UNIVERSITY OF MEDICINE AND PHARMACY
''CAROL DAVILA'', BUCHAREST
DOCTORAL SCHOOL

PERIOPERATIVE HEMODYNAMIC MANAGEMENT IN LIVER TRANSPLANT PATIENTS

Summary of the PhD Thesis

PhD COORDINATOR:
PROF. UNIV. DR. DICULESCU MIRCEA

PhD Student:
BREZEANU (JIPA) LAVINIA NICOLETA

2023

CONTENT

Introduction

Liver transplantation is the treatment of choice for end-stage liver disease. Since the first successful liver transplant in 1967, the survival rate has improved considerably. [1] Despite numerous developments in surgical techniques, immunosuppression as well as perioperative anaesthetic management, anaesthesia in liver transplantation is considered the greatest challenge for the anesthesiologist. It requires extensive experience as well as a good knowledge of the pathophysiology of liver disease and its systemic manifestations.

The increasing survival rate of cirrhotic patients has led to a significant increase in the number of patients awaiting liver transplantation. Thus, liver transplant patients are older and have more associated comorbidities. [2] The cirrhotic patient is a high risk patient with cardiovascular, pulmonary, renal and coagulation disorders. [3]

Characteristic for cirrhotic patients is the presence of a hyperdynamic status, with increased cardiac output and decreased systemic vascular resistance. Some patients present cirrhotic cardiomyopathy with impaired contractility and prolonged QT. [4] The early diagnosis of hemodynamic instability during liver transplantation as well as its prompt management is one of the important factors for a favorable prognosis. Various modalities have emerged over time for adequate cardiac output monitoring. The pulmonary artery catheter was initially used, but studies have shown that it is no longer the gold standard for cardiac output monitoring in liver transplantation. [5]

In this paper, we sought to elucidate some aspects related to the hemodynamic profile of patients with liver cirrhosis and its modification during the three important surgical stages. The objectives of the present study included the characterization of hemodynamic disturbances encountered during liver transplantation and their variations during the three surgical stages. Another objective of the work was to study the correlation between the amount of bleeding, the severity score and the duration of survival and occurrence of complications. Considering the practical applicability of the obtained results, the present study followed the amount of blood products transfused and the probability of postoperative complications occurence according to them.

In order to achieve these objectives, in this work we compiled a group of patients undergoing liver transplantation between January and December 2019. To analyze the hemodynamic status, the data obtained using the PiCCO cardiac output monitoring system were recorded. The collection of hemodynamic data was carried out in the pre-anhepatic, anhepatic and neohepatic stages, but also in case of the occurrence of important hemodynamic changes.

I. General part

1.1 The cirrhotic patient - particularities

The hyperdynamic circulation specific to patients with liver cirrhosis is characterized by an increase in cardiac output (CO), heart rate as well as a decrease in systemic vascular resistance (SVR) and arterial pressure. [6] Regarding systemic circulation, arterial vasodilatation causes an apparent hypovolemia, the compensatory vasoconstrictor system becomes ineffective and arterial hypotension occurs. In early stages these changes can be compensated by the increase in cardiac output. In advanced stages, arterial hypotension occurs and compensatory mechanisms are activated: sodium (Na) and water retention, activation of vasoconstrictor systems (sympathetic system, renin angiotensin aldosterone and vasopressin) with an increase in heart rate, CO and stroke volume - SV. [7]

The heart of cirrhotic patients shows numerous changes, there is an increase in the end-diastolic volume of the left ventricle (LVEDV) as well as the volume of the left atrium, septal hypertrophy, hypertrophy and dilation of the right ventricle (RV), cardiomegaly. All of these correlate with increased BNP (B-type natriuretic peptide). [8,9] Studies have shown that alcoholic cirrhotic patients have more frequent coronary artery disease than patients with non-alcoholic cirrhosis. [10] Cardiac ultrasound has proven to be extremely important for the evaluation of patients on the waiting list. Echocardiography can assess LVEF, pulmonary artery pressure as well as the presence of hepatopulmonary syndrome. [11] Depending on the results obtained,

further investigations may be performed to rule out portopulmonary hypertension (right heart catheterization). [12]

Hepatopulmonary syndrome is one of the important respiratory complications in cirrhotic patients. It causes a decrease in the diffusion capacity, alteration of the ventilation/perfusion ratio, intrapulmonary vascular dilatations, as well as low arterial oxygen saturation. [13] Portopulmonary hypertension is confirmed by the association between portal hypertension and pulmonary hypertension. Symptoms appear progressively, dyspnoea, retrosternal pain or even syncope, and treatment includes administration of diuretics, vasodilator substances and oxygen therapy. Liver transplantation performed in cirrhotic patients with a mean PAP value >35 mmHg is associated with increased postoperative mortality. [14,15]

1.2 Liver transplantation

Since 2007, the MELD score has been used to allocate liver grafts to patients with liver cirrhosis. [16] Liver transplantation can be performed with a whole liver or with a liver fragment, and the surgical intervention is divided into 3 important surgical stages, the pre-hepatic stage, the anhepatic stage and the neohepatic stage. [17] Considering the surgical technique, it can be done by the piggy back method: preservation of the inferior retrohepatic vena cava or by the classical method (resection of the retrohepatic IVC), both with a significant impact on the hemodynamic status of the transplanted patient. [18] The anesthetic team has the important role of evaluating the patient's degree of tolerance during this maneuver, the severity of the cardiovascular instability as well as its management.

Due to the improvement of surgical techniques, the anesthetic-surgical experience acquired, as well as the increase in the number of patients included on the transplant list, the potential recipients are older and have multiple associated comorbidities. They require an adequate and complex preoperative evaluation for the successful performance of liver transplantation. Echocardiographic evaluation is routinely performed in all patients on the transplant list; Troponin I and BNP are measured, elevated values suggesting worsening cardiac function. Evaluation of coronary artery disease is performed in all patients with at least 2 risk factors by noninvasive stress tests - dobutamine cardiac ultrasound and SPECT. [19] Depending on the protocol of each liver transplant center, other non-invasive examinations such

as cardiac MRI and coronary CT angio can be performed – a calcium score >400 Housefield is associated with clinically significant CAD. There are other ways to assess functional status: the 6-minute walk test, the cardiopulmonary exercise test (CPET) or metabolic equivalents (METs). The results correlate with the incidence of cardiac events and the prognosis of patients after transplantation. [20,21]

Liver transplantation is an operation with high surgical risk performed under general anesthesia. Despite the development of surgical techniques and complex anesthetic monitoring, this intervention remains a challenge for the anesthesiologist due to the involvement and multiorgan changes. [22] The operation is performed under general anesthesia, patients are hemodynamically monitored with invasive devices and rapid infusion machines and viscoelastic tests are used to control coagulopathy. Hemodynamic management is specific to each surgical stage. Depending on the surgical technique, the anhepatic phase is characterized by marked cardiovascular instability because the hepatic outflow is obstructed and the blood flow is sequestered in the portal system. It will cause a significant decrease in preload, cardiac output and blood pressure. Hemodynamic stability is maintained with the help of vasoactive and inotropic substances. Coagulation disorders are very important because factor synthesis is non-existent in this phase. Graft reperfusion can cause reperfusion syndrome, worsening pulmonary hypertension to right heart failure, and increased intracranial pressure.

Adequate hemodynamic monitoring is extremely important in patients undergoing liver transplantation. There is no standard monitoring for transplant patients, there are several options with a number of advantages and disadvantages. The type of monitoring used varies depending on the center where the intervention is performed, the experience of the surgical team, the economic status of the respective country, the preoperative assessment and optimization of the patient, the surgical technique. The anesthesiologist is responsible for choosing the best option based on the needs of each patient. [23]

Invasive blood pressure monitoring is imperative for all patients undergoing this surgery. Hemodynamic cardiac output monitoring with the PiCCO system requires a central arterial pressure signal (femoral artery) for thermodilution calibration. [24] Cirrhotic patients present with a hyperdynamic status, and cardiac output is the most frequently used parameter to assess cardiovascular status in case of hemodynamic instability. Recent studies have shown the use of transesophageal

echocardiography with a frequency of 87-94% in US liver transplant centers; 38% of these use routine TOE during liver transplantation. [25] The use of TOE offers the opportunity to directly evaluate the right and left cavities, preload, the presence of thrombosis or gas embolism, Takotsubo cardiomyopathy. The use of TOE in the setting of severe hypotension or hypoxia is crucial. [26]

The PiCCO system allows cardiac output measurement by analyzing the pulse waveform but also by the transpulmonary thermodilution method. It requires the placement of a thermodilution catheter at the level of the femoral artery; it is a less invasive method than pulmonary artery catheter. Another advantage is the determination of global end-diastolic volume and can be used to calculate intrathoracic blood volume and the amount of extravascular water as a marker of interstitial pulmonary edema. [24]

II. Special part

2.1 Results

In order to achieve the research objectives, the present study included 70 patients who underwent liver transplantation in the liver transplant center of the Fundeni Clinical Institute between January and December 2019 and who were hemodynamically monitored invasively through the PiCCO (Pulse Contour Cardiac Output) system. The inclusion of patients in this study was performed immediately preoperatively and demographic data, laboratory data, severity scores, liver disease etiology, transfusion of blood products as well as hemodynamic parameters measured using the PiCCO device in the 3 surgical stages (IC, SVRI, GEF, GEDI, ELWI). Postoperative data were recorded: duration of postoperative mechanical ventilation, complications, intensive care unit length of stay and 30/90 days mortality. Data was collected in Microsoft Excel and processed using the Python 3.9 programming language.

70 patients, 38 men (54.2%) and 32 women (45.8%) diagnosed with liver cirrhosis and undergoing liver transplant surgery were included in this study. The median age of the patients is 53.5 years. 27% (19) of the transplanted patients were

diagnosed with liver cirrhosis-HCV, 21.5% (15 patients) liver cirrhosis-HBV+HDV, 21.5% (15 patients) toxic nutritional liver cirrhosis, a number of 7 patients presented Wilson's Disease , and 2 patients underwent liver transplantation for acute liver failure.

The mean Meld severity score for liver transplant patients was 18 points. In the present study, 10 patients were transplanted with a related donor liver segment, and the remaining 60 patients received a brain dead donor whole liver. The median value of ascites fluid drained intraoperatively was 900 ml. 50% of patients presented with less than 1000 ml of ascites fluid. A proportion of 44.28% of patients (n=31) developed complications in the immediate postoperative period.

2.1.1 Variation of the hemodynamic parameters during the 3 important surgical stages

During the surgical intervention, significant variations in the hemodynamic parameters were observed with a significant decrease in the cardiac index, the global ejection fraction as well as the global end diastolic volume in the anhepatic stage compared to the pre-anhepatic one.

In the anhepatic phase due to clamping of the inferior vena cava, all patients showed a significant decrease in cardiac output. In this stage, compared to the pre-hepatic stage, half of the patients show a decrease in the cardiac index by more than 40%. The median value is -0.4, which represents a decrease of 40%. In the neohepatic stage, following declamping and increased venous return, cardiac index tends to return to its initial value. More than half of the studied patients present a cardiac index value greater than 10% compared to the value in the pre-hepatic phase.

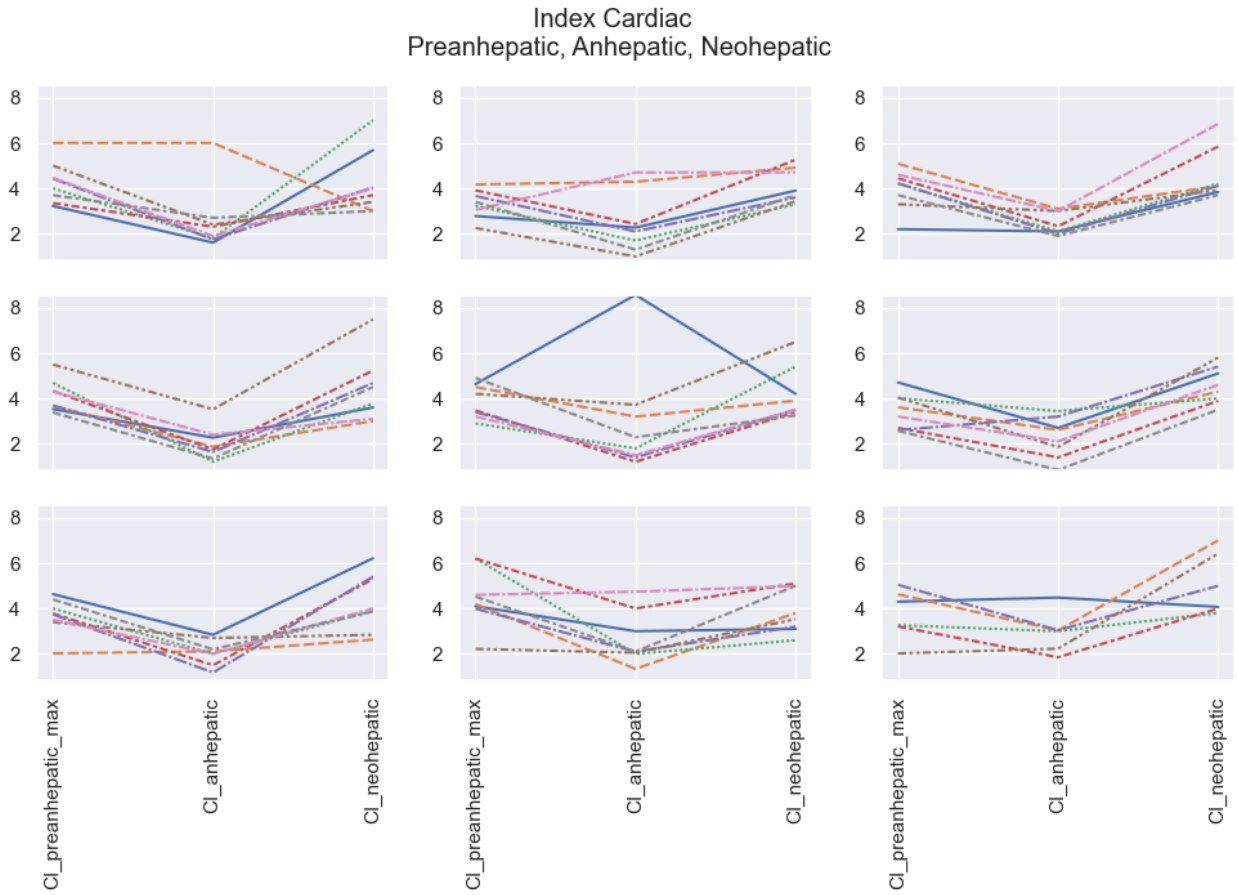

Figure 1. Cardiac index variation during the surgical phases

Secondary to important changes in cardiac output, changes in systemic vascular resistance also occur. In the anhepatic stage, secondary to the significant decrease in cardiac output, there is a significant increase in SVRI, more than 75% of patients show an increase in SVRI. After vena cava declamping and resumption of hepatic circulation, SVRI tends to return to baseline, but 60% of patients will have lower systemic vascular resistance compared to the prehepatic phase. Using the PiCCO system, the global ejection fraction can be calculated. In the studied group, the average global ejection fraction value was 33.7% in the pre-hepatic stage. In the anhepatic stage, there is a decrease in preload with a decrease in GEF, 78% of patients show decreases in the global ejection fraction, with a median value of 30%. In the neohepatic stage compared to the initial stage of the transplant, the preanhepatic stage, the tendency is to increase the GEF above the value from initial phase. Thus 60% of patients show an increase in global ejection fraction, with a median value of 10%.

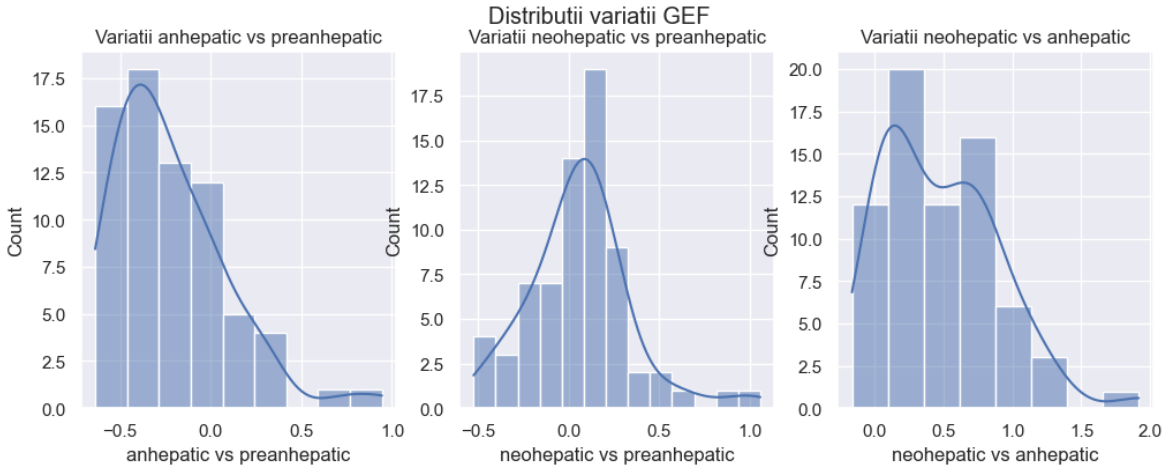

Figure 2. Distribution of global ejection fraction

Another advantage of hemodynamic monitoring is the possibility of characterizing the volume status in various stages of the surgical intervention using the GEDI parameter. The average value of GEDI in patients in the studied group was 667 ml/kg in the pre-hepatic stage. In the anhepatic stage, 75% of patients show a decrease in GEDI. After inferior vena cava declamping and resumption of hepatic circulation, 75% of patients show increases of up to 70% in GEDI, and the remaining 25% show decreases in GEDI.

The dose variation in vasopressor support, noradrenaline in the studied group, is in accordance with the hemodynamic status presented above during the 3 stages of liver transplantation. Most patients (over 90%) will need minimal vasopressor support in the pre-hepatic stage (mean value 0.22 mcg/kgc/min). In the anhepatic stage, due to the significant decrease in cardiac output, there is an important increase in the noradrenaline dose with a median value of 380%. In the neohepatic stage, the need for vasopressor support decreases, the dose of noradrenaline is similar to the initial one, the median value of the variation being 0, with the mention that approximately 25% of patients still register increases of 150-250% compared to the pre-hepatic stage. The average value of serum lactate in the pre-hepatic stage is 2.49 mmol/L, 4.17 mmol/L in the anhepatic stage and in the neohepatic stage the average value is 3.92 mmol/L. In the anhepatic stage of the transplant, we observe that half of the patients show increases of more than 70% of the serum lactate value compared to the initial stage. 98% of all patients show increases in serum lactate at this stage. The last phase of liver transplantation is characterized by a discrete decrease in the lactate value compared to the anhepatic stage (median value of -10%).

2.1.2 The impact of bleeding on hemodynamic status and outcome

The median intraoperative bleeding is 3000 mL in the study group. 75% of the patients have a bleeding amount of less than 6000 ml. From the group of patients studied, 31 (44.28%) developed postoperative complications. Patients who experienced postoperative complications were observed to have a higher degree of intraoperative bleeding compared to those without complications. Following the logistic regression model performed, it can be observed that the complications variable is significantly different from 0 because the p-value is 0.002 (below 0.05). Thus, the probability of postoperative complications depending on the amount of bleeding is shown in the graph below.

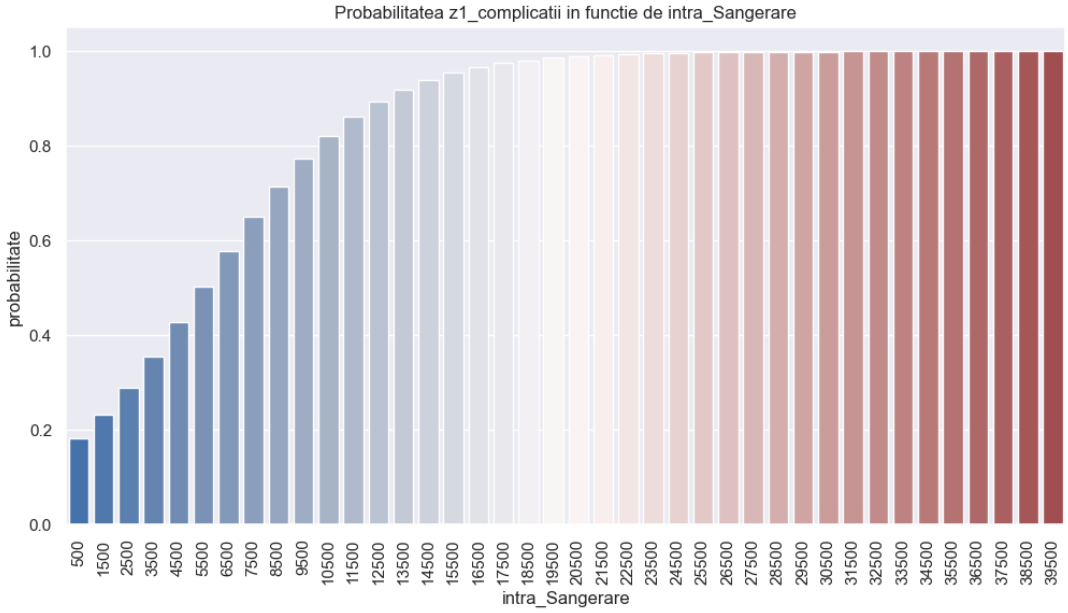

Figure 3. Probability of complications depending on the intraoperative bleeding

The graph above shows there is a 50% probability of postoperative complications if the bleeding exceeds 6500 ml. In case there is a larger amount of bleeding, of around 10,000 ml, we will have an 80% chance of complications after liver transplantation.

In this study group, 7 patients (10%) did not survive 30 days after liver transplant surgery. We observe that the variable survival at 30 days is significantly different from 0 because the p-value is 0.002 (below 0.05). With a bleed of 10,000 ml there is a 90% chance of survival at 30 days. In case of a larger amount of bleeding,

22000 ml, the chances of survival at 30 days are reduced to 50%. 8 patients (11.42%) do not survive 90 days after surgery. Most of the deaths occurred within 1 month, this is the critical period after liver transplantation. With a blood loss of about 5500 ml there is a 92% chance of survival at 90 days. In case of a larger bleeding, of 10000 ml the chances of survival are reduced to 82%. A major bleed of about 20,000 ml will decrease the chances of 90-day survival by 50%.

The logistic regression model performed demonstrates that the length of stay in the intensive care unit is not influenced by the amount of intraoperative bleeding, it is not a statistically significant link (p-value 0.239). Also, the age of the patients does not influence the amount of bleeding. It is noted that the R-squared value is 0, so 0% of the variation is explained by the age of the patients. The coefficient for age is -0.4892, which means that as age increases, bleeding decreases, but the p-value is 0.994, so statistically insignificant.

2.1.3 The link between the serum lactate level (in the anhepatic/neohepatic phases) and the evolution of transplant patients

The median value of anhepatic serum lactate is 3.8 mmol/L. 50% of patients have serum lactate values above 5 mmol/L in the anhepatic phase. The logistic regression model performed shows that the variation of lactate in the anhepatic stage is explained in proportion to 13% by the variation of the intraoperative bleeding. This is statistically significant, with a p-value of 0.002. The median length of stay in the intensive care unit is 6 days. A correlation is observed between the lactate level in the anhepatic phase and the length of stay in the intensive care unit. The number of ICU days increase on average by 0.53 when lactate increases by one unit. This model shows that 9% of the variation in postoperative length of stay is explained by the variation of the anhepatic lactate. This is statistically significant, with a p-value of 0.012. The median value of neohepatic lactate is 3.7 mmol/L. Through the statistical tests used, we observe that the lactate level in the neohepatic phase does not correlate with the prolonged stay in the intensive care unit (p-value 0.17).

Patients who developed postoperative complications have a higher lactate value in the neohepatic phase than those who did not develop complications. The way the neohepatic lactate variable affects the postoperative complications is investigated

by a logistic regression model. It can be seen that the neohepatic lactate variable is significantly different from 0 because the p-value is 0.033. Thus, the probability of postoperative complications depending on the value of serum lactate in the neohepatic stage is shown in the graph below. A serum lactate level of 5 mmol/L in the neohepatic stage determines a 50% probability of complications.

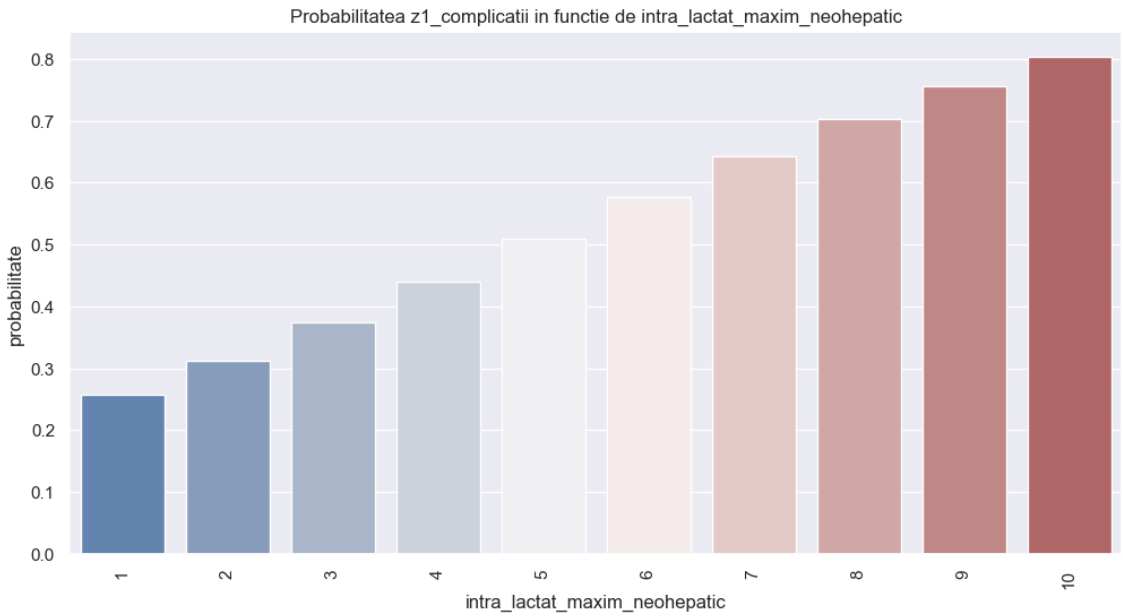

Figure 4. Probability of complications depending on the neohepatic lactate

2.1.4 Evolution of patients according to the type of liver transplant (whole liver or liver segment from a living donor)

In the present study 10 (14.2%) patients underwent liver transplantation with a liver segment from a related donor, and the remaining 60 (85.8%) patients underwent whole liver transplantation from a brain dead donor. A higher value of intraoperative bleeding is observed in patients who received a liver segment compared to those who received a whole liver transplant. From the performed regression it is observed that only 6% of the bleeding variation is explained by the liver transplant from the related donor. In the case of a living related liver transplantation we will have an average of 5283 ml more bleeding compared to a whole liver transplant. (p-value 0.045). The length of stay in the intensive care unit shows no statistically significant differences in patients with livers from related donors versus those with livers from brain dead donors. (p-value 0.62). Regarding postoperative complications,

in the case of whole liver transplantation 40% of patients develop postoperative complications, while in the case of those with living related, 70% of them develop complications after surgical intervention, but with a statistically insignificant value, p -value 0.09. We cannot be very sure about this difference, probably because there are few data and the statistical test requires the collection of more data on transplant patients.

Patients transplanted with a whole liver from a brain-dead donor will have a 95% chance of survival at 30 days, while those with TH-LR will have a lower 30-day survival, there is a 60% chance of survival. (p-value 0.004)

2.1.5 How does the amount of ascites influence the evolution of patients?

The median value of the amount of ascites drained intraoperatively is 900 ml. Half of the transplant patients present with an amount of ascites greater than 1000 ml. The tests performed demonstrate that there is a correlation between the amount of ascites drained intraoperatively and the occurrence of acute kidney injury on postoperative day 1. A logistic regression is performed which confirms the statistical significance (p-value 0.027). A percentage of 7.1% of the occurrence of postoperative acute kidney injury is explained by the amount of ascites drained intraoperatively in patients undergoing liver transplantation.

2.1.6 The impact of transfusion of blood products and the occurrence of postoperative complications

The study conducted shows that those patients who received red blood cell transfusions developed more complications than those who did not receive RBC transfusions. From the performed test it appears that the RBC variable is significantly different from 0 because the p-value is 0.001 (below 0.05). Transfusion of 7 RBC units will result in a 50% probability of postoperative complications. Also, patients who received fresh frozen plasma transfusions developed more complications than those who did not receive fresh frozen plasma. Transfusion with 5 units of fresh frozen plasma will increase the chance of postoperative complications by 40%. Similar to the investigations above, statistical tests were also performed to investigate the correlation between the transfusion of cryoprecipitate and platelets, respectively, with the occurrence of complications after liver transplantation. The tests proved that

there is no relationship between these variables and the occurrence of complications in the post-liver transplant period.

The correlation between RBC transfusion and duration of postoperative mechanical ventilation was studied. It was observed that there is a correlation between these 2 variables, confirmed by the logistic regression performed (p-value 0.002). A percentage of 13.7% of the prolonged duration of postoperative mechanical ventilation is influenced by the transfusion of red blood cells. The same statistical tests were performed to see if the transfusion of cryoprecipitate and platelets, respectively, influence the duration of postoperative mechanical ventilation. It has been shown that they do not influence in a statistically significant way the duration of mechanical ventilation, there is no link between these variables. Also, the statistical tests performed demonstrated that there is no statistically significant relationship between the intensive care unit length of stay and the transfusion of intraoperative blood products, respectively red blood cells, fresh frozen plasma, cryoprecipitate or platelets

2.1.7 Occurrence of graft dysfunction in liver transplant patients

The collected data shows that patients who have a higher anhepatic serum lactate level are more likely to develop postoperative graft dysfunction. It can be seen that the anhepatic serum lactate variable is significantly different from 0 because the p-value is 0.009 (below 0.05). When the lactate value in the anhepatic phase is 8 mmol/L, there is a 50% chance of graft dysfunction immediately after liver transplantation. The level of serum lactate in the neohepatic phase affects the variable graft dysfunction occurring postoperatively. We observe that the neohepatic serum lactate variable is significantly different from 0 because the p-value is 0.03 (below 0.05). Thus, the probability of postoperative graft dysfunction according to serum lactate level in the neohepatic stage is shown in the graph below.

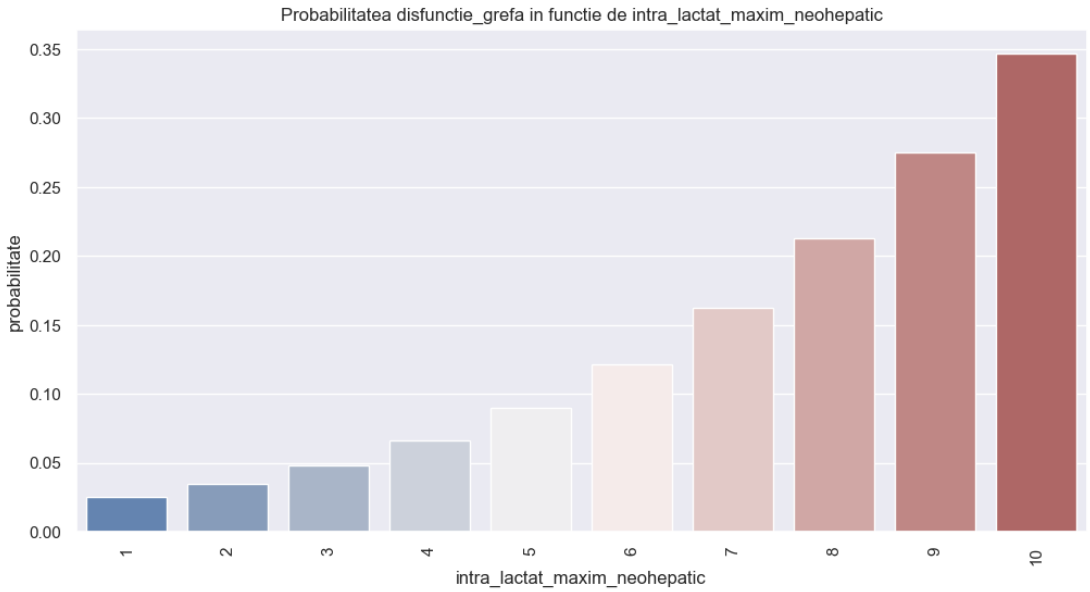

Figure 5. Probability of graft dysfunction depending on neohepatic lactate

In this group we also studied the connection between preoperative portal vein thrombosis and serum albumin levels in liver transplant patients. It is noted that patients who experienced portal vein thrombosis had a lower preoperative albumin level than those without thrombosis. It turns out that the portal vein thrombosis variable has a statistical value different from 0, but with a p-value at the limit of significance, of 0.059. A serum albumin level of 2 mg/dl is associated with a 35% probability of portal vein thrombosis in patients with liver cirrhosis.

In the final stage of this study we analyzed the factors that can influence the occurrence of postreperfusion syndrome (PRS). Applied statistical tests showed that bleeding does not contribute to the occurrence of PRS (p-value 0.09). From the logistic regression performed, it was demonstrated that only 5% of the occurrence of PRS is influenced by the transfusion of red blood cells, a statistically insignificant link (p-value 0.06). So the red blood cell increases by an average of 3 units in patients with postreperfusion syndrome. Liver transplant duration increases by an average of 44 minutes in those who experience postreperfusion syndrome.

Conclusions and personal contributions

The present thesis reports the variation of hemodynamic parameters determined with the help of the PiCCO system during the 3 important surgical stages during liver transplantation. The surgical technique used causes an important decrease in preload and cardiac output with implications for cardiovascular status. The invasive cardiac output monitoring system is extremely important during liver transplantation due to the marked hemodynamic instability that can occur and can provide us with additional information related to cardiac output, dosing of vasopressor/inotropic substances as well as guiding volume management and patients' response to volume repletion. The study showed that in the anhepatic phase there is an important decrease in the cardiac output, the global ejection fraction as well as the global end-diastolic volume. In the neohepatic stage, more than half of the studied patients present a value of cardiac output higher than 10% compared to the value in the pre-hepatic phase.

Intraoperative bleeding has been shown to influence the outcome of transplant patients, there is a 50% chance of postoperative complications if bleeding exceeds 6500 mL. Most of the deaths occurred within 1 month postoperatively, this is the critical period after liver transplantation. With a blood loss of about 5500 ml there is a 92% chance of 90 days survival.

Patients transplanted with a living donor liver segment experience a greater amount of bleeding compared to those transplanted with a whole liver. The length of stay in the intensive care unit as well as the occurrence of postoperative complications are not influenced by the type of graft used.

Statistical tests performed on this group of patients provide information related to the probability of 30/90 days survival and the occurrence of complications according to variables such as intraoperative bleeding, Meld severity score. Also, the maximum anhepatic and neohepatic lactate values provide data related to the probability of complications and graft dysfunction. Intraoperative transfusion of blood products correlates with the occurrence of postoperative complications and prolonged duration of mechanical ventilation.

The results of the present study open new hypotheses for future studies regarding hemodynamic monitoring of cardiac output during liver transplantation. The usefulness of transesophageal ultrasound in comparison with invasive means of monitoring of the hemodynamic status is one of the objectives of the following study.

Selective references:

1. Meirelles Júnior RF, Salvalaggio P, Rezende MB, Evangelista AS, Guardia BD, et al. Liver transplantation: history, outcomes and perspectives. Einstein (Sao Paulo). 2015 Jan-Mar;13(1):149-52.
2. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, Van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. BMJ open. 2015;5(5):e006971
3. Jimenez-Romero C, Caso Maestro O, CambraMolero F, et al. Using older liver grafts for liver transplantation: where are the limits?. World J Gastroenterol. 2014;20(31):10691-10702
4. Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. World J Gastroenterol. 2014;20(10):2555–63.
5. Rudnick MR, Marchi LD, Plotkin JS. Hemodynamic monitoring during liver transplantation: A state of the art review. World J Hepatol. 2015 Jun 8;7(10):1302-11.
6. Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57(2):268–78.
7. Møller S, Hobolth L, Winkler C, Bendtsen F, Christensen E. Determinants of the hyperdynamic circulation and central hypovolaemia in cirrhosis. Gut. 2011;60:1254–9.
8. Wiese S, Bendtsen F, Møller S. Cardiovascular biomarkers in cirrhosis and portal hypertension—relation to cardiac and circulatory dysfunction. In: Patel VC, Preedy VR, editors. Biomarkers in cardiovascular disease. 1st ed. Dordrecht: Springer; 2016. p. 573–99
9. Wong F, Liu P, Lilly L, Bomzon A, Blendis L. Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. Clin Sci. 1999;97(3):259–67.
10. Zhao J, Li N, Sun H, Liang C. The prevalence of coronary artery disease in patients with liver cirrhosis: a meta-analysis. Eur J Gastroenterol Hepatol. 2018;30(1):118–20

11. Harinstein ME, Iyer S, Mathier MA, Flaherty JD, Fontes P, Planinsic RM, et al. Role of baseline echocardiography in the preoperative management of liver transplant candidates. Am J Cardiol. 2012;110(12):1852–5
12. Ripoll C, Yotti R, Bermejo J, Banares R. The heart in liver transplantation. J Hepatol. 2010;54:810–22.
13. Møller S, Krag A, Madsen JL, Henriksen JH, Bendtsen F. Pulmonary dysfunction and hepatopulmonary syndrome in cirrhosis and portal hypertension. Liver Int. 2009;29:1528–37.
14. Raevens S, Geerts A, Van Steenkiste C, Verhelst X, Van Vlierberghe H, Colle I. Hepatopulmonary syndrome and portopulmonary hypertension: recent knowledge in pathogenesis and overview of clinical assessment. Liver Int. 2015;35(6):1646–60
15. Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology. 2006;41(6):1407–32
16. Trivedi HD. The Evolution of the MELD Score and Its Implications in Liver Transplant Allocation: A Beginner's Guide for Trainees. ACG Case Rep J. 2022 May 4;9(5):e00763.
17. Makowka L, Stieber AC, Sher L, Kahn D, Mieles L, Bowman J, Marsh JW, Starzl TE. Surgical technique of orthotopic liver transplantation. Gastroenterol Clin North Am. 1988 Mar;17(1):33-51
18. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg. 1989;210:649–52.
19. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American association for the study of liver diseases and the american society of transplantation. Hepatology. 2014;59:1144–65.
20. Wray CL. Liver transplantation in patients with cardiac disease. Semin Cardiothorac Vasc Anesth. 2018;22:111–21.
21. Hogan BJ, Gonsalkorala E, Heneghan MA. Evaluation of coronary artery disease in potential liver transplant recipients. Liver Transpl. 2017;23:386–95.
22. Aggraval S, Bane BC, Boucek BC, Planinsic RM, Lutz JV, Metro DG, et al. Simulation: a teaching tool for liver transplantation anesthesiology. Clin Transplant. 2012;26:564–70.

23. Feltracco P, Biancofuore G, Ori C, Saner FH, Della Rocca G. Limits and pitfalls of haemodynamic monitoring systems in liver transplantation surgery. Minerva Anesthesiologica. 2012;78:1372–84.
24. Rudnick MR, Marchi LD, Plotkin JS. Hemodynamic monitoring during liver transplantation: A state of the art review. World J Hepatol. 2015 Jun 8;7(10):1302-11.
25. Wax DB, Torres A, Scher C, Leibowitz AB. Transesophageal echocardiography utilization in high-volume liver transplantation centers in the United States. J Cardiothorac Vasc Anesth. 2008;22:811–3
26. Khurmi N, Seman M, Gaitan B, Young S, Rosenfeld D, Giorgakis E, et al. Nontraditional use of TEE to evaluate hepatic vasculature and guide surgical management in orthotopic liver transplantation. Case Rep Transpl. 2019;19:1–6.

List of articles published within the doctoral research:

Brezeanu LN, Brezeanu RC, Diculescu M, Droc G. Anaesthesia for liver transplantation. An update. J Crit Care Med.2020 May 6;6(2):91-100
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7216023/

Jipa LN, Diculescu M, Droc G. The influence of intraoperative fluid management on postoperative pulmonary complications in liver-transplant patients. Arch Balk Med Union. 2017;52(3):278-284
https://umbalk.org/wp-content/uploads/2017/09/06.The_influence_of_intraoperative_fluid.pdf

Brezeanu L, Evans M, Milan Z. Anaesthesia for Liver Transplantation in Anaesthesia *for Hepatico-Pancreatic-Biliary Surgery and Transplantation.* Springer Nature 2021. p 161-176