EXTRACORPOREAL ORGAN SUPPORT (ECOS): New concept for integrated organ support - How much of this does ADVOS already represent?

Chair: Prof. Dr. Michael Bauer, Jena / Prof. Dr. Wolfang Huber, Munich

ADVITOS INDUSTRY SYMPOSIUM

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In this symposium different diagnoses will be discussed in relation to multi-organ failure as a systemic disease. The advantages of a combined and individually scalable therapy by extracorporeal support of the three main detoxification organs, liver - lung - kidney, will be presented according to the latest state of science.

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Multi-organ failure as a systemic disease: When to treat? How long to treat? With which components of the Extracorporeal Organ Support (ECOS) concept?

Prof. Dr. Wolfgang Huber, Munich

- Patients rarely develop a single organ failure, usually multiple organs fail. The mortality of multi-organ failure correlates with the number of failed organs.
- Due to the combination of kidney and liver replacement, the additional CO_2 elimination and the possibility to influence the acid-base balance, ADVOS offers itself as a support system for multi-organ failure.
- The ADVOS therapy is safe. Despite the patients‘ mean SOFA Score of 12, the circulatory effects of ADVOS initiation were very low.
- CO_2 elimination can improve ventilation parameters by providing more PEEP and longer inspiratory time.
- The prerequisite for ADVOS treatment is a reversible basic situation of the patient or a reasonable therapy goal, e.g. bridging until transplantation. In analogy to ARDS - ECMO started too late has a poor outcome. If the therapeutic goal is no longer reasonably achievable or there is unstoppable progression of the underlying disease, ADVOS should be terminated.

It is rare for patients to develop a single organ failure; more often, multiple organs fail. Therefore, it is plausible to support multiple organs simultaneously with ADVOS.
ADVOS eliminates water-soluble and protein-bound substances as well as CO_2 and enables acidosis compensation. Treatment should be started early, preferably already at a single-digit SOFA Score, recommends **Prof. Dr. med. Wolfgang Huber, II Medical Clinic, Klinikum rechts der Isar, Technical University of Munich**.

The mortality of a multiple organ failure correlates with the number of failed organs. In isolated organ failure, it is about 15 to 25%, liver failure plus one additional organ failure have a mortality of 64 to 75%. Particularly critical is the combination of liver and kidney failure with a median survival time of 14 days. The severity of multi-organ failure is assessed with various scores such as SAPS, APACHE II or SOFA Score. The SOFA Score has been validated in 16 countries and is not only suitable for the day of admission, but also for follow-up assessment.

Meanwhile, there is also a simplified SOFA Score (eSOFA). The eSOFA takes into account only one criteria for circulation (start of a vasopressor), ventilation (start of ventilation), renal failure (creatinine doubling), liver failure (bilirubin doubling) and coagulation (platelets <100,000/µl Blut) as well as lactate (>2 mmol/l). The Glasgow Coma Scale, however, is not included. In validation studies, the eSOFA performed well, in some cases better than the SOFA.

Highest mortality in liver failure

In an Austrian study, circulatory or pulmonary failure each increased mortality by about 50%. A bilirubin increase to over 3 increased mortality by a factor of 2.2. When bilirubin reached values above 10, mortality increased by 290%. In cirrhotic patients, it depends on the number of organ failures: Without further organ dysfunction, mortality is 4%, one additional organ failure already means 45% mortality, and with three additional organ failures, the prognosis is only a 10% probability of survival.

ADVOS: Multiple organ support at the same time

Due to the combination of kidney and liver replacement, the additional CO_2 elimination and the possibility to influence the acid-base balance, ADVOS offers itself as a support system in cases of multi-organ failure. ADVOS contains a blood circuit and a dialysate circuit. In order to be able to eliminate protein-bound substances as well, albumin is added to the dialysate circuit. The toxin-loaded dialysate flows into the ADVOS circuit, where it is purified. It is divided into two flows, the acidic and basic HW flows. Through targeted pH changes and an increased temperature, the albumin folds up and releases the bound toxins again, which are then separated out in the filters. The flows are recombined after the filters, with mutual neutralization restoring the desired dialysate pH. The purified dialysate is again pumped into the dialysate circuit and passed by the blood. The binding sites on the albumin are free again and can thus take up toxins once more. Adding acid or base can also be used to modulate the acid-base balance. In addition, fewer protons can be added to the dialysate to treat metabolic acidosis. The reduction of protons and bicarbonate in the dialysate enables CO_2 elimination.

ADVOS improves the respiratory part of the SOFA at least indirectly by CO_2 elimination. At the same time, we can improve the ventilation parameters through more PEEP and longer inspiratory time. As with all extracorporeal procedures, there are potential risks, such as loss of platelets and, at least theoretically, hypotension. In addition, ADVOS positively affects liver and kidney parameters, and the CNS benefits from the removal of encephalopathy toxins.

Is ADVOS efficient?

In a preclinical ischemia model with interruption of the hepatic artery and portae vein, intracranial perfusion pressure was better maintained with ADVOS than with controls. ADVOS also favorably affected circulation and the cardiac index remained stable. Water-soluble substances such as creatinine, urea and ammonia as well as protein-bound substances such as nitrate were well eliminated. The survival of the animals was significantly better with ADVOS.

A second trial simulated the septic organ failure. The animals bile duct was ligated and an endotoxin was injected. With ADVOS, blood pressure remained stable, and it decreased significantly in controls. ARDS was less severe with ADVOS, FiO_2 requirement was lower; ammonia and bilirubin were efficiently eliminated. Adverse events were not observed; fibrinogen and platelets did not differ in both groups.

Safe use in humans

In the first 7 patients 163 ADVOS treatments were performed, with a single patient receiving 101 treatments alone. This demonstrated that the procedure was safe and certification was granted in July 2013. Based on the first 14 patients (about 300 treatments), the Munich physicians analyzed efficiency and safety. All patients were very ill, the CLIF-SOFA Score was 15. This corresponds to an expected mortality of 80%. A single treatment reduced bilirubin by an average of 32% (absolute: 8.3 mg/dL), creatinine by 27% (absolute: 0.6 mg/dL), and urea by 37% (absolute: 18 mg/dL). These elimination rates were at least as high as with MARS or the PROMETHEUS systems, Prof. Huber emphasized.

CO_2 removal

For the first time, ADVOS was used in an HIV-positive multimorbid patient with ileus, bipulmonary infiltrates, strongyloides infection and massive

catecholamine requirement (75 mg/h norepinephrine) for CO_2 elimination. Within 12 hours, ADVOS was used to reduce the norepinephrine dose to 16 mg/h and to achieve CO_2 compensation.

Risks

ADVOS is a highly potent procedure that withdraws 500 ml of blood from patients. The Munich-based researchers documented the effects on the circulation in 50 treatments of 16 patients with PICCO monitoring. Despite the patients' mean SOFA Score of 12, the circulatory effects of ADVOS induction were very small. Compared with the situation before ADVOS, on average no changes in heart rate, only a minimal drop in blood pressure, and a minimal change in central venous pressure were observed after initiation of the procedure. Stroke volume index and cardiac index decreased by 5%, but Prof. Huber considered this not clinically relevant. Pulmonary parameters and ejection fraction remained unchanged. The most sensitive parameter, Cardiac Power Index, decreased by 10%. A clinically relevant 15% decrease in cardiac index was registered in 5 of 50 treatments. The ADVOS connection has very little effect on the circulation, concluded Prof. Huber.

Ultrafiltration

In 36 of the 50 treatments there was relevant ultrafiltration. Achieved ultrafiltration and predefined target correlated very well, the dose of norepinephrine did not have to be increased. Only 10 out of 36 treatments exceeded the predetermined ultrafiltration goal by more than
20% below. Predictive for non-achievement of the ultrafiltration target were decreases in GEVDI, cardiac index, or stroke volume immediately after attachment.
The comparison of circulatory parameters before the start of ADVOS and after the end of ADVOS confirms the neutrality of the procedure: despite ultrafiltration, no significant change was found in any parameter. Also, a decrease in cardiac index of at least 15% was observed in only 3 of 50 treatments.

Starting the ADVOS

The prerequisite for an ADVOS treatment is a reversible basic situation of the patient or a therapeutic goal, e.g. bridging to transplantation. In analogy to ARDS - ECMO started too late has a poor outcome - therapy should be initiated in time. If patients have been hospitalized for a long time and have high bilirubin with marked renal failure, the prognosis is poor.
The results of the EOLIA study can be used to infer when an extracorporeal procedure is useful.[1] For pO_2, patients who were not treated too late, benefited significantly from ECMO. In addition, the mortality of patients with $PaCO_2/FiO_2$ ≥66 mmHg was significantly reduced. Patients with high $PaCO_2$ (≥55 mmHg) had a better prognosis with ECMO. In contrast, ECMO offered no benefit (approximately 50% mortality in both groups) to patients who were connected too late (SOFA Score >11), whereas ECMO significantly reduced mortality in patients with a SOFA <11 from 39% to 22%.

Ending the ADVOS

Once the therapeutic goal is no longer reasonably achievable, transplantation is impossible, or there is unstoppable progression of the underlying disease, ADVOS should be terminated. These are clear criteria. It is more difficult to terminate treatment if the course is favorable. Based on laboratory parameters such as bilirubin, which ADVOS directly influences, it is difficult to judge this. Coagulation parameters, which are substituted daily, are also not suitable for therapy control. Prof. Huber recommends instead a dynamic liver function test with indocyanine green, which reflects blood flow, parenchymal function and biliary excretion. This can be determined online in 6 minutes via a finger clip. If the indocyanine green plasma disappearance rate increases, at least an outlet test is warranted.

Retransfusion

After completion of the ADVOS treatment the 500 ml of blood collected is retransfused to the patient within 5 minutes. During this process CVD, GEDVI as well as stroke volume and power index increase on average and the stroke volume variation (SVV) decreases. Already after 30 seconds, when only 50 ml of blood have been returned, the Cardiac Power Index decreases. 61% of retransfusions increased the Cardiac Power Index by at least 10%, 51% by ≥15%. Patients who respond excessively to retransfusion may have been overly filtered. Prof. Huber reduces the filtration of these patients at the next treatment or adjustes the balance slightly more positive.

Hypoxic hepatitis or cholestasis – What is behind the diagnoses?

Prof. Dr. Michael Bauer, Jena

- The classic notion of shock liver assumes that tissue breakdown leads to an inflammatory response, and the inflammatory mediators further trigger cholestasis.
- In patients with ischemic liver failure, LDH and GOT rise first, bilirubin follows with a delay of a few days. However cholestasis is likely to develop very rapidly, only bilirubin responding with a considerable time lag.
- Indocyanine green indicates cholestasis more quickly than bilirubin. Already at ICU admission, the indocyanine green plasma disappearance rate is different from survivors and patients who will die.

- The 28-day mortality of patients with transaminase elevation after shock is about 40-50%. However, the remaining 50-60% are by no means cured. These patients need to be closely linked to a specialized outpatient clinic and specific care.

Shock liver (ischemic hepatitis) and cholestasis are typical clinical pictures in intensive care medicine.
However, the extent of cholestasis is often recognized late, since conventional laboratory parameters such as bilirubin react with a delay of several days, reported **Prof. Dr. med. Michael Bauer, Clinic for Anesthesiology & Intensive Care Medicine, Jena University Hospital.**

Shock, perfusion failure and mitochondrial (dys)function

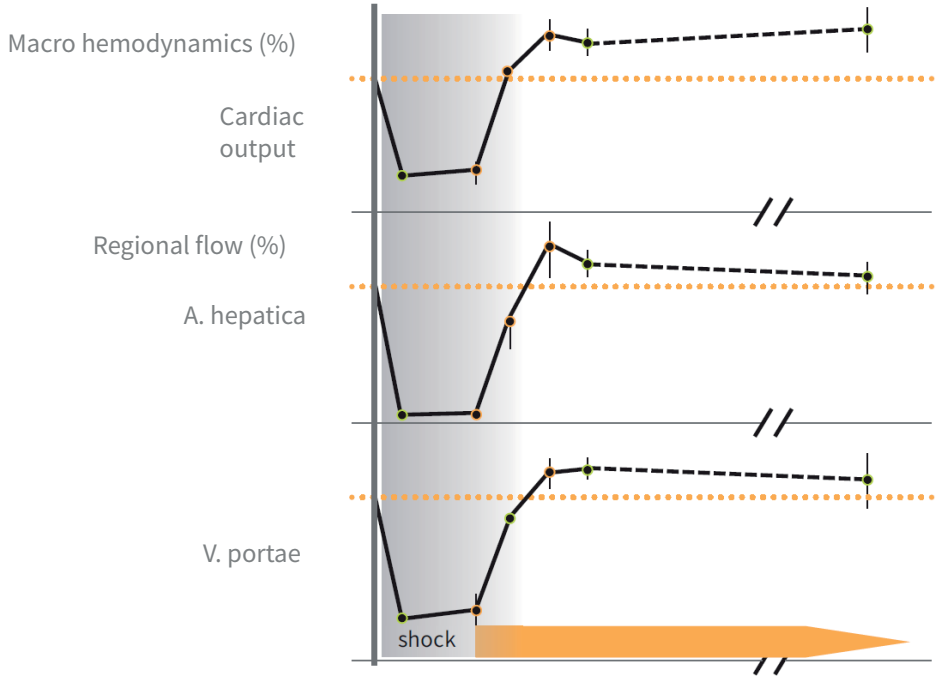

Figure 1: Blood flow in A. hepatica and V. portae in a hemorrhagic shock model; By Bauer 1997[3]

Ischemic liver failure is as old as intensive care medicine. Already more than 45 years ago, it was reported about 15 consecutive patients who were treated postoperatively in the intensive care unit for abdominal aortic aneurysm with covered rupture.[2] In these patients, LDH and GOT initially increased, followed by bilirubin after a few days. LDH and GOT indicate a large ischemic tissue destruction in the liver, the delayed increase in bilirubin represents cholestasis. The classical conception of the shock liver assumes that tissue destruction leads to an inflammatory response, and that the inflammatory mediators subsequently trigger cholestasis. In the surgical intensive care unit in Jena, about 10% of patients develop transaminase duplications with secondary bilirubin elevation. The incidence has increased in recent years, because sicker and sicker patients are treated.

What happens in ischemic hepatitis?

In a hemorrhagic shock model, Prof. Bauer lowered blood pressure for 2-3 hours and then initiated reperfusion.[3] While the blood flow in the V. portae decreased proportionally to cardiac output, perfusion stopped completely in the hepatic artery (Figure 1). The consequence was an isolated ischemia of the hepatocytes in the outflow region of the veins, while sufficient oxygen was still available and the liver cells survived. However, this pericentral necrosis is not the main problem, from which the liver can recover. More problematic is that the bile ducts are supplied exclusively by branches of the hepatic artery and the V. portae does not contribute to this at all (Figure 2). Therefore, the bile epithelia were also irreversibly damaged. In the clinic, such patients can can sometimes only be saved by a liver transplant, reported Prof. Bauer.

In laboratory chemistry, transaminases indicate cell necrosis in the pericentral region, alkaline phosphatase and gamma-GT represent the much more dangerous destruction of the biliary epithelia. Once the ischemia has been overcome, the inflammatory cells lead to post-acute damage. This contributes significantly to the increase in bilirubin a few days later and the diagnosis of cholestasis. However, cholestasis is likely to develop very rapidly, with only the bilirubin reacting with considerable delay.

Bile is pumped into hepatocyte

In order to increase the surface area of the hepatocytes that produce bile, the liver cells are equipped with a brush border in the direction of the bile duct. In cholestasis, the finger-shaped brush fringes are not on the cell surface but are folded in. The bile is no longer pumped out of the cell, but instead enters in vesicles under the cell membrane. Since the bile is not excreted into the bile ducts, severe cholestasis develops. In parallel phase I and phase II drug metabolism is disturbed. The cytochrome P450-dependent detoxification comes to a standstill and the pharmacology of the drugs that these patients receive is completely turned upside down. In addition, toxic bile-related substances such as bile acids accumulate. Because of these severe disorders, patients who become icteric have such a poor prognosis. The various liver functions such as protein synthesis (INR, fibrinogen, albumin), detoxification (ammonia), gluconeogenesis (glucose) and excretion (bilirubin) can be monitored by specific markers. Markers

Ischemic damage of the liver - laboratory

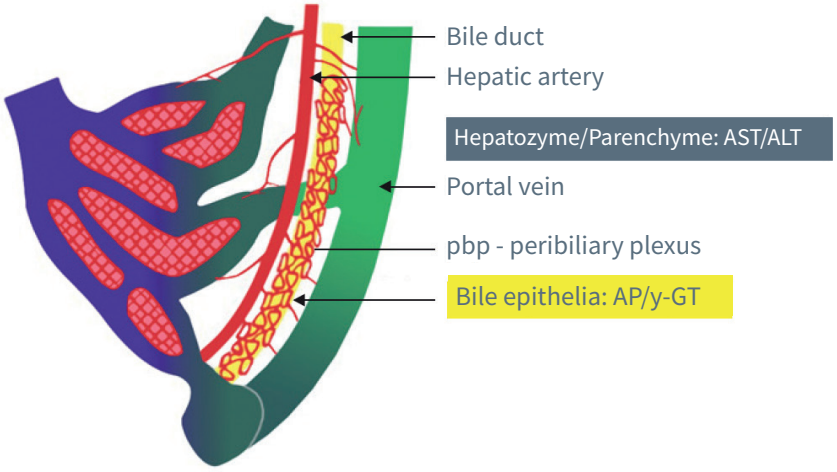

Figure 2: Vascular supply of liver and bile ducts by V. portae (green) and A. hepatica (red)

for hepatobiliary cell damage (ALT, AST, GLDH, γ-GT, AP) are also available. In addition, ultrasound examination should exclude the possibility of an underlying obstruction.

Sensitive parameter: Indocyanine green plasma disappearance rate

Healthy individuals absorb the dye indocyanine green rapidly, after 30 minutes it reaches the liver, after a few hours it is in the intestine. In sepsis and cholestasis, however, indocyanine green remains in the liver and is not excreted into the bile ducts. Indocyanine green indicates cholestasis earlier than bilirubin. Already on admission to the intensive care unit, the Indocyanine green plasma disappearance rate differs between patients who survive later and patients who will die.

100-fold atorvastatin plasma concentration

Prof. Bauer demonstrated how dramatically cholestasis affects the pharmacokinetics of drugs using atorvastatin (Figure 3).[4] If sepsis patients with clinically unapparent excretory limitations receive a single 20 mg dose of atorvastatin, they achieve plasma concentrations 40-50 times higher than healthy subjects. Because of the complete failure of phase 1 and phase 2 excretion into the bile ducts, the plasma concentrations rise in a completely unpredictable manner. If a cytrochrome P450 inhibitor (metronidazole) is also administered, the atorvastatin plasma concentration doubles again, i.e. it increases a hundredfold. The medication accumulates in the hepatocyte because it cannot be detoxified or removed. The hepatocyte becomes a „waste bag“ for the toxins.

Extremely high mortality

Liver cells of sepsis patients are often overwhelmed with medication. The metabolites no longer reach the bile and „drug induced liver injury“ occurs. For the patients, this means a very poor prognosis:
The 28-day mortality of patients with transaminase elevation after shock is about 40-50%. The remaining 50-60% are by no means cured. After one year only 9 % of patients with hyperbilirubinemia at discharge („they go yellow to rehab“) survive. Also patients without jaundice have a significant mortality, the one-year survival rate is just under 30%.[5] These patients must be closely linked to a specialized outpatient clinic and given specific care, advises Prof. Bauer. If they are sent to rehabilitation, they often come to the center much too late when problems arise.

Organ dysfunction in acute and chronic liver insufficiency - Lessons from Internal Medicine

Acute liver failure differs from conventional acute liver disease with coagulopathy and icterus by the development of hepatic encephalopathy. If hepatic encephalopathy develops rapidly, the prognosis is better because of the high regenerative potential of the liver. If, on the other hand, it takes a month or more until hepatic encephalopathy, this is an indication of a lack of recovery tendency.

Patients with pre-existing liver disease are often not recognized in surgical medicine. If the surgeon recognizes intraoperatively that the liver does not look good, danger is imminent. Many of these patients have acute-on-chronic liver failure with very poor prognosis. This is often the result of an infection such as spontaneous bacterial peritonitis or septic complication. Prognosis can be assessed with adapted scoring systems: A CLIF-SOFA Score <11 is associated with mortality of about 50%; at 12 or higher, mortality reaches 100%. Patients without pre-existing liver disease with CLIF-SOFA ≥12 have a mortality of 70%.

High mortality in preoperative hyperbilirubinemia

Prof. Bauer demonstrated the impact of liver function on survival using 240 patients with surgically treated endocarditis.[6] Patients who never developed hyperbilirubinemia already had a mortality of 40%, and there was a 20% increase in postoperative hyperbilirubinemia. However, if bilirubin levels were already elevated preoperatively, mortality was about 80%.

Cholestasis - clinical consequences

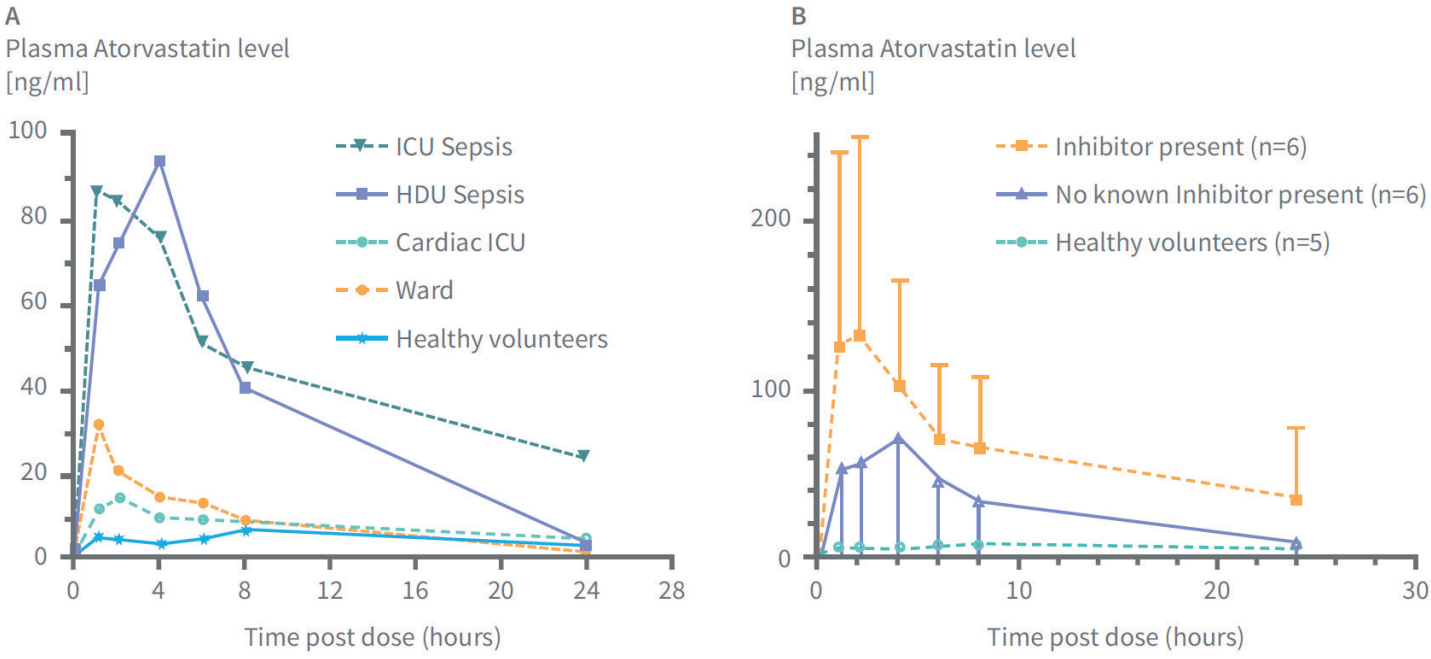

Figure 3: Atorvastatin plasma concentration after administration of a 20 mg single dose in healthy and sepsis patients; according to Kruger PS et al. 2009[4]

Central role of liver dysfunction
– Example infective endocarditis

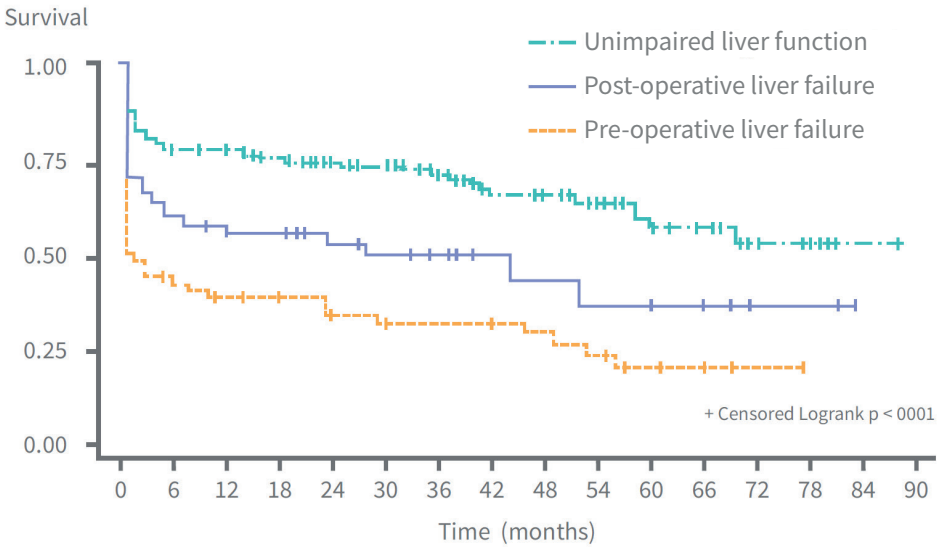

FIgure 4: Liver dysfunction and survival; according to Diab 2017[6]

Literature

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