)
Male/female	121/60
Indications for liver transplnatations	
Alchoolic cirrhoses(+27HCC)	86
Viral Cirrhoses(+24 HCC)	33
Metabolic cirrhoses	14
Fulminant hepatitis	9
Bilairy cirrhoses	12
Autoimmune cirrhoses	7
Metabolic liver disease	4
Other cirrhoses	9
Other malignancy	2
HCC on criptogenic cirrhoses	5
Previous abdominal upper surgery	20(11%)
MELD median (range)	23(6-40)
MELD>30	67(37%)
Bilirubin	66(3-795)
Platelet count	81(20-359)
Protrombine time	42(8-100)

Table 2 : Anthropometrics and liver morphology characteristic of patients population

Height , median(range)	172 cm(145-196)
Weigth , median(range)	77 Kg (43-140)
BMI, median (range)	26Kg/m^2(16-45)
Obesity (%)	47(25.9%)
Sagittal abdominal diameter (SAD), median (range)	144mm(76-247)
Intra-abdominal fat (IAF), median(range)	10mm(0.1-38)
Outer abdominal fat (OAF), median (range)	19mm(4-62)
Splenomegaly	83(45.8%)
Liver morphology	
Atrophy	82(45.3%)
Segment 1 encirclement of the vena cava	78(43%)
Length of the IVC covered by the segment 1 (L-IVC), median,range	78.7 mm(35.3-150.2)
Portal vein thrombosis	16(8.84%)
Portosystemic shunts	139(76.8%)
Ombilical	80
Splenorenal	11
Gastric, œsophageal varices	70
TIPS	12
Ascite	84(46%)
Severe portal hypertension	59(32.6%)
Liver weight, median (range)	1308 gr(688-5600)

Table 3: Operative outcomes of patient's population

Operative time, median(range)	345 minutes(180-720)
Cold ischemia time, median (range)	413 minutes(172-731)
Transitory porto-caval shunt	131(72%)
Passive shunts	63
Portocaval shunt	68
Red blood cell units median (range)	4(0-23)
Plasma unit median (range)	4(0-45)
No blood red cell transfusion (%)	34(18.7%)
Perioperative continuous replacement therapy	40(22.10%)
Multiple graft arteries	38(21%)
Mortality (90 days)	6(3.31%)
Arterial thrombosis	3(1.66%)
Portal vein thrombosis	1(0.05%)
Caval stenosis	1(0.05%)
Biliary complications	21(11,6%)
Reoperation	28(15%)

Table 4: Interphase comparison of 181 patients undergoing first piggyback liver transplantation.

	Phase 1(n=70)	Phase 2(n=30)	Phase 3 (n=81)	P (1vs2)	P (2vs 3)	P (1vs3)
AGE	53.5	53.6	56.0	0.96	0.28	0.17
MELD	22.9	23.9	25.5	0.71	0.48	0.18
MELD>30	24(34%)	11(36%)	32(39.5%)	0.82	0.82	0.50
Bilirubin	144	180	136	0.40	0.22	0.78
Prothrombin time	49	46.8	42.9	0.65	0.40	0.10
Previous upper abdominal surgery	6(8,7%)	5(16,6%)	9(11.1%)	0.30	0.52	0.78
Obesity	21(30%)	8(26%)	18(22.2%)	0.81	0.62	0.35
BMI	26.8	27.6	26.9	0.44	0.40	0.95
Ascites	35	14	35	0.82	0.67	0.33
Spontaneous shunts	56(80%)	25(83%)	58(71, 6%)	0.78	0.23	0.25
Splenomegaly	27(38.5%)	14(46.6%)	42(51.8%)	0.50	0.67	0.14
Sagittal abdominal diameter (SAD), median (range)	146.4	146.0	139.5	0.94	0.18	0.14
Intra-abdominal fat (IAF)	12.6	14.7	10.4	0.17	**0.005**	**0.04**
Outer abdominal fat (OAF)	21.6	21.8	19.6	0.75	0.11	0.42
ECD donors	44(62%)	20(66%)	59(73%)	0.82	0.48	0.16
IVC covered by Segment 1>8cm	43(64%)	14(50%)	17(20%)	0.25	0.13	**<0.0001**
IVC covered by segment 1	83.4	86.7	75.9	0.47	**0.006**	**0.02**
IVC encircled by segment 1	43(61.4%)	11(36.6%)	41(50, 6%)	**0.02**	1.00	0.13
Operative time	388.8	344.8	326.9	**0.004**	**0.0004**	**<0.0001**
Overnight LT	14(20%)	2(6%)	17(21%)	0.13	0.09	1.00
Cold ischemia time	482.1	434	375	**0.03**	**0.0005**	**<0.0001**
Transitory porto-caval shunt	57(81%)	14(46%)	59(72.8%)	**0.0007**	**0.01**	0.24
Early portal section	25(35%)	13(43%)	63(77.7%)	0.50	**0.001**	**<0.0001**
Multiple arterial reconstruction	15(21%)	9(30%)	14(17.1%)	0.44	0.18	0.51
Red blood cell unit	6.00	3.90	3.71	**0.02**	0.79	**0.0006**
Plasma unit	8.50	3.06	2.7	**0.005**	0.72	**<0.0001**
No blood red cell transfusion (%)	9(12.8%)	4(13%)	21(25, 2%)	1.00	0.20	**0.04**
>6RBC	34(55.5%)	6(23%)	18(30%)	0.09	0.60	**0.005**
Liver weight	1480	1407	1425	0.61	0.52	0.59
Mortality	2(2.86%)	0(0%)	4(4.94%)	1.00	0.57	0.68
Reoperation	12(17%)	4(13%)	12(14,8)	0.77	1.00	0.82

Retransplantation	2(2.8%)	0(0%)	1(1.2%)	1.00	1.00	0.59
1-year survival	92%	96%	96%	0.37	0.25	0.93

Table 5: Univariate and multivariate analysis of risk factors predicting longer operative time to perform liver transplantation.

	Univariable						Multivariable					
Variables	**Beta**	**SE**	**Wald**	**OR**	**CI95%**	**P**	**Beta**	**SE**	**Wald**	**OR**	**CI95%**	**P**
MELD>30	0.15	0.18	0.84	0.85	(0.59-1.23)	0.39						
Male gender	-0.06	0.19	-0.36	0.93	(0.64-1.36)	0.71						
Obesity	0.62	0.20	3.12	1.87	(1.01-1.08)	**0.003**						
IAF	0.01	0.01	1.15	1.01	(0.99-1.04)	0.29						
OAF	0.01	0.008	2.06	1.01	(0.49-1.13)	0.24						
Platelet count	0.001	0.001	1.05	1.00	(0.73-2.57)	0.31						
Prothrombin time	0.009	0.003	2.41	1.00	(1.05-2.48)	**0.02**						
Severe portal Hypertension	0.03	0.19	0.17	1.03	(0.70-1.51)	0.86						
Portal vein thrombosis	0.31	0.31	1.00	1.37	(0.82-1.69	0.36						
AUD	0.006	0.003	2.13	1.00	(1.00-1.01)	**0.04**						
Liver atrophy	-0.48	0.17	-2.71	0.614	(1.51-2.50)	**0.007**						
Retrohepatic -IVC length	0.02	0.004	4.77	1.02	(1.01-1.02)	**0.000003**	0.01	0.003	3.46	1.01	(1.00-1.01)	**0.0006**
Retrohepatic -IVC covered by segment 1 > 8 cm	0.62	0.17	3.56	1.86	(1.32-2.63)	**0.0006**						
IVC encirclement	0.16	0.18	0.90	1.18	(0.59-1.23)	0.39						
Previous upper abdominal surgery	0.97	0.27	3.48	2.64	(1.52-4.58)	**0.0006**	0.68	0.20	3.32	1.97	(1.32-2.96)	**0.001**
Spontaneous shunt	-0.29	0.21	-1.36	0.74	(0.99-1.04)	0.30						
Splenomegaly	0.11	0.18	0.62	1.11	(0.78-1.60)	0.53						
Early portal section	-1.33	0.17	-7.82	0.26	(0.18-0.36)	**0.00004**	-0.86	0.15	-5.51	0.42	(0.30-0.57)	**0.0001**
Portocaval shunt	0.52	0.19	2.68	1.69	(1.00-1.01)	**0.01**	0.52	0.14	3.60	1.68	(1.26-2.23)	**0.0003**
Liver weight	0.0003	0.0001	2.42	1.00	(1.05-2.48)	**0.02**						
Surgeon experience	-0.009	0.001	-7.40	0.99	(0.98-0.99)	**0.00001**	-0.005	0.001	-5.15	0.99	(1.00-1.01)	**0.00006**
Multiple graft arteries	0.48	0.21	2.21	1.61	(1.00-1.01)	**0.01**	0.33	0.15	2.09	1.39	(1.02-1.91)	**0.03**

Overnight LT	-0.49	0.23	-2.14	0.60	(1.05-2.48)	**0.02**						