From the Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Surgery
Karolinska Institutet, Stockholm, Sweden

OUTCOME AFTER LIVER RESECTION: EPIDEMIOLOGICAL AND CLINICAL STUDIES WITH SPECIAL FOCUS ON THE ROLE OF POST-HEPATECTOMY LIVER FAILURE

Stefan Gilg

Karolinska Institutet

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Outcome after liver resection: epidemiological and clinical studies with special focus on the role of post-hepatectomy liver failure (PHLF)

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Stefan Gilg

Principal Supervisor:

Adjunct Professor Bengt Isaksson
Uppsala University
Division of Surgical Sciences
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Co-supervisor(s):

Cecilia Strömberg, PhD
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Surgery

Associate Professor Greg Nowak
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Transplantation Surgery

Professor Michael Björnstedt
Karolinska Institutet
Department of Laboratory Medicine
Division of Pathology

Opponent:

Professor Ajith Siriwardena
University of Manchester
Department of Biology, Medicine and Health
Division of HPB Surgery

Examination Board:

Associate Professor Per Nilsson
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Colorectal Surgery

Professor Peter Naredi
University of Gothenburg
Department of Clinical Sciences
Division of Surgery

Associate Professor Soo Aleman
Karolinska Institutet
Department of Medicine
Division of Gastroenterology and Rheumatology

“However difficult life may seem, there is always something you can do and succeed at.” (Stephen Hawking)

To my family

ABSTRACT

Background: Liver surgery has undergone significant developments over the last three decades. However, population-based data are scarce, and there is limited knowledge of the impact on mortality and possible treatment modalities of a feared complication following hepatectomy, post-hepatectomy liver failure (PHLF). In theory, extracorporeal liver support with the Molecular Adsorbent Recirculating System (MARS) might have several positive effects in patients with PHLF. Until today, only very few single-center experiences have been reported with overall poor patient outcome. However, controlled, prospective data for the use of MARS in patients with PHLF are missing.

Aims: To investigate long-term results after hepatectomy in Sweden in a population-based setting. To evaluate the impact of PHLF on short-term mortality. To retrospectively analyze the outcome of patients with PHLF being treated with MARS. To prospectively evaluate safety and feasibility of an intensified MARS treatment protocol in patients with PHLF.

Methods: In paper I and II, data between 2002 and 2011 from different patient registries were used to assess outcome related to different types of liver resections and differential diagnosis. In paper II, a part of the data from paper I (between 2005 – 2009) were used to identify patients who died within 90 days from surgery. Data were then completed with additional information from local patient journals at the respective hospital. For paper III, all patients who were treated with MARS for PHLF at Karolinska University Hospital Huddinge and Hospital Clinic, Barcelona, were retrospectively analyzed. For paper IV, a prospective pilot study was performed, including all patients with PHLF between 1st of December 2012 and 30th of May 2015. Safety, feasibility, and outcome were assessed.

Results: Liver resections are performed with a very low short-term mortality and favorable long-term outcomes. 5-year survival in patients resected for colorectal liver metastasis (CRLM) was around 60%, and re-resection for CRLM significantly improved long-term survival. In a population-based setting, PHLF is whether the leading cause or significantly contributes to 90-day mortality, in more than 40% of all cases. Our data confirmed known risk factors for PHLF like extended hepatectomy or hepatectomy due to cholangiocarcinoma. In a retrospective series, 13 patients were identified who have been treated with MARS due to PHLF. A trend towards improved long-term survival was seen in patients being treated early and more frequent after hepatectomy. In a prospectively, controlled cohort study we found it to be safe and feasible to initiate MARS treatment in patients with PHLF early after hepatectomy according to a standardized treatment protocol. Short and long-term survival was improved compared to a historical control group.

Conclusion: In Sweden, liver resections are performed with favorable outcome both in regards to short-term and long-term results. PHLF is even in a population-based setting the single most important factor causing short-term mortality after hepatectomy. It is safe and feasible to use MARS in patients with PHLF early after hepatectomy and both short- and long-term survival might be improved.

LIST OF SCIENTIFIC PAPERS

I. Gilg S, Sparrelid E, Isaksson B, Lundell L, Nowak G, Strömberg C
Mortality-related risk factors and long-term survival after 4460 liver resections in Sweden-a population-based study
Langenbecks Arch Surg. 2017 Feb;402(1):105-113

II. Gilg S, Sandström P, Rizell M, Lindell G, Ardnor B, Noren A, Strömberg C, Isaksson B
The impact of post-hepatectomy liver failure on mortality- a population-based study
Manuscript

III. Gilg S, Escorsell A, Fernandez J, Garcia Valdecasas JC, Saraste L, Wahlin S, Nowak G, Stromberg C, Lundell L and Isaksson B
Albumin Dialysis with Mars in Post-Hepatectomy Liver Failure (PHLF): Experiences from Two HPB Centers
Surgery Curr Res. 2015; 6: 252.

IV. Gilg S, Sparrelid E, Saraste L, Nowak G, Wahlin S, Stromberg C, Lundell L, Isaksson B
The molecular adsorbent recirculating system in posthepatectomy liver failure: Results from a prospective phase I study. Hepatology Communications. 2018 Mar 8;2(4):445-454. doi: 10.1002/hep4.1167. eCollection 2018 Apr.

CONTENTS

LIST OF ABBREVIATIONS

PHLF	Post-hepatectomy liver failure
MARS	Molecular Adsorbent Recirculating System
CRLM	Colorectal liver metastasis
FLR	Future liver remnant
ISGLS	International Study Group of Liver Surgery
ALPPS	Associating Liver Partition and Portal vein Ligation for Staged hepatectomy
SPAD	Single Pass Albumin Dialysis
AoCLF	Acute-on-chronic liver failure
ALF	Acute liver failure
ICG	Indocyanin-green
RCT	Randomised controled trial
HGF	Hepatocyte growth factor
IL-6	Interleukin 6
POD	Post operative day
MELD	Model for End-Stage Liver Disease
HPB	Hepato-pancreatico biliary
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
RCR	Retrospective chart review

1 INTRODUCTION

Liver resection has gone trough a tremendeous development over the last decades and represents standard-of-care for treatment of the majority of liver tumors (1-4). Because of this progress in liver surgery, the limits of resectability for many primary and secondary liver tumors have extended along with improved outcome (5). Though, short-term mortality after hepatic resection has steadily decreased and today its incidence ranges from 2% to 5%. However, those figures are mostly generated from single, high volume centres (2, 6) or publications that use specific, non-population-based data as source (7, 8). Only few studies strive after a population-based approach. However, those publications elucidate only very short study periods (9, 10) or cannot provide results on long-term survival (11, 12).

Posthepatectomy liver failure (PHLF) has been identified as a major risk factor for mortality after liver resection. According to different studies, the incidence of PHLF varies largely between 0-30% and may be accounted as the main reason of postoperative mortality related to liver surgery (reported figures ranging from 18% to 75%) (13-18). Furthermore, PHLF causes prolonged stay in intensive care units, prolonged hospitalisation and up to 4 times higher overall treatment costs (19). So far, known major risk factors for postoperative liver failure are comorbidity, a pre-existent liver disease and a small remnant liver volume after surgery (14, 20). Despite its potentially fatal impact the complex pathophysiology of PHLF is still poorly understood and treatment options are very limited. Currently, there are no specific treatment options for PHLF and management is mainly restricted to resolve complications like bile leakage, infections as well as the prevention of further liver damage caused by e.g., thrombosis or hemorrhage as well as administration of liver toxic drugs (14, 21). More specific treatment options might be found in extracorporeal liver support therapies. Different devices and techniques have been developed during the last decades, mainly to treat acute liver failure or bridge patients to liver transplantation (22). Enormous efforts have been undertaken in the development of bio-artificial devices that could not only contribute to detoxification but also cover other tasks of liver function like synthesis of coagulation factors (23). However, due to limited availability those devices are not clinically implemented yet. In contrast, today there are other, Albumin-based devices available, mainly focusing on detoxification, such as the Single Pass Albumin Dialysis (SPAD) or the Molecular Adsorbent Recirculating System (MARS) (24). The MARS device has due to different reasons become the most popular amongst all liver support devices (25). However, until today there is no prospective, controlled study evaluating possible beneficial effects of this treatment in patients with PHLF.

In summary, a population-based analysis of mortality and long-term survival after liver resections as well as the elucidation of factors contributing to mortality and in particular to post-hepatectomy liver failure would be highly beneficial. Furthermore it is crucial to further determine whether or not MARS has a potential value in the treatment of patients with PHLF.

2 BACKGROUND

2.1 HEPATECTOMY - HISTORICAL BACKGROUND AND DEVELOPMENT OF LIVER SURGERY

In modern literature, the first scientific reports describing hepatectomy as a possible treatment for liver diseases were published in 1888 by the German surgeon Carl Johann August Langenbuch who resected the left liver lobe of a patient, ligating the vessels and bile ducts (26). The first procedures describing liver resection for gallbladder cancer were published in 1901 by Stevens (27) and in 1905 by Hutchinson (28), both performing a wedge resection of the liver in order to remove a gallbladder cancer they concurrently found with gallstone disease. Since then, liver surgery experienced a tremendous development.

The probably most essential improvements liver surgery went through, took place from the 1950´s onwards. Firstly, Claude Couinaud described the anatomy of the liver in a new way, dividing it into 8 functional segments with individual blood supply and outflow along with segmental bile drainage. This still serves as the gold standard for today's liver surgery (29). However, it took almost 30 years until the French surgeon Henri Bismuth described liver resections based on these novel anatomic findings, thus founding modern anatomical liver surgery (30). Further technical advancement, like the introduction of ultrasound (31, 32), novel surgical techniques like clamping of the portal triad (33) along with improved technical equipment for liver transection (34-36) contributed to the rapid development of liver surgery over the last decades.

A key issue of modern liver surgery is the potential of the liver to recover after partial hepatectomy; a fact known since the ancient Greek mythology and the myth of Prometheus (37). Today, liver regeneration after hepatectomy probably is the best-described human model of organ recovery (38-41), and hepatectomies with resection of up to 80% of the liver volume are performed safely in expert centers around the world (42-44). In recent years, the borders of resectability have been pushed even further by introducing techniques to increase the future remnant liver (FLR), like portal vein occlusion techniques (45, 46) or two-step hepatectomies (47, 48). The latest development within liver surgery is the so-called in-situ split or ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy), a specific 2-step procedure for patients with a too small future liver remnant. Initially described by Schnitzbauer et al. in 2012 (49), this technique has the potential to push the borders of resectability even further (50, 51).

2.2 OUTCOME AFTER HEPATECTOMY FOR MALIGNANT DISEASES

Malignant tumors in the liver originate from the liver itself (intra- and extrahepatic bile duct cancer, gallbladder cancer, hepatocellular cancer) or from metastasis of extra-hepatic cancers. Hepatectomy for primary liver cancers, especially peri-hilar cholangiocarcinoma, remain challenging and most patients are un-resectable at time of diagnosis or need pre-treatment to

release biliary obstruction or increase the FLR (52). After resection of the tumor, those patients have a poor outcome with the highest incidence of both 30 and 90-day mortality of all liver resections as well as poor long-term survival due to a high frequency of R1 resections and vascular invasion leading to early disease recurrence (53, 54). However, data on long-term outcome are rare and based on single-center reports (2, 55, 56) or data originating from certain medical registers (4). On the other hand, outcome for patients with colorectal liver metastasis (CRLM) has improved significantly over the last decades. From the first reports of the beneficial effect of resection for CRLM in the 1980´s and 90´s (1, 57, 58) paradigms have been shifted many times. Today, patients with CRLM are potentially curable due to improved chemotherapy, re-resection and the introduction of other treatment modalities like local ablation techniques (e.g., radio-frequency ablation) (59-61). Even initially un-resectable patients have today, after successful downstaging by neo-adjuvant chemotherapy, the chance to undergo hepatectomy with curative intent (62, 63). A recently published score-system gained a good prognostic value in predicting the individual risk after hepatectomy for initially un-resectable liver metastasis and could demonstrate a good long-term outcome for a certain group of patients (64). However, in general, little is known about the short- and long-term outcome of these patients in a population based setting.

2.2.1 Prediction of complications/outcome after hepatectomy

Regarding patient outcome after hepatectomy, it is important to differentiate between 3 contributing causes with potentially influence on the results: 1. the underlying disease (e.g., cancer), 2. the medical background of the patient and 3. complications related to the treatment (hepatectomy). In order to stratify patients at risk for postoperative complications, several risk scores have been developed. Breitenstein et al. developed a risk score to predict severe complications following liver resection according to the Clavien-Dindo classification, based on American Society of Anesthesiologists category, transaminases levels (aspartate aminotransferase), extent of liver resection (>3 vs <3 segments), and the need for an additional hepaticojejunostomy or colon resection (65). In a systematic review, Yu et al.. screened 34 articles evaluating the predictive value of different scores in predicting postoperative complications and outcome (66). However, many scoring systems lack a solid validation. Therefore, the power of prediction on an individual level remains unclear. This might be a reason why preoperative risk scores have not been applied broadly in clinical practice.

2.3 LIVER REGENERATION AFTER PARTIAL HEPATECTOMY

Liver regeneration after partial hepatectomy is one of the most complex processes in the human body and extensively studied (67-69). The loss of liver tissue ignites a complex process in order to recuperate the original size of the liver (69). A large amount of key players contributing to this have been identified, including cytokines like IL-6 (70) or HGF (41), neurotransmitters like Serotonin (71), cellular factors like beta1-integrin (72) or hormones and their receptors like Insulin (73). Loss of these factors unavoidably alters or impairs liver regeneration after hepatectomy. Not only the expression and presence of all these factors, but

even the timely coordination of regeneration is considered to be of crucial importance in order to re-establish functional liver parenchyma. This is of special importance, as contributing liver and stem cells recovering at different time points after hepatectomy and disturbance have been identified as a cause of PHLF, too (67, 69). Liver regeneration is initiated immediately after completed hepatectomy, with a massive change of gene expression in hepatocytes (74). This induces amongst others HGF release, and up to 95% of resting hepatocytes start with the cell cycle by entering mitosis (40). Subsequently, the extracellular matrix along with blood vessels and bile ducts are reestablished (41, 75). Liver regeneration will be terminated when the liver has achieved a size large enough to provide homeostasis, a process described by Michalopoulos et al. as "hepatostat" (69). Disturbance of liver regeneration or removal of too much liver tissue might induce overshooting hepatocyte proliferation, leading to dysfunctional hepatocyte clusters, intra-cellular cholestasis, apoptosis and prolonged inflammation (76). Accordingly, a deceleration of liver regeneration after massive hepatectomy in rats has shown to positively influence recovery of both hepatic parenchyma and function (77). Nevertheless, the majority of data originates from animal studies in rodents; models to obtain equivalent knowledge in humans are living-donor hepatectomy (78, 79) or the ALPPS procedure (80, 81). However, as liver regeneration in humans differ from rodents, many questions remain unanswered.

2.4 POST-HEPATECTOMY LIVER FAILURE

Post-hepatectomy liver failure (PHLF) is a serious complication after hepatectomy. The main reason is a "small for size" situation of remaining liver tissue after extensive resection in relation to underlying quality of liver parenchyma (13, 20). Despite its potentially fatal impact on patient outcome, many aspects regarding PHLF are still poorly understood. Firstly, there are large differences regarding the incidence of PHLF in the literature. Related numbers range from 0.7% - 9.1% according to a review article by van den Broeck et al. (14). This trend was confirmed by a single-center analysis were the overall incidence of PHLF was found to be 9% according to the International Study Group of Liver Surgery (ISGLS) criteria (82). Another study found, when using the "50:50" and "peak bilirubin" criteria, an incidence of PHLF of 7% in patients with colorectal liver metastasis (83). The two most recent multicenter studies confirmed the incidence of PHLF between 5% and 9% (17, 18). However, those data are exclusively originating from tertiary hospitals. Furthermore, no population-based data on the incidence and risk factors for PHLF are available. In order to be able to offer liver resection as a potential curative treatment even to borderline resectable patients, an effective treatment of PHLF would be of great value. In fact, treatment options have, despite intensive research, not improved substantially over the last decades (84). Recent recommendations are mainly based on treatment algorithms for acute liver failure and aim to prevent further liver damage by draining bile leakage and abscesses, treat infections, secure enteral nutrition and the avoidance of liver-toxic drugs (85, 86).

Thus, enormous efforts are undertaken to avoid PHLF. Pre-operative volumetric measurement is a standard procedure in today's expert centers to accurately determine the

FLR (87-89). In addition, there are several other preoperative tests to assess the individual hepatic functional capacity of every individual patient, in particular metabolic tests like the Indocyanin-green (ICG) test (90, 91), the LIMAX test (92) or radiology-based tests like hepatocyte-specific scintigraphy (93) or segmental magnetic resonance imaging, a rather new but highly promising technique (94, 95). Unfortunately, none of these tests can predict exactly how much liver volume is safe to resect in the individual patient as many other factors contribute to the functional hepatic reserve, like the presence of steatosis (96), cirrhosis (97) or parenchymal changes following chemotherapy like the "Sinusoidal Obstruction Syndrome" after oxaliplatin (98) or the "Chemo-Associated Steato-Hepatitis" after irinotecan (99). However, recommendations have been established and in our center, we accept today up to 80% resection for completely unharmed liver tissue, up to 70% in patients after chemotherapy and maximum of 60% in patients with cirrhosis. In patients with cirrhosis, portal hypertension and an ICG retention rate at 15 min (RR15) >20% are considered to be contra-indications for hepatectomy. However, despite this pre-operative workup it still remains difficult to completely avoid certain risk factors and thereby PHLF.

2.4.1 Definitions of PHLF

Another important problem to address is the need for a standardized definition of PHLF. A recent review by Lafaro et al. discussed several definitions proposed in the literature (84). Probably, the most commonly used definition is represented by the “50:50 rule” or also called “Balzan criteria”, a predictive score using a combination of bilirubin and Quick value to predict the individual mortality risk on postoperative day 5 (100). The cut-offs predicting a mortality risk >50% (bilirubin >50 µmol/l and Prothrombin time (Quick) <50%) were initially defined according to a retrospective single-center experience and could be confirmed in a later prospective study (101). In addition, Mullen et al. found in a large single-center cohort a peak-bilirubin >7 mg/dl to be highly predictive for mortality related to hepatectomy. The ISGLS made the most recent attempt to define PHLF. According to a consensus decision, PHLF is graded into 3 different severities, A, B and C. Grade A is defined by deviating liver values on POD 5 but otherwise normal clinical course. In contrast, patients are classified Grade B PHLF if they deviate from a normal course but do not require invasive treatment and finally Grade C patients who do require invasive treatment (102). This definition was evaluated in a retrospective single-center analysis that showed a significant increase in mortality from 2% in patients with Grade A PHLF up to 44% in patients with Grade C PHLF (82). However, studies still use several definitions making it difficult to compare results in the literature.

2.4.2 Risk factors and Pathophysiology of PHLF

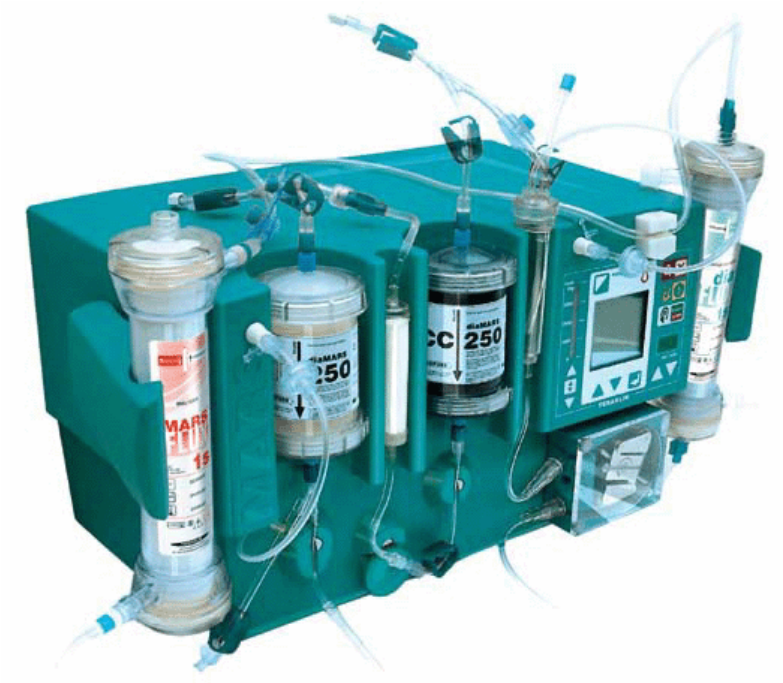
The pathophysiology of PHLF differs considerably from pathophysiology in patients with acute (103) or acute-on-chronic (104) liver failure. After major hepatectomy, several changes in liver-specific blood samples, metabolism, the coagulation system, immune function and hepatic blood flow occur, varying dependent on the extent of resection (105). Most of them recover within one week from hepatectomy and more details are given above (chapter 2.3).

Several key factors are contributing to the pathophysiology of PHLF and they can be divided into pre-, peri- and postoperative factors. Pre-operatively, the quality of underlying liver parenchyma (e.g., cirrhosis) has been identified as a crucial risk factor (97). Additionally, neo-adjuvant chemotherapy with oxaliplatin may induce the “sinusoidal obstruction syndrome", a veno-occlusive disease of the liver leading to necrosis, congestion and partially cholestasis (98, 106). Another well-described effect of chemo-associated toxicity is the development of "Chemo-Associated Steato-Hepatitis" after Irinotecan (99). Intra-operatively, there are two major risk factors for the development of PHLF; massive hemorrhage leading to hypotension and requiring blood transfusion, subsequently inducing ischemia-related damage to liver tissue (16, 20, 107). Another contributing factor is the ischemia reperfusion injury after inflow obstruction during hepatectomy, a phenomenon well known from liver transplantation (108). After hepatectomy in pigs, it was shown that nitric oxide contributes to increased cell death in the liver after warm ischemia induced by Pringles maneuver (109). Postoperatively, the so-called small-for size situation along with portal hypertension has been identified as a reason for increased necrosis and Kupfer-cell dysfunction (110, 111), thus contributing to the development of PHLF. Even though the liver is regenerating, there is a prolonged sensitivity to factors influencing liver volume restoration, like sepsis or postoperative hemorrhage and patients frequently die in a combined picture of PHLF and other severe complications and not of PHLF alone (107).

2.5 MOLECULAR ADSORBENT RECIRCULATING SYSTEM

In the early 1990´s, a promising treatment option emerged for patients suffering from acute or acute-on-chronic liver failure with the development of extracorporeal liver support therapy (112). In 1993, Stange et al published a methodical description of the removal of Albumin bound toxins against a recycled Albumin solution (113). In theory, this should enable treatment possibilities with greater detoxification capacity than, e.g. hemofiltration alone combined with much less side effects than, e.g. plasma exchange (114). This system was then further developed and became clinically available as the Molecular Adsorbent Recirculating System (MARS), distributed initially by Teraklin AG, Rostock, Germany (Figure 1). Initial clinical results in patients with ALF, AoCLF and primary non-function after orthotopic liver transplantation showed promising results (115) and the MARS system became the most popular and most intensively studied device amongst all liver support systems to date.

Figure 1. MARS monitor (Teraklin AG, Rostock, Germany)

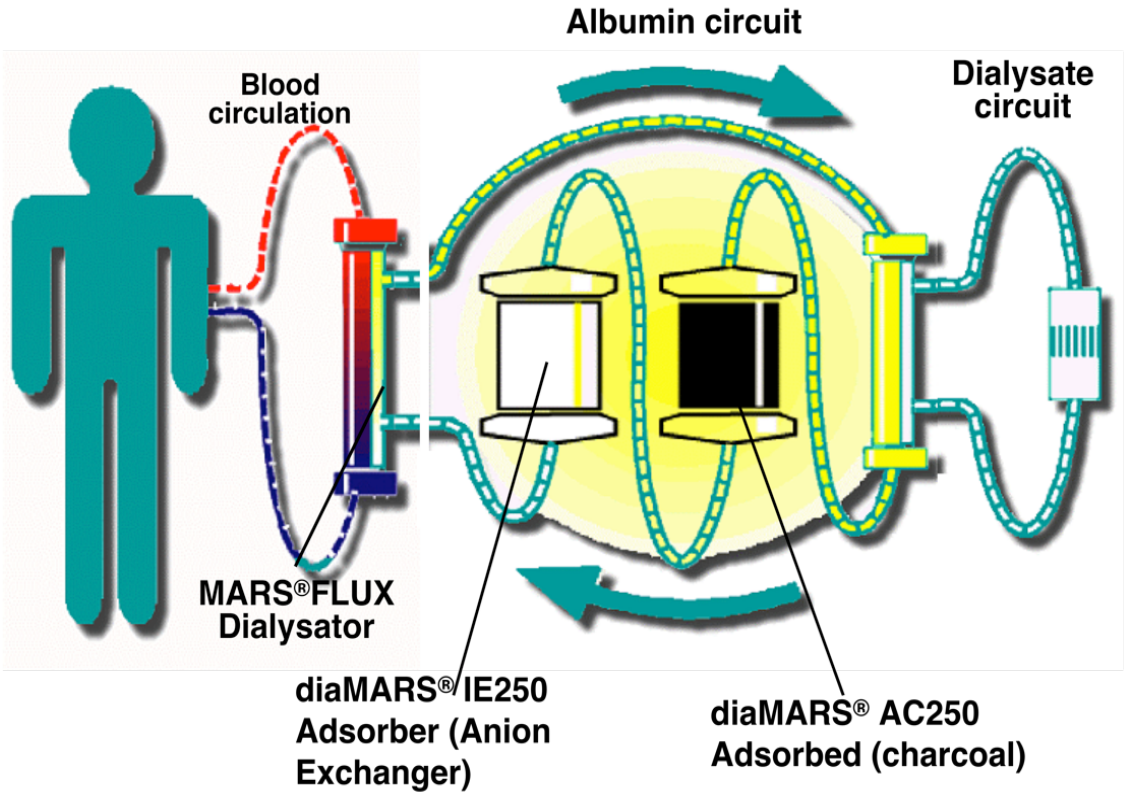


(with permission of Matthias Löhr)

2.5.1 Technical aspects of MARS

MARS consists of a closed-loop with Albumin containing a dialysate circuit driven by an additional, standard hemodialysis machine (e.g., Prismaflex, Fresenius). The purification of the blood is achieved via a low-flow-dialyzer (MARS FLUX) and the dialysate is then recycled over an uncoated Charcoal column and an Anion exchanger column (Figure 2).

Figure 2. The Molecular Adsorbent Recirculating System (MARS)



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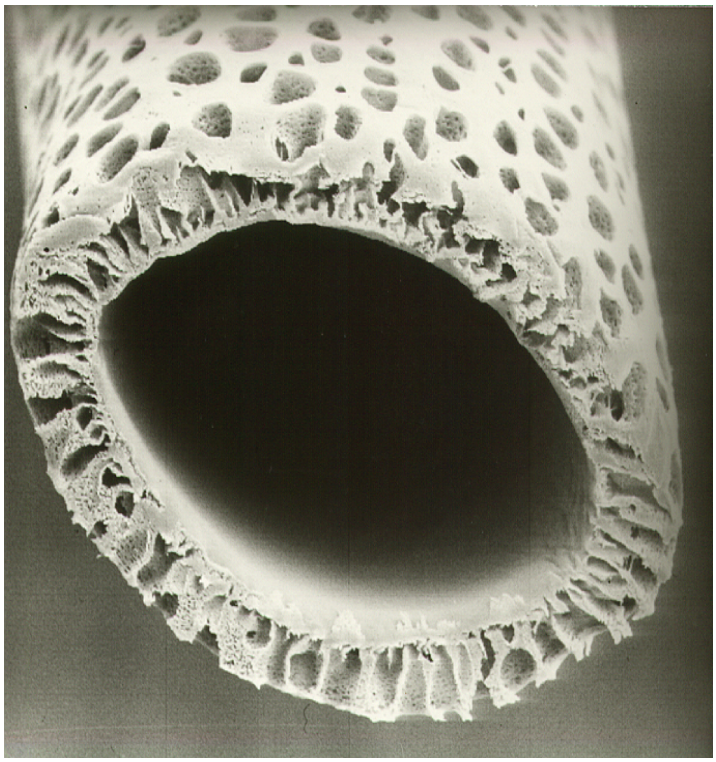
Of all parts, the MARS Flux Dialysator could be considered as the most important element of the MARS system. In a pioneering work, Stange and Mitzner published their results in 1996, using a hybrid membrane consisting of a highly permeable hollow fiber (Figure 3) in combination with biologically attached transport proteins (Albumin), enabling selective transport of molecules between patients' blood and the dialysate (116). By using this membrane, the MARS device is able to remove both water-soluble, and Albumin-bound toxins. The Albumin in the closed dialysate loop is then recycled over a charcoal adsorber together with an anion exchanger allowing to last one MARS session up to 24 hours until the filter system has to be changed (117).

Figure 3. Cross-section of a hollow-fibre of the MARS-Flux filter



(with permission of Matthias Löhr)

2.5.2 Clinical experience with MARS

In clinical studies, MARS has shown a potential benefit for patients with acute (ALF) or acute-on-chronic liver failure (AoCLF) by stabilizing hemodynamic parameters with ensuing improvement of liver and kidney functions (118-120). Clinical improvement was also observed in patients with hepato-renal syndrome or critical-ill patients with concomitant liver failure (121, 122). Despite one prospective controlled trial suggested an improved 30-day survival after MARS treatment in patients having an acute deterioration superimposed on chronic liver failure (123), there is until today no RCT that could demonstrate a statistically significant survival benefit related to MARS treatment, neither in patients with acute-on-chronic liver failure (124) nor in patients with acute liver failure (125).

2.5.3 MARS in PHLF

The use of MARS in the PHLF situation is based on the hypothesis, that extracorporeal liver support might disburden liver function from detoxification along with liver-toxic metabolites, thus facilitating recovery after hepatectomy. However, only a few single-center reports have been published describing the experiences with MARS treatment solely for PHLF. Those reports contain a small number of patients, present heterogeneous treatment groups and all

are lacking standardized treatment protocols. The outcome was poor with few if any surviving patients (119, 126-129). Probably due to the disappointing results, since the early 2000´s there was no attempt made to evaluate the potentially beneficial effects of MARS in PHLF in a systematic way. Thus, based on the currently available literature, it is difficult to draw any conclusions about feasibility, safety, and efficacy of MARS treatment in patients with PHLF.

2.5.4 Potential effect of MARS on liver regeneration after hepatectomy

In detail, there are several effects of MARS treatment, observed when treating patients with acute or acute-on-chronic liver failure, which might be beneficial even in the PHLF situation. Firstly, MARS has proved to a certain degree to be effective in removal of Albumin-bound toxins (130, 131) and to improve the redox state of Albumin (131, 132). Thus, a reduced toxin-load in the recovering liver might support liver function in a way that could facilitate liver regeneration. Even portal hypertension after partial hepatectomy has been identified as a highly prognostic risk factor for the development of PHLF (110). As observed in patients with acute on chronic liver failure, MARS has a potential to decrease portal pressure, which could enhance the chance for a successful regeneration of the liver remnant (133). A major impact on liver regeneration might emanate from a possible influence on plasma levels of cytokines, as one study observed a clear correlation between liver volume increase 14 days postoperatively and plasma concentration of hepatocyte-growth factor (HGF) (134). In accordance, in one retrospective study by Donati et al., an increase of HGF under MARS treatment was observed (135), which might contribute to enhanced liver regeneration, too. On the other hand, it was shown in an animal model with a 90% partial hepatectomy, that a deceleration of regeneration by blocking key pathways (MEK/ERK) has led to improved outcome due to a better synchronization of the different liver cells under recovery (77). IL-6 is known as a key promoter of liver regeneration (70, 136). In clinical studies, it could be demonstrated that MARS has the potential to remove IL-6 from plasma (25). Potentially, a decrease of IL-6 plasma concentration might contribute to a more synchronized liver regeneration after hepatectomy, too, thus avoiding impairment of liver function and the development of persistent PHLF.

In summary, MARS could offer many beneficial effects for patients suffering from PHLF and related clinical effects should be further evaluated in prospective, controlled trials.

3 AIMS

The aims of this thesis were:

I. To investigate outcome after hepatectomy in Sweden in a population-based setting

II. To evaluate the impact of PHLF on short-term mortality following hepatectomy in a population-based setting

III. To retrospectively analyse the experience with MARS for treatment of PHLF and to critically review the available literature

IV. To prospectively evaluate safety and feasibility of early MARS treatment in patients with PHLF according to an intensified treatment protocol

4 METHODS

4.1 PAPER I

4.1.1 Study design

The study was designed as a retrospective, population-based register study in order to evaluate mortality and long-term outcome following hepatectomy in Sweden between 2002 and 2011.

4.1.2 Patients

In order to identify the study population and to obtain the relevant data the Swedish in-hospital registry, the national cancer registry, the "causes of death" registry and the registry of domestic and international relocations were used. Patients were identified in the Swedish in-hospital registry based on procedure specific codes for hepatectomy (the Tenth Revision of the International Classification of Diseases and Procedures, ICD10; JJB00, JJB10, JJB20, JJB30, JJB40, JB50, JJB53, JJB60, JJB71, and JJB96) and then linked to the other registries using patients personal national registration number in order to obtain patient related data. The methods and registries used were described elsewhere (137, 138).

4.1.3 Ethics

The study was approved by the regional ethical board in Stockholm (DN 2010/1872-31/2).

4.1.4 Statistical analysis

Data were stratified in order to allow for risk factor analysis with implication for short-term mortality and long-term survival. Liver biopsies, ablations, and de-roofing of liver cysts were not considered in the analysis. Re-do resections were calculated as new event. Means ± standard deviations were computed for continuous variables, proportions for categorical variables. Long-term survival following hepatectomy was assessed by the Kaplan-Meier method. Cox proportional hazard ratios (HRs) with 95% confidence intervals (CI) were used for univariable and multivariable analysis of risk factors/hazard association; Age, sex, comorbidity, extent of resection, diagnosis and hospital category were used in the regression model. Introducing the variables stepwise into the multivariable regression model tested potential confounding effects. P values <0.05 were considered to be statistically significant. For statistical analyses, SPSS Version 20 for Windows was used (SPSS, Inc., Chicago, IL).

4.2 PAPER II

4.2.1 Study design

The study was designed as a retrospective, population-based register study in order to evaluate the impact of PHLF on 90-day mortality following hepatectomy in Sweden between 2005 and 2009

4.2.2 Patients

Patient selection was done likewise paper I apart from the following changes:

Study time was set from the 1st of January 2005 to 31st of December 2009. Patients with ICD10 procedure code for hepatectomy were identified in the Swedish in-hospital registry and correlated to other registries in accordance to Study I. These patients and, in addition, local hospital registries were used in order to identify patients positive for 90-day mortality following hepatectomy. As 90% of all liver surgery is performed at University hospitals, therefore data acquisition was exclusively focused on these 7 hospitals. For those patients who were identified, additional data regarding pre-, per- and postoperative course were obtained from local patient journal systems. The obtained data are available at the local hospital registries only and cannot be made available for the entire population.

4.2.3 Ethics

The study was approved by the regional ethical board in Stockholm and covered by the same application and approval as Study I (DN 2010/1872-31/2).

4.2.4 Statistical analysis

Data were calculated as means ± standard deviations for continuous variables, and proportions for categorical variables. In order to verify the population-based approach, the entire background cohort identified in the in-hospital registry was compared with those positive for 90-day mortality identified in local hospital registries. Patients positive for 90-day mortality were then analyzed, divided into a PHLF and no-PHLF group. Primary PHLF was defined by the 50:50 criteria. Secondary PHLF was defined as liver failure occurring in the later postoperative course secondarily to complications. Chi-Square and Fisher´s Exact Test were used to compare proportions where appropriate and P-values <0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS Version 20 for Windows (SPSS, Inc., Chicago, IL).

4.3 PAPER III

4.3.1 Study design

The study was designed as a retrospective cohort study including all patients who were treated with MARS due to PHLF a two major HBP centers, Karolinska, Stockholm and Hospital Clinic, Barcelona between 1st of November 2003 and 30th of November 2012.

4.3.2 Patients

Patients were identified in local hospital databases and relevant data was obtained retrospectively from electronic patient charts in the in-hospital patient management system. Patients were subjected to hepatectomy in one of the participating centers and developed PHLF due to various reasons. Patients who were treated with MARS with PHLF as indication were included and evaluated. Primary PHLF was defined according to the 50:50 criteria. Secondary PHLF was defined as PHLF occurring as result of liver failure associated with severe postoperative complications such as bleeding, bile leakage, sepsis or multiorgan failure due to, for example, cardiac infarction or pulmonary embolism.

4.3.3 Ethics

The study was approved by the regional ethical board in Stockholm and covered by the same application and approval as Study I and II (DN 2010/1872-31/2).

4.3.4 MARS treatment

MARS treatment was performed via a double lumen central vein catheter. A PRISMA flex machine (PRISMA, Gambro, Lund, Sweden) was connected to the MARS system in the first four patients in Stockholm and in all patients in Barcelona, whereas a MULTIFILTRATE (Fresenius Medical Care AG, Bad Homburg, Germany) system was used in the latter four Stockholm patients. Anticoagulation was achieved whether with systemic heparin in non-coagulopathic patients or local anticoagulation with citrate in all Stockholm patients. Every MARS session was planned to last a minimum of 6 hours.

4.3.5 Statistical analysis

Statistical analysis was performed using JMP (Version 5.1.2). The results are reported as mean $\pm$ SD, median (ranges) or n (%). Students t-test was used when appropriate and p-values <0.05 were considered significant.

4.4 PAPER IV

4.4.1 Study design

The study was designed as a prospective phase I safety and feasibility study in order to assess a novel MARS treatment protocol in patients with PHLF.

4.4.2 Patients

All patients being subjected to major or extended hepatectomy from 1st of December 2012 onwards were eligible for enrolment. According to the study protocol, patients were screened for clinical and laboratory signs of PHLF until the 4th postoperative day. If patients fulfilled the inclusion criteria, mainly the 50:50 criteria as a definition for primary PHLF, patients were offered study inclusion on the 5th postoperative day. In total, 14 patients met the inclusion criteria and 10 patients were finally included in the study until 31st of May 2015 and treated according to the study protocol. Exclusion criteria were age >80 years, uncontrolled bleeding or sepsis, any relevant and untreated surgical complication (such as mechanical bile duct obstruction, clotting of the hepatic artery, or portal vein thrombosis) and platelet count of $<20 \times 10^9$/L. Patients with secondary PHLF (caused by any postoperative complication leading to PHLF later than POD 5) were not included in the study.

4.4.3 Ethics

The study was approved by the regional ethical board in Stockholm (DN 2013/149-31/2).

4.4.4 MARS and ICU treatment

According to the study protocol, MARS treatment was initiated between POD 5-7 in all patients. A minimum of 5 treatment cycles had to be completed within 8 days from the first MARS treatment. At persisting liver failure (elevated liver-specific blood samples) a maximum of 7 treatments were applied. MARS cycles were considered sufficient after a minimum of 6 h continuous treatment. Due to technical reasons, MARS treatment had to be performed at the local intensive care unit. There, MARS treatment was done via a double lumen catheter inserted into the internal jugular or femoral vein. A continuous renal replacement therapy (MultiFiltrate; Fresenius Medical Care AG, Bad Homburg, Germany) system was used to run the MARS monitor (Baxter, Lund, Sweden). The blood flow on the MultiFiltrate machine was adjusted to 90-150 mL/minute, and the albumin flow on the MARS monitor was set to 150 mL/minute. Dialysate and replacement fluid flow were set to receive a renal dialysis dose of 35 mL/kg/hour. Anticoagulation of the MARS circuit was done by local anticoagulation with citrate as described before (139). Intensive care unit (ICU) treatment was standardized prior to study onset in accordance with the guidelines for treatment of acute liver failure, including renal hemodialysis (continuous veno-venous hemofiltration) along with MARS treatment, mechanical ventilation, drainage of fluid collections, directed treatment with antibiotics and antifungals, and parenteral nutrition if needed (14).

4.4.5 Assessment of safety, feasibility, and efficacy of MARS treatment

In order to assess primary safety outcomes of early MARS treatment we evaluated the following variables:

1. Bleeding complication and the need for blood transfusions
2. Platelet count (termination of MARS or transfusion below $20x10^9/L$)
3. Severe electrolyte or acid-base derangements deemed secondary to local citrate anticoagulation of the MARS circuit resulting in early termination of MARS treatment

Feasibility was defined by the number of screened patients eligible for study inclusion related to those who finally have been included and treated according to the study protocol. In addition, we assessed drop-out of patients due to other than safety reasons (logistical or technical reasons). Efficacy was assessed by relevant blood samples prior to and after every single MARS session and at defined time points in the follow up (until demission, POD 60 and 90, if possible). The Model for End-Stage Liver Disease (MELD) score (140) was calculated in each patient before and after MARS treatment. Encephalopathy was graded according to the West Haven criteria (141). Standard vital signs as blood pressure, heart rate, and oxygen saturation were monitored accordingly to ICU standard. In order to detect adverse events, clinical investigation of the patient was performed before and after each MARS session. Clinically significant complications were considered as an adverse event (the adverse event changed patient management, the patient required additional hospital care, the patient become permanently disabled, or the adverse event was considered to be life- threatening).

4.4.6 Statistical analysis

Data generated before study inclusion on POD 5 were collected retrospectively from the individual in-hospital patient files. From POD 5 onwards, data were collected prospectively. Categorical data were expressed as frequencies with percentages. Continuous variables are displayed as medians with interquartile range (IQR). The Wilcoxon signed rank test was performed to assess paired nonparametric data (blood samples and MELD score), and the significance level was set at $p < 0.05$. One patient (patient number 8) was considered to be an outlier and was excluded from statistical analysis. Statistical analysis was performed using SPSS software version 24.0.0.0.

5 RESULTS

5.1 PAPER I

During observation time, a total of 4 460 (2 381 (53.4%) female, 2 079 (46.6%) male) hepatectomies were performed. Median age was 64 and 374 patients were operated two or more times. The number of patients who underwent hepatectomies in university compared to non-university hospitals significantly changed over the study period. Thus, the incidence of liver resections increased from 2.5 per 100 000 inhabitants in 2002, to 8.1 per 100 000 inhabitants in 2011. Comparing the first with the second 5-year period, the number of liver resections at non-university hospitals decreased slightly from 336 to 312/5 years. At the same time, the number of hepatectomies performed at university hospitals increased from 1283 to 2529/5 years. In regards to the extent of resection, there was an increase from n=1 013 to n=1 832 in minor resections, from n=479 to n=791 in major resections and from n=127 to n=218 in extended resections, respectively. The vast majority of major and extended hepatectomies were done at university hospitals (96% years 2002-2006, 99% 2007-2011). Major and extended resections showed a significantly higher mortality risk compared to minor resections (Figure 1). With no change over the entire study period, for minor resections, the median postoperative hospital stay was 9 days, after major resection 11 days and after extended resection 13 days. For all hepatectomies, 30- and 90-day mortality were 1.8 and 3.1%, respectively, with no significant change over the study period. After stratification for the extent of hepatectomy, we found significant differences in 30- and 90 mortality (Table 1). Comparing non-university with university hospitals, a significant difference in regards of 30- and 90-day mortality was found (30- and 90-day mortality in non-university hospitals: 3.8 and 6.6%; in university hospitals: 1.6 and 2.8%, $p<0.001$). The corresponding Kaplan-Meier estimation of survival following hepatectomy is displayed in Figure 2. In all patients, indications for hepatectomy were liver metastasis (n=2 644; 59%), HCC (n=393; 9%), GBC (n=254; 6%), ICC (n=129; 3%), and ECC (n=76, 2;%). In 10% of all cases, a diagnosis other/unclear was applied (n=452), in 2.5% bowel cancer (without “metastasis”, n=110), in 2% other liver malignancies (n=61) and 8% had a benign diagnosis (n=341). 5-year overall survival was 50% for patients with “liver metastasis”, 40% for HCC, 38% for GBC, 30% for ICC and 20% for ECC. The related Kaplan-Meier estimation is displayed in Figure 4.Re-resections were mainly performed in patients with diagnosis liver metastasis (78%) and resulted in a significant improvement of long-term outcome (Figure 5). Uni- and multivariable risk factor analysis revealed several significant risk factors for long-term survival after hepatectomy (Table 2). Age, comorbidity, male gender and hepatectomy performed in non-university hospitals showed to increase mortality risk significantly. University and non-university hospitals were considered to be equal with high and low volume hospitals and therefore excluded from multivariable analysis (due to co-linearity). In addition, diagnosis of ICC, ECC, and GBC were also recognized as independent risk factors for death, defining diagnosis “liver metastasis” as the baseline. Finally, long-term survival was impaired in patients

operated at non-university hospitals compared to those who underwent surgery at university hospitals (p<0.001).

Table 1. Postoperative 30- and 90-day mortality specified for the Extent of Liver resection

Extent of resection	n	Mortality % 30 days	90 days
Minor resections	2845 (63,8%)	1,4	2,3
Major resections	1271 (28,5%)	2,1	3,2
Extended resections	344 (7,7%)	4,3	7,5

Minor resections (≤ 2 Couinaud segments), Major resection (3-4 Couinaud segments), Extended resection (> 4 Couinaud segments)

Figure 1. Kaplan-Meier survival estimates for minor, major and extended hepatectomy

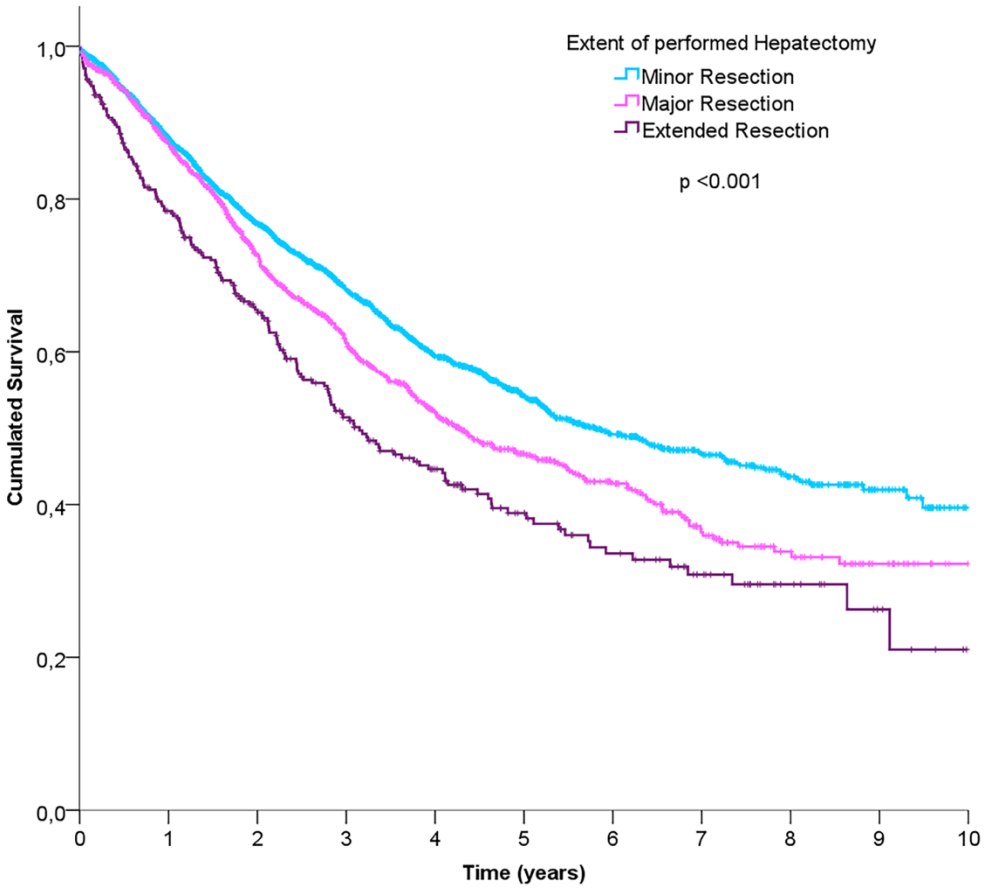


Table 2. Results of uni- and multivariable (Cox) regression analysis of risk factors for mortality (long-term survival)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Demography				
Age ≤54 y	1.00		1.00	
Age 55-63 y	1.39 (1.19-1.61)	<0.001	1.16 (0.99-1.35)	n.s
Age 64-71 y	1.90 (1.65-2.20)	<0.001	1.55 (1.34-1.79)	<0.001
Age ≥72 y	2.43 (2.11-2.80)	<0.001	1.90 (1.64-2.22)	<0.001
Female sex	1.00		1.00	
Male sex	1.20 (1.09-1.32)	<0.001	1.11 (1.01-1.22)	<0.05
Comorbidity				
Charlson 0	1.00		1.00	
Charlson 1-2	1.44 (1.30-1.59)	<0.001	1.36 (1.22-1.50)	<0.001
Charlson 3-4	1.90 (1.26-2.87)	<0.001	1.83 (1.20-2.78)	<0.05
Charlson ≥5	3.23 (1.90-5.47)	<0.001	3.06 (1.80-5.21)	<0.001
Diagnosis				
CRLM	1.00		1.00	
HCC	1.23 (1.06-1.44)	<0.05	1.16 (0.99-1.36)	n.s.
ICC	1.78 (1.41-2.25)	<0.001	1.76 (1.38-2.23)	<0.001
ECC	2.21 (1.70-2.93)	<0.001	2.15 (1.62-2.87)	<0.001
GBC	1.42 (1.19-1.70)	<0.001	1.53 (1.27-1.85)	<0.001
CRC	0.97 (0.73-1.30)	n.s.	0.71 (0.52-0.95)	<0.05
Other malignancy	0.83 (0.55-1.26)	n.s.	0.83 (0.55-1.26)	n.s.
Benign	0.15 (0.10-0.22)	<0.001	0.19 (0.13-0.28)	<0.001
Other	0.68 (0.57-0.81)	<0.001	0.74 (0.62-0.88)	<0.05
Study period				
2002-2006	1.00			
2007-2011	1.05 (0.95-1.16)	n.s.		
Extent of hepatectomy				
Minor	1.00		1.00	
Major	1.24 (1.12-1.38)	<0.001	1.18 (1.05-1.31)	<0.05
Extended	1.64 (1.40-1.92)	<0.001	1.10 (1.28-1.78)	<0.001
Hospital Volume				
High volume	1.00			
Low volume	1.17 (1.05-1.32)	<0.05		
Hospital structure				
University Hospital	1.00		1.00	
Non-university Hospital	1.46 (1.26-1.69)	<0.001	1.57 (1.35-1.83)	<0.001
Re-resection				
No	1.00		1.00	
Yes	0.40 (0.31-0.50)	<0.001	0.44 (0.34-0.56)	<0.001

HR, hazard ratio; 95% CI, 95% confidence Interval; CRLM, colorectal cancer liver metastasis; HCC, hepato-cellular carcinoma; ICC, intra-hepatic cholangiocarcinoma; ECC, extra-hepatic cholangiocarcinoma; GBC, gallbladder cancer; CRC, diagnosis of colorectal cancer coded for liver resection but without diagnosis" metastasis"; other malignancy, other liver malignancies; other, other and unclear diagnosis

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Figure 2. Kaplan-Meier survival estimates for hepatectomies performed at university vs. non-university hospitals

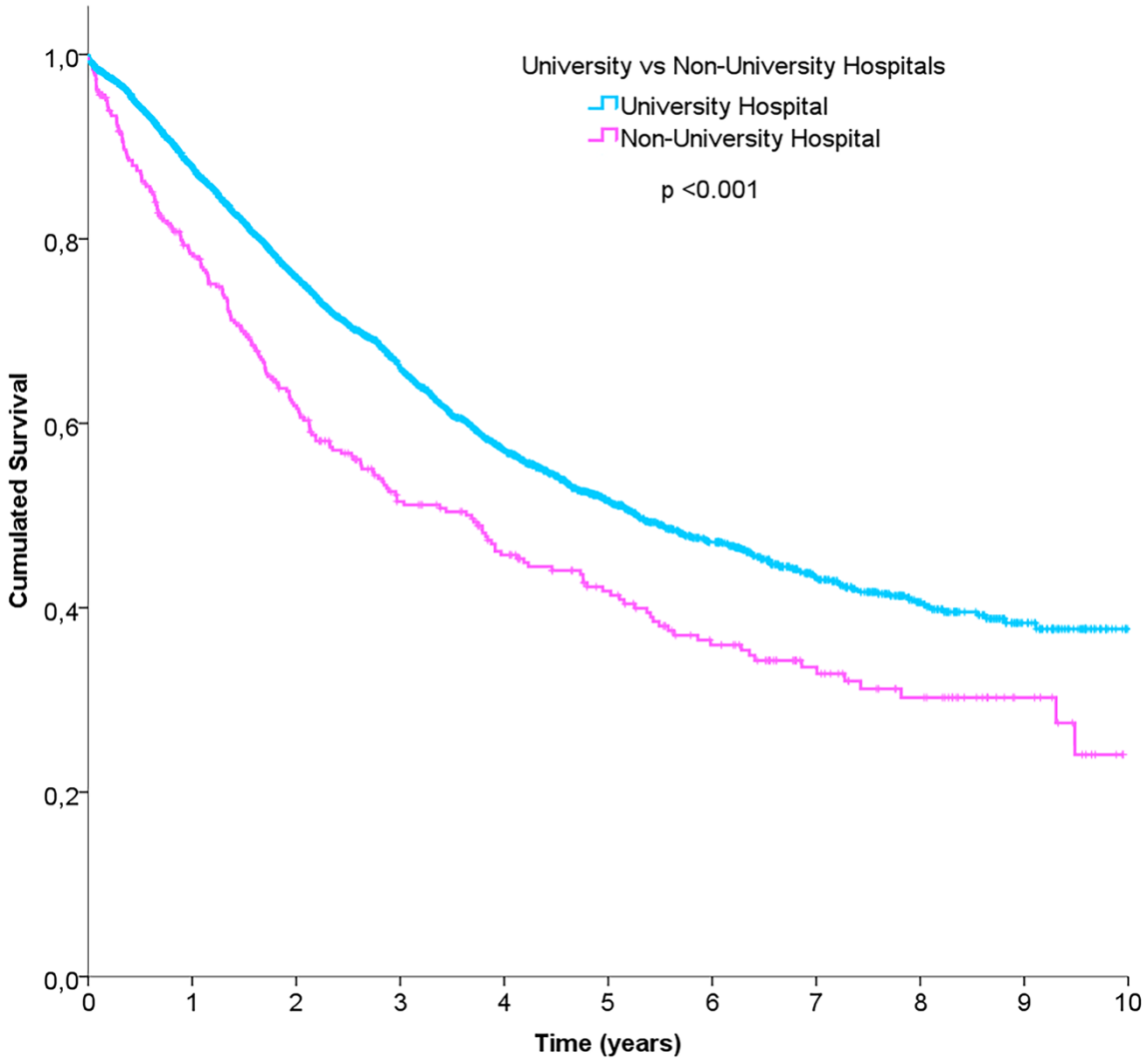


Figure 3. Kaplan-Meier survival estimates for different malign diagnosis

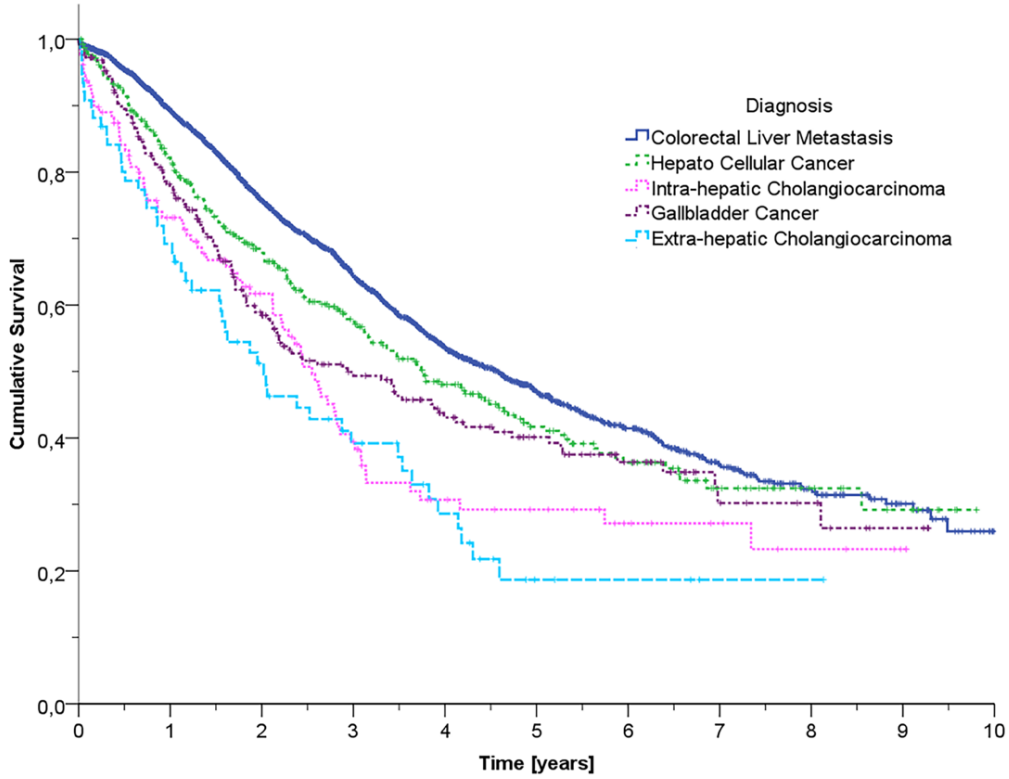
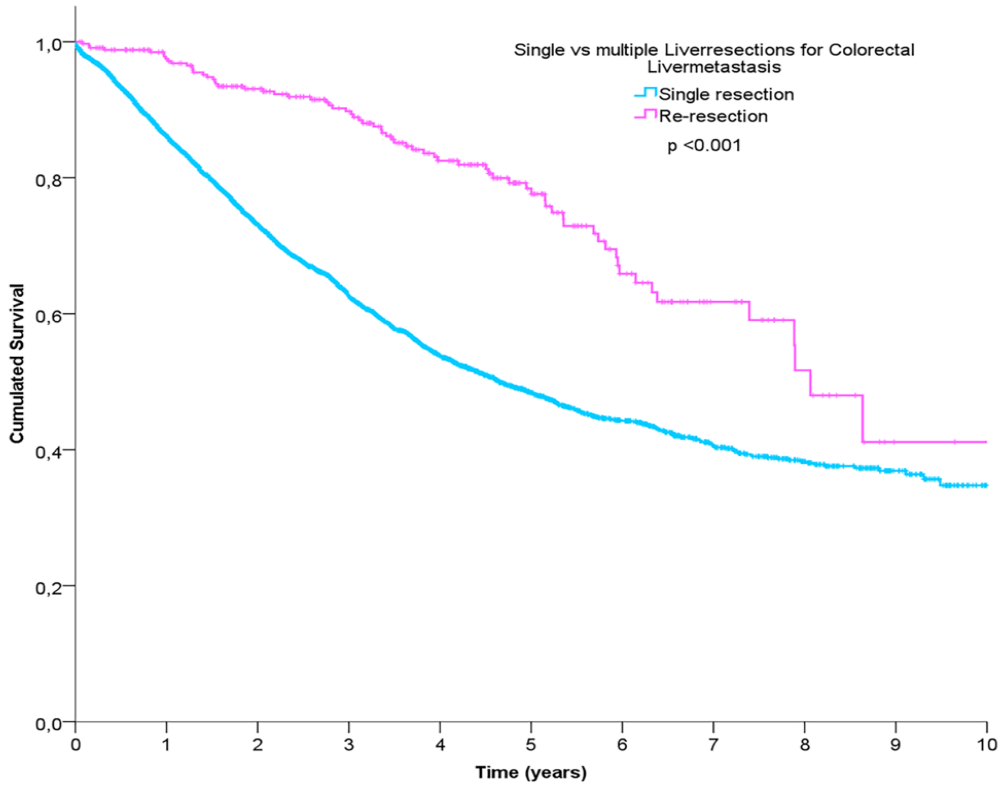


Figure 4. Kaplan-Meier survival estimates for single vs re-resection for CRLM



5.2 PAPER II

During 2005-2009, a total of 2461 liver resections were performed in 2241 patients (220 re-resections) with an age of 61.6 (13.6) years (mean, std) in all Swedish hospitals. 1322 patients (53.7%) were male and 1490 patients (60.5%) underwent hepatectomy due to CRLM, 150 (6.1%) due to HCC, 88 (3.5%) due to CCC, 129 (5.2%) due to GBC and 604 (24.5%) due to other or benign diagnosis. 2194 (89%) hepatectomies were performed in 1993 patients (201 re-resections) at one of the seven university hospitals. Of these patients, 1546 (62.8%) were subjected to minor hepatectomy, 718 (29.2%) to major and 197 (8.0%) to extended liver resection. 267 liver resections were performed in non-university hospitals and 30-day mortality was 1.5% and 90-day mortality 3.0%. Overall 30- and 90- day mortality was 1.4% and 2.7%, respectively and did not differ from mortality observed in university hospitals (1.4% and 2.6%, respectively). All patients positive for 90-day mortality at non-University hospitals underwent minor resections only, two for metastasis and the remaining six concomitant to other procedures. According to the in-patient's registry, we identified 56 patients who died within 90 days from surgery in one of the seven university hospitals. In the local registries, we identified 46 patients (80.7%) positive for 90-day mortality who were subjected to elective hepatectomy and thereby accessible for further data acquisition. Additional information regarding the study population, both the background population of liver resections and those positive for 90-day mortality, is shown in Table 1. In the group with 90-day mortality, there is a significant overrepresentation of male sex, severely ill patients (Charlson score 1 and $\geq$ 2) , diagnosis of cholangiocarcinoma and gallbladder cancer as well as major and extended hepatectomy. Subdividing all patients with 90-day mortality in a PHLF and no-PHLF group, 19 patients (41%) were allocated to the PHLF group. Of those, 16 patients fulfilled the 50:50 criteria. The remaining 3 patients were allocated due to PHLF developed in the later course as a consequence of secondary complications. In all patients, PHLF was considered to be the main reason for death, whether alone or in combination with multi-organ failure. In the no-PHLF group, we allocated 27 patients (59%). Three, respectively two patients had elevated bilirubin or INR on POD 5 but no patient fulfilled the 50:50 criteria. These patients did not develop liver failure in the later course. Comparing the baseline characteristics in the PHLF and no-PHLF group, there were significantly greater proportions of patients with CCC ($p=0.01$) and after extended hepatectomy ($p=0.019$) in the PHLF group. On the other hand, in the no-PHLF group there were more patients after minor resections ($p<0.001$). Additional data is shown in Table 2. When comparing pre-operative variables, we could not identify any significant difference between the PHLF and no-PHLF group. Data are detailed in Table 3. Intra-operatively, we found a statistically significant higher proportion of patients with vascular reconstructions in the PHLF group ($p=0.026$). Other variables did not differ significantly and details are shown in Table 4. Analyzing a compilation of variables related to the postoperative course of patients, we found several significant differences in between the PHLF and no-PHLF group. Bilirubin > 50 μg/L and INR <1.5 were significantly more often found in the PHLF compared to the no-PHLF group on POD 3 already ($p<0.001$). In the postoperative course, even encephalopathy of any

grade was found more frequently in the PHLF group than in the no-PHLF group (p<0.001). In contrast, transfusion of blood products was found more often in the no-PHLF group (p=0.036). No other significant differences were found and all postoperative variables are compiled in Table 5.

Table 1. Group of all liver resections in Sweden 2005-2009 compared with the 90-day mortality group

		Hepatectomies		90-day mortality		
		N	%	N	%	p
Total		2461		46		
Age (mean, std) years		61.6 (13.6)		67.4 (8.1)		n.s.
Male sex		1322	53.7	33	71.7	n.s.
Comorbidity Charlson score 0		1671	67.9	10	21.7	<0.001
	1	700	28.4	26	56.5	<0.001
	≥2	90	3.7	10	21.7	<0.001
Diagnosis	CRLM	1490	60.5	22	47.8	n.s.
	HCC	150	6.1	3	6.5	n.s.
	CCC	88	3.5	10	21.7	<0.001
	GBC	129	5.2	11	23.9	<0.001
	Benign or other	604	24.5	16	34.8	n.s.
Type of resection	Minor	1546	62.8	16	34.8	<0.05
	Major	718	29.2	13	28.3	n.s.
	Extended	197	8.0	17	37.0	<0.05

CRLM, colorectal liver metastasis; HCC, hepato-cellular cancer; CCC, cholangiocarcinoma; GBC, gallbladder cancer; n.s., non-significant

Table 2. Data from medical charts on resected patients who died within 90 days at university hospitals

	PHLF-group (N= 19)		No-PHLF-group (N=27)		p
	N	%	N	%	
Age (mean, std) years	(67.5, 7.1)		(67.7, 8.7)		n.s
Male sex	13	68.4	19	73.1	n.s
Comorbidity					
Charlson 0	3	15.8	6	22.2	n.s
Charlson 1	10	52.6	16	59.3	n.s
Charlson ≥2	6	31.6	4	14.8	n.s
Diagnosis					
CRLM	7	36.8	14	53.8	n.s
HCC	2	10.5	1	3.8	n.s
CCC	8	42.1	2	7.7	=0.01*
GBC	2	10.5	9	34.6	n.s
Type of resection					
Minor	1	5.3	15	57.7	<0.001**
Major	9	47.4	7	26.9	n.s
Extended	9	47.4	4	15.4	=0.019**

*Fisher's exact test, **Chi-square test; n.s., non-significant; CRLM, colorectal liver metastasis; HCC, hepato-cellular cancer; CCC, cholangiocarcinoma; GBC, gallbladder cancer

Table 3. Pre-operative data on PHLF and no-PHLF patients

	PHLF-group (N=19)		Non PHLF-group (N=27)		p
	N	%	N	%	
BMI≥30	4	21	4	15	n.s
Smoking	1	5	3	11	n.s
Diabetes	6	32	3	11	n.s
Hypertension	6	32	12	44	n.s
Hepatitis	0	0	3	11	n.s
ASA≥2	16	84	20	74	n.s
Preoperative chemotherapy	3	16	5	18	n.s
Cholestasis at time of surgery	7	37	5	19	n.s
PVE	3	16	1	4	n.s

BMI, body mass index; ASA, American Society of Anesthesiologists score; PVE, portal venous embolization; n.s., non-significant

Table 4. Intra-operative data on PHLF and non PHLF patients

	PHLF-group (N=19)		Non PHLF-group (N=27)		p
	N	%	N	%	
Pringle	7	37	10	37	n.s
TVE	1	5	0	0	n.s
Resection of extrahep bile ducts	8	42	6	22	n.s
Vascular reconstruction	4	21	0	0	=0.026*
Combination with other surgery	0	0	4	15	n.s
Combination with ablation	0	0	4	15	n.s
Operative bleeding>2000 ml	8	42	8	30	n.s

*Fisher's exact test; TVE, total vascular exclusion; extrahep, extra-hepatic; n.s., non-significant

Table 5. Postoperative data on PHLF and non PHLF patients

	PHLF-group (N=19)		Non PHLF-group (N=27)		p
	N	%	N	%	
Cirrhosis	4	21	3	11	n.s
Steatosis	4	21	10		n.s
Fibrosis	5	26	3	11	n.s
POD 3					
Bilirubin≥50 µg/L	15	79	3	11	<0.001**
INR>1.5	15	79	1	4	<0.001**
POD 5					
Bilirubin≥50 µg/L	16	84	3	11	<0.001**
INR>1.5	16	84	2	7	<0.001**
Platelets<100x10(9)/L	5	26	2	7	n.s
Creatinine>120 µmol/L	7	37	3	11	n.s
Postoperative transfusion	5	26	15	55	=0.036**
Bile leakage	2	11	7	26	n.s
Surgical intervention	5	26	10	37	n.s
PTC/ERCP	2	11	2	7	n.s
Infection	6	32	14	52	n.s
Aspiration	1	5	3	11	n.s
Portal thrombosis	5	26	1	4	n.s
Encephalopathy	8	42	0	0	<0.001*

*Fisher's exact test, **Chi-square test; n.s., non-significant; POD, postoperative day; INR, international normalized ratio; PTC, percutaneous-transhepatic-cholangiography; ERCP, Endoscopic retrograde cholangiopancreatography

5.3 PAPER III

In total, 13 patients (5 Hospital Clinic, 8 Karolinska Huddinge) were identified and included in the analysis. 7 patients had CRLM, 5 had primary hepato-biliary malignancy and 1 patient had a neuroendocrine disorder, MEN 1. Additional demographic and clinical data is shown in Table 1. In order to distinguish between patients, they were categorized into primary and secondary PHLF. Primary PHLF was defined by the 50:50 criteria, and secondary PHLF was defined by liver dysfunction following postoperative complications in the later postoperative course.

In the group with primary PHLF, we identified 9 patients fulfilling the 50:50 criteria (100). In these patients, treatment was initiated between POD 3 and 21 (median POD 8). A median of 3 (range 2-6) MARS sessions were performed in each patient. In total, four out of nine patients (44%) survived 90-days postoperatively. Three of them were alive one year after surgery. Comparing surviving and non-surviving patients, we could not identify significant differences in regards to the point of time of treatment start or treatment intensity. However,

we observed a trend towards more frequent MARS treatment in the surviving group (Survivors, median 5, range 4-6; non-survivors, median 2, range 2-3). MARS did not result in significant changes in bilirubin, creatinine, ALAT, platelets or INR. The safety profile of MARS treatment was good with no complications directly related to MARS treatment.

Four patients were allocated to the secondary PHLF group. In these patients, secondary PHLF occurred due to pulmonary embolism (POD 5) and a ruptured pseudo-aneurysm of the hepatic artery (POD 22) in patient 1. Patient 2 suffered from an acute bleeding from the hepatic artery on POD 11. Patient 3, firstly had an acute bleeding from a duodenal ulcer which was leading to a stroke, followed by rectal bleedings on POD 17, and in patient 4, there occurred a septic shock on POD 30 leading to secondary PHLF.

In patients with secondary PHLF, MARS treatment was started later between POD 17 and 39 (median POD 32). Overall, the four patients received 1-4 treatment cycles (median 2). None of the patients survived.

Table 1. Demographic and clinical data of the study population

Patient	age	gender	Treatment year	Hospital	Indication for surgery	surgical procedure	liver failure	50:50 criteria	treatment start (POD)	MARS cycles completed	outcome (90 days)
1	48	f	2003	KH	Locally advanced gallblader cancer	Extended right sided HH + Whipple procedure	secondary	no	17	2	died POD 24
2	56	m	2005	KH	suspicious gallblader cancer	Seg 5 and 4b + extrahepatic bile ducts	secondary	no	34	1	died POD 58
3	53	m	2008	HC	CRCm	extended right sided HH	primary	yes	3	3	died POD 7
4	70	m	2008	KH	CRCm	right sided HH, local resection seg 3	secondary	no	39	4	died POD 66
5	59	m	2008	KH	CCC	left sided HH	primary	yes	3	2	died POD 7
6	48	m	2008	KH	CRCm	right sided HH, local res seg 3, caudate lobe	primary	yes	8	6	alive
7	77	m	2009	HC	CRCm	right sided HH, RFA lateral seg	secondary	yes	30	2	died POD 34
8	59	m	2009	KH	CCC	extended right sided HH and caudate lobe	primary	yes	7	6	alive
9	61	m	2011	HC	CRCm	extended right sided HH	primary	yes	8	4	alive
10	59	m	2011	KH	CRCm	right sided HH	primary	yes	8	2	died POD 18
11	74	f	2011	KH	gallblader cancer	extended right sided HH	primary	yes	6	2	died POD 17
12	63	m	2012	HC	MEN -1 met	right sided HH, local resection seg 3	primary	yes	21	2	died POD 45
13	64	m	2012	HC	CRCm	extended right sided HH	primary	yes	19	6	alive

m (male); f (female); KH, Karolinska University Hospital Huddinge, Stockholm; HC, Hospital Clinic, Barcelona; CRLM, colorectal cancer metastasis; CCC, cholangiocarcinoma; MEN, multiple endocrine neoplasia, HH, hemihepatectomy; POD, postoperative day.

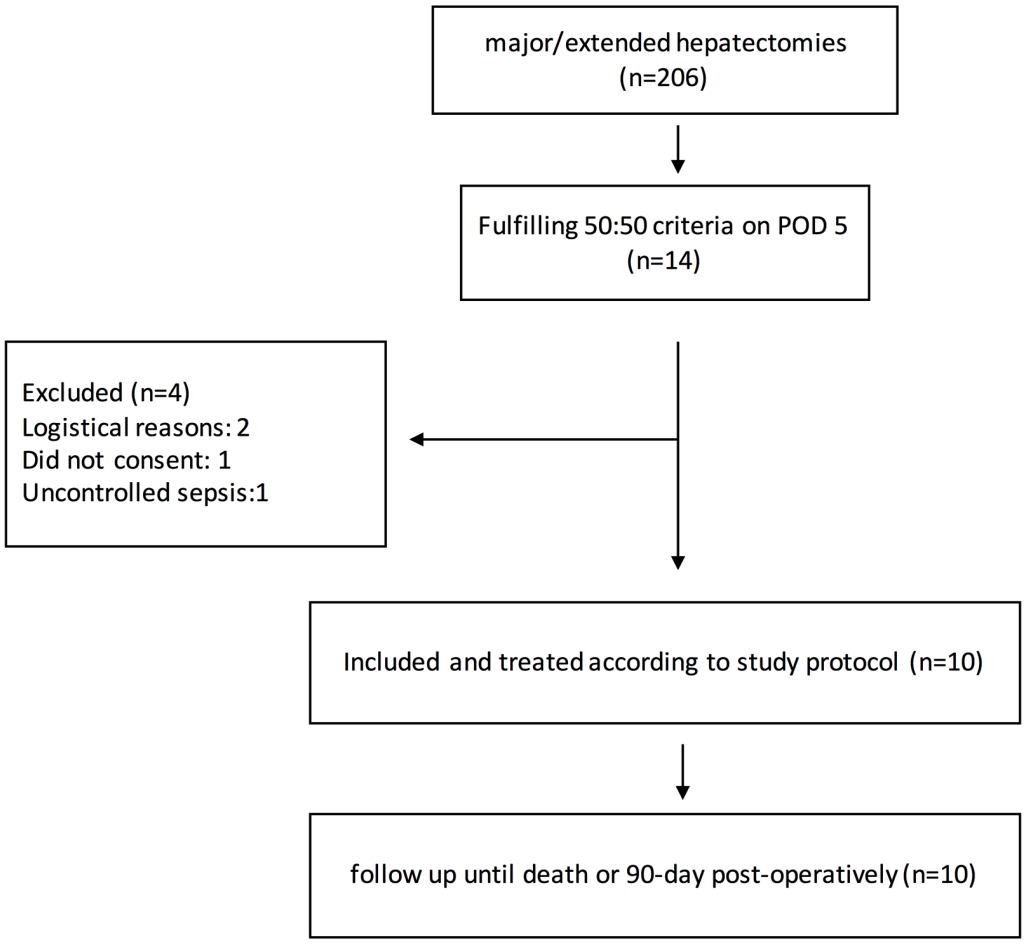
5.4 PAPER IV

From December 1st 2012 to May 31st 2015, 206 patients underwent major/extended hepatectomy and were screened for the study at Karolinska University Hospital. Regarding feasibility, 10 out of 14 patients who fulfilled the inclusion criteria on POD 5 could be included in the study and treated according to the protocol (Figure 1). The study population consisted of six male and four female patients (median age of 69 years (range 49-77)). According to the main safety outcome measures, there were no severe complications or

mortality during or after MARS treatment. We observed no bleeding and there was no need to transfuse blood products due to MARS treatment. Electrolytes and acid-base balance were kept within safety limits by standard replacement therapy. Two patients experienced flow problems with the central line which had to be replaced twice.

However, in one patient (patient no. 8), we observed a severe increase of bilirubin (peak total bilirubin about 1000 micromol/L) along with a modest increase of INR (range between 2 and 3). We could exclude mechanical bile duct obstruction by repeated radiology (CT, MR, and MRCP) and ERCP. Unfortunately, we could not identify a reason for this development despite repeated discussions with experts in the field.

Figure 1. Study flow chart



Indication for surgery was colorectal cancer liver metastases in 5 patients, perihilar cholangiocarcinoma in 4 patients and hepatocellular cancer in 1 patient. Additional demographic data is shown in Table 1.

Table 1 Patient characteristics of the study population

Patient	Age	Sex	BMI	Diabetes	CVD	Smoker	Indikation	Cx	Surgery
				0 = no; 1 = yes	0 = no; 1 = yes	0 = no; 1 = yes		0 = no; 1 = yes	
1	71	m	24	0	0	0	CCC	0	Extended right hepatectomy
2	75	f	31	0	0	1	CRLM	1	Extended right hepatectomy
3	65	f	21	1	0	0	CCC	0	Extended right hepatectomy
4	68	m	23	0	1	0	CCC	0	Extended right hepatectomy
5	66	f	23	1	1	0	CCC	0	Extended right hepatectomy
6	77	f	20	0	0	0	CRLM	1	Right hepatectomy + seg 1
7	72	m	25	0	1	0	HCC	0	Extended right hepatectomy
8	57	m	31	0	0	0	CRLM	1	Right hepatectomy + local seg 4
9	72	m	29	0	0	0	CRLM	0	Right hepatectomy + local seg 4
10	49	m	26	0	0	0	CRLM	1	Extended right hepatectomy
median (IQR)	69,5 (10)		24,5 (7)						

BMI = body mass index; CVD = cardio-vascular disease; PVE = portalvein embolisation; m = male; f = female; CCC = cholangiocarcinoma; CRLM = colo-rectal liver metastasis; HCC = hepatocellular cancer; Cx = neoadjuvant chemotherapy; seg = liver segment;

In average, the mean preoperative FLR/BW ratio was 0.55 (IQR 0.25) and the mean standardized FLR 26.1% (IQR 11.3%). In two patients, portal venous embolization (PVE) was performed preoperatively and FLR-increased by 28% and 24%, respectively. In order to assess patients FLR postoperatively, calculations were done retrospectively on CT´s performed for clinical indications. This was the reason, why the investigations were done at different time points, making it difficult to compare the results. In all patients we observed an increase of FLR within 25 days from surgery. Completing information on volumetric measurements is displayed in Table 2.

Table 2 Volumetric measurements

Patient	FLR segments	FLR preop	FLR/BW	sFLR preop	Liver dysfunction **	TELV pre op	Specimen weight	Postop CT	Postop volume	Increase postop
		mL	preop	%	0 = no; 1 = yes	(calculated)	grams		mL	volume mL/day
1	1-3	140	0.22	10.2	0	1371	1117	POD 94	730	6.3
2	1-3	480	0.58	28.8	0	1665	1305	POD 23	897	18.1
3	1-3	190	0.33	14.9	0	1271	766	POD 25	804	24.6
4	2-3	250/320 *	0.45	20.4	1	1568	950	POD 12	803	40.3
5	1-3	290/360 *	0.62	28.8	1	1248	1295	POD 49	945	119
6	2-4	295	0.58	26.5	0	1114	726	POD 5	488	38.6
7	2-3	840	0.88	41.4	0	2028	1983	POD 5	1388	109.6
8	1-4	510	0.52	25.7	1	1983	1000	POD 24	1525	42.3
9	1-4	370	0.38	18.4	1	2011	1049	POD 15	910	36
10	1-3	535	0.61	28.3	1	1893	1320	POD 23	1084	23.9

* pre/post portal venous embolisation; FLR = future liver remnant; sFLR = standardized future liver remnant; BW = body weight; preop = preoperatively, postop = postoperatively; TELV = total estimated liver volume; ** persistent liver dysfunction on POD 90; CT = computed tomography

Two out of ten patients had severe postoperative complications (Clavien-Dindo $\geq$ 3b); in one patient, re-operation was needed due to hemorrhage and in one patient ERCP was done in general anesthesia in order to achieve stenting of the common bile duct. More details regarding histopathology and intra-/postoperative complications can be found in Table 3.

Table 3 Histopathology and complications

Patient	Pathology	Inflammation grade	Fibrosis grade	Steatosis grade	Specimen weight grams	Complication intra-/postoperatively
1	GBC, T3 N1 R1	1	2	2	1117	Postop bleeding, re-op POD 4
2	CRLM, focal R1	0	2	3	1305	HE
3	IG4 cholangitis	0	2	0	766	Bile leakage, conservative treatment, HE
4	CCC, T2b N2 R1	1	1	1	950	Ascites, sepsis
5	GBC, T3 N0 R1	1	3	0	1295	HE
6	CRLM, focal R1	0	1	2	726	HE, systemic infection
7	HCC, T3b V1 R0	1	2	2	1983	HE, bile leakage, conservative treatment
8	CRLM, focal R1	1	2	2	1000	Intra-op injury of the left bileduct, ERCP, Stent
9	CRLM, focal R1	0	1	2	1049	None
10	CRLM, focal R1	0	1	1	1320	Intraop bleeding, ascites

GBC = gallbladder cancer; CRCm = colo-rectal liver metastasis; CCC = cholangiocarcinoma; HCC = hepato-cellular cancer;
HE = hepatic encephalopathy (Westhaven grade 2 or higher); ERCP = endoscopic retrograde cholangio-pancreatography

In all patients, MARS treatment was initiated within seven days from surgery. Due to a lack of resources at the ICU, in two patients MARS treatment could not be performed continuously but had to be interrupted (for two and three days, respectively). This did not represent a protocol violation as all patients underwent at least five completed MARS sessions within eight days from the start of treatment. Clotting of the MARS filter occurred in one treatment cycle, and this MARS session was repeated with a new filter. Excluding patient no. 8 from statistical analysis, we observed a significant decrease of both bilirubin and INR under MARS treatment (bilirubin $p = 0.042$; INR $p=0.023$). On the other hand, there was no significant impact on creatinine, CRP, ammonia, platelets, and MELD score (Figure 2). Four patients showed signs of hepatic encephalopathy at time of ICU admittance (Westhaven grade II or higher). One of these patients developed respiratory failure and was put on mechanical ventilation. After three MARS cycles, the patient had improved substantially, and mechanical ventilation was terminated. The remaining three patients improved clinically as well, and no need for parenteral nutrition and mechanical ventilation occurred. Additional information on ICU and MARS treatment is given in Table 4.

Table 4 ICU and MARS treatment

Patient	SAPS Score	MELD before MARS	MELD after MARS	MARS start	MARS end	MARS sessions	MARS pause days	CRRT/ renal failure	Mechanical ventilation
1	80	18	22	POD 7	POD 14	7 (4+3)	2	1	0
2	67	23	18	POD 6	POD 12	5	0	0	0
3	72	19	12	POD 5	POD 12	5	0	0	0
4	60	22	24	POD 7	POD 17	7 (3+4)	3	0	0
5	67	21	20	POD 6	POD 13	7	0	1	0
6	72	20	14	POD 6	POD 11	5	0	0	0
7	91	20	13	POD 5	POD 10	5	0	0	3 days
8	61	24	31	POD 7	POD 13	7	0	1	0
9	61	19	17	POD 6	POD 10	5	0	0	0
10	68	21	16	POD 7	POD 12	5	0	0	0
median (IQR)	67,5 (13)	21 (5)	19 (9)						

SAPS = simplified acute physiology Score; MELD = model for end-stage liver disease; CRRT = continious renal replacement therapy;
POD = post-operative day

Outcome of the study population was no 60-day mortality and 1/10 (10%) 90-day mortality. Disease free one year survival was 50%. All patients recovered in terms of liver function

parameters. All remaining four patients suffered of disease recurrence (perihilar cholangiocarcinoma in one and colorectal liver metastasis in three) and succumbed between POD 130 and 348. 3/4 showed signs of chronic liver dysfunction. Additional information on patient outcome is shown in Table 5.

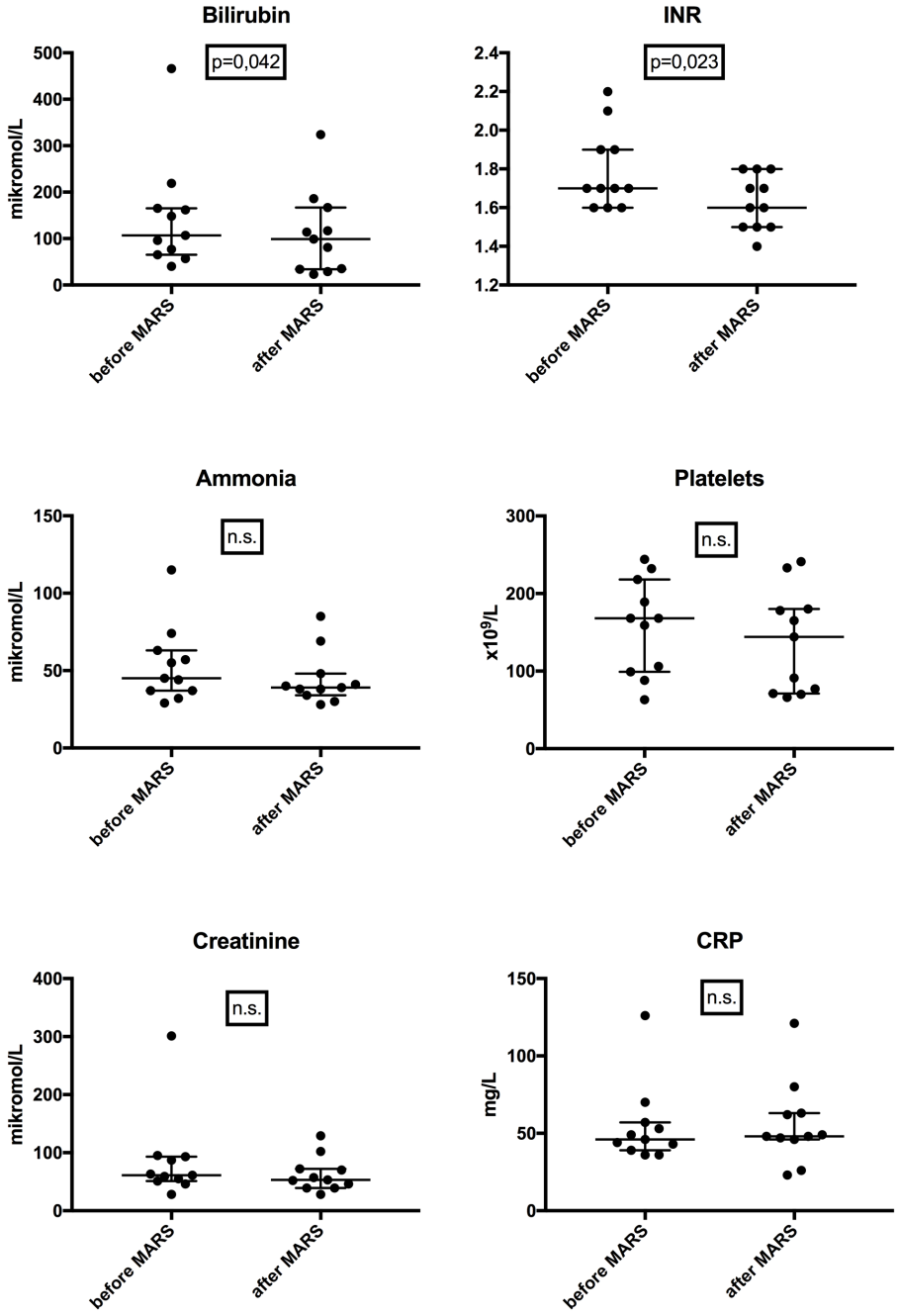
Table 5 Patient outcome and survival

Patient	Hospital stay/days (until 1. demission)	Bilirubin POD 90 mikromol/L	INR POD 90	60-day mortality 0 = no; 1 = yes	90-day mortality 0 = no; 1 = yes	Liver dysfunction** 0 = no; 1 = yes
1	35	18	1.3	0	0	0
2	46	18	1	0	0	0
3	35	37	1.3	0	0	0
4	128	427	1.4	0	0	1
5	90	619	2.5	0	1	1
6	20	n.a.	n.a.	0	0	0
7	39	353	1.2	0	0	1
8	46	380	1.8	0	0	1
9	24	38*	1.4*	0	0	1
10	30	24	1.5	0	0	0
median (IQR)	37 (29)	195 (396)	1,4 (1,0)			

POD = post operative day; na = not available; * = on POD 144; ** = liver dysfunction on POD 90

In a historical cohort of patients between January 2010 and November 2012, 248 patients were operated with major or extended hepatectomy. 11 patients (4.4%) met the 50:50 criteria on POD 5. 60- and 90-day mortality rates were 64% (7/11). Thus, we could validate the 50:50 criteria in our institution as sound instrument in order to predict 60- and 90-day mortality.

Figure 2. Blood samples before/after MARS treatment



6 DISCUSSION

6.1 GENERAL DISCUSSION

6.2 STUDY DESIGN

6.2.1 Population-based register studies

With increased centralization and specialization of cancer treatments, data on patient outcome, complications and survival often originate from highly specialized centers (6, 82, 142, 143). Data obtained might be biased in many ways, by e.g., patient selection, higher quality of care at high volume centers, publication bias of poor vs. favorable results, etc. (144). Therefore, a transfer of results from single center experience on an entire population might not be suitable. To avoid this problem, population-based studies represent a unique methodological way in order to answer research questions. This approach implicates many favorable aspects, like the possibility to access a huge amount of already existing data at low costs leading to a high quality of scientific studies (145). However, even population-based evaluations suffer from several disadvantages. The intended variables may not be available, inappropriate registered or coded incorrectly leading to ambiguous results (146, 147). Hence, a control for confounders might be difficult (148). Both, study I and II used population-based register data in order to answer the research questions. In previous studies, a good to very good data quality of the registries could be validated (149). In addition, for study II there was a usage of data from local hospital registries, too. Thus, study II might not be considered as completely population-based, as part of the data used were obtained from other than population-based registries. Thereby, the study might be seen as a combination of 2 different study types, a population-based register study and a retrospective chart review, which is discussed below.

6.2.2 Retrospective chart review study

Another study approach is represented by the retrospective chart review (RCR). When doing this kind of study, a sample of retrospectively collected data from already existing databases, e.g., hospital charts, is used in order to answer the research question (150). However, several issues have to be discussed, addressing both advantages as well as limitations of this study design. An advantage is that RCR is a cheap and fast way to obtain relevant data and to answer research questions in order to guide the design of prospective studies (150). Limitations are numerous and extensively discussed be Vassar et al. (151). Most importantly, a lack of clearly defined study plans, misconduct in data registration and under-powering of the study sample might be mentioned. In this thesis, study III used a RCR design in order to answer the research question. Given the patient cohort that was investigated, under-powering was a major issue as MARS treatment in the PHLF situation was done in so few patients. Partially, we tried to minimize this limitation by conducting a multicenter study in order to broaden the study population. A related problem was represented by the heterogeneity of

patients in the treatment group, making it impossible to control for confounders with the identified number of patients.

6.2.3 Prospective pilot study

In study IV, we defined safety and feasibility as the primary outcome. In accordance, the study was designed as a phase I safety and feasibility study. This kind of study design is primarily known from pharmacological studies and phase I is analogs to "first in men". Even though MARS was used in human beings before, the indication and especially the treatment protocol was not studied before, thus justifying this approach and definition. However, the study design could be described as a prospective pilot study, too. The purpose was to test an intensified treatment protocol at a different time point of the postoperative course, compared to earlier experience. Systematically obtained data was not available prior to this study. In order to validate our inclusion criteria and patient outcome, data of a historical patient cohort was used for analysis. The used study design implicates limitations in regards to statistical power of the results. However, given the very low incidence of the studied condition, there was no study design available being more suitable in order to test our research hypothesis, and, secondarily, making it possible to design a prospective randomized trial in the future based on the results from the pilot trial.

6.3 STUDY RESULTS AND IMPLICATIONS FOR THE FUTURE

6.3.1 Study I

The present study found an overall low 30- and 90-day mortality compared to a previous study conducted in France (9). At the same time, the numbers of performed liver resections increased significantly in Sweden. However, this increase was restricted to university hospitals and reflects an ongoing, nationwide process of centralization, gathering certain cancer treatments at selected high volume centers, what in Sweden is equally to university hospitals. At the same time, our results demonstrated a much better short and long-term outcome of patients treated at university hospitals compared to non-university hospitals, an effect observed before (152) which further supports the centralization process. This effect was even seen for other tumor entities in the upper gastrointestinal area before, e.g., pancreatic or esophageal cancer (153, 154). This effect remained even after correction for several confounders. Interestingly, not even surgeon or hospital volume alone was identified as a significant risk factor in the meta-analysis of Brusselaers et al., analyzing 16 studies on esophagectomy due to cancer (153). In our study, another positive effect in respect to the long-term outcome was found for patients who were re-resected for CRLM. This represents off course a very selected group of patients, but, thus our results confirm earlier observations from single centers in a population-based setting (155-157) and support aggressive surgical strategies in case of localized cancer recurrence. A very important issue identified by this study is the overall very low mortality following hepatectomy in Sweden. Comparing our results with the French study by Farge et al. (9), several differences can be identified. Firstly, Sweden has another case-mix with a lower number of cirrhosis patients subjected for

hepatectomy. As cirrhosis was identified as major risk factor for poor outcome after hepatectomy (20), this finding might contribute significantly to improved outcome in Sweden. Another remarkable aspect was seen in a much lower incidence of hepatectomy /inhabitant in Sweden compared to France. Whether this reflects a difference in the incidence of diseases treatable by liver surgery or is an expression for differences in patient selection, remains unclear. However, as France was from the very beginning a leading country in terms of development of liver surgery (30, 158, 159), a more conservative patient selection and as a consequence, a more favorable patient outcome in Sweden, might be assumed. Regarding outcome in relation to the underlying diagnosis, our study confirmed earlier reports, with the best long-term survival for patients with CRLM and poorest outcome for primary biliary cancers (4, 7, 12).

In the future, further centralization should be supported in order to decrease mortality related to primary biliary malignancies due to improved research and treatment strategies. Register-based studies should be repeated periodically in order to assure the quality of cancer treatments and to identify further needs for improvement.

6.3.2 Study II

Our study confirms that PHLF has to be considered as one of the main reasons for postoperative short-term mortality even in a population-based setting. As shown previously, specific risk factors significantly contribute to death in the PHLF group compared to those patients with 90-day mortality due to other reasons than PHLF.

PHLF is considered a severe complication following hepatectomy with a frequently dismal outcome (84, 160). However, there are several remaining problems in the understanding and description of PHLF. The maybe most important limitation is found in the problem of defining PHLF as this massively influence the incidence of PHLF. In the year 2005, Balzan et al. were the first to publish a risk score, a combination of bilirubin value and INR on postoperative day, to predict in-hospital mortality following hepatectomy (100) and the accuracy of this so-called “Balzan” or “50:50” criteria was prospectively confirmed later on (101). However, several reports could not confirm the accuracy of the 50:50 criteria but proposed other variables in order to define PHLF and predict patient outcome. The most important ones are represented by the ISGLS criteria (102), the Mullen or “peak-bilirubin” criteria (15) and the Hyder score (161). Recent reports focused on validating especially the ISGLS criteria (17, 162), but on the other hand, even the “50:50” criteria, as well as the Mullen criteria, are still used in current publications (83, 163). In recent years, several reviews have summarized the available literature regarding PHLF and discussed important issues like definition and prevention, risk factor analysis, management and outcome of patients with PHLF (84, 160, 164, 165). Compared to the reviewed reports, our study provides several advantages. A major benefit is represented by the study design with a population-based approach, covering all hepatectomies in Sweden over a 5 year period. This is a unique methodology in the evaluation of PHLF and implicates improvement of data quality as they do not contain any selection bias compared to single center data (6, 82, 166).

Another advantage is represented by the large number of patients included in the study, which increases the statistical power of the results. As we have observed in a previous study, mortality following hepatectomy is lower in Sweden (167) compared to other population-based data (9, 10). All University Hospitals in Sweden apply national, evidence-based guidelines for patient selection prior to surgery. However, patient mix/characteristics with a lower number of patients with, e.g. cirrhosis and a more conservative patient selection in regard to, e.g. age, might contribute to lower short-term mortality in Sweden. Despite this differences in terms of patient selection, even in the present study, PHLF contributes to or is the single cause in 40% of all deaths within 90 days from surgery. At non-university hospitals, we identified 8 patients positive for 90-day mortality. All of them were subjected to minor resections, and we considered this as a consequence of the ongoing process of centralization of major liver surgery to expert centers in Sweden. Thus, the case mix of non-university hospitals is not representative anymore, as only minor resections are left and in consequence, the risk for PHLF as cause of death should be minimal at these hospitals.

On the other hand, there are several limitations in the present study. Due to the retrospective study design, it might be assumed that the quality of the obtained data is not as good as compared to prospectively collected data and several variables had to be excluded from analysis due to this problem. Another issue could be seen in the period of time for the data collection, which was set from the year 2005 to 2009. However, data of this paper have been, as stated in the methods, partially published before (167). The first publication raised several scientific questions which we were able to address in the present study. In addition, from 2009 onwards, there was a new registry, the national liver registry, introduced in Sweden. Data from this registry might be, after validation, available in the near future for a follow-up study of the present report. Another problem was the mismatch of cases positive for 90-day mortality in the Swedish Hospital Discharge Registry compared to local hospital registries. The most likely explanation might be incorrect coding in the Swedish Hospital Discharge Registry, or even more likely, liver resections have been performed by other specialties than liver units, e.g., trauma units, colorectal surgeons or urologists. Therefore, it might not have been possible to identify this cases in the local hospital registries, where only data on elective hepatectomies were available. As major and extended hepatectomies and thereby the risk for PHLF are more unlikely to be missed in this situation, there could be an underestimation of deaths due to other causes in our final patient population, and thus, the impact of PHLF could be overestimated for the whole population. Finally, due to the study design, we are not able to present the incidence of PHLF in the entire population as these data, mainly blood samples, are not available in the used nationwide registries.

In summary, PHLF represents a major risk for short-term mortality and measures have to be taken to improve both, avoidance and treatment, of patients with PHLF.

6.3.3 Study III

According to our experience, we found the use of MARS to be safe in the PHLF situation with a related short-term survival superior to previous reports.

Since its introduction in 1993 (114), MARS has become the most popular one amongst all extracorporeal liver support devices. In several clinical studies, it was shown that MARS is a safe procedure, being able to significantly remove both protein-bound and water-soluble toxins along with an improvement of both kidney and liver function (118, 121, 123, 133). However, in 2 large randomized controlled trials, MARS failed to demonstrate a significant impact on patient survival (124, 125).

Until today, 20 patients from 5 reports are found in the literature in whom MARS was used as a treatment for PHLF (119, 127-129, 168). Survival was very poor in all reports, and a lack of standardized treatment protocol was apparent. In contrast, we observed a 44% 90-day survival in patients with primary PHLF defined according to the Balzan criteria (100). An obvious difference between survivors and non-survivors was the number of performed MARS cycles. All survivors received a minimum of 4 treatments. This is in line with earlier reports of MARS treatment in other types of liver failure where a minimum of 3 consecutive treatments was considered necessary in order to achieve adequate treatment effect (125, 169, 170). In patients with secondary PHLF, which was defined as PHLF as a consequence of postoperative complication, MARS treatment was applied in the later postoperative course, with zero 90-day survival. Poor results in this situation were observed earlier (128, 129) and in conclusion, MARS treatment does not seem to be justified in this situation. The timing of MARS treatment is most likely a very critical issue. Liver regeneration is initiated immediately at the end of hepatectomy (41). Recent studies suggested bilirubin on POD 3 (171) or phosphorus levels on POD 2 (172) as early, independent prognostic factors for predicting PHLF. So, theoretically, it might be beneficial to start with MARS even earlier than POD 5, but only if evidence for the power of predictive scores earlier than POD 5 has been strengthened. When the PHLF situation is established, it can be speculated about several beneficial effects of MARS on liver regeneration in order to turn around the clinical picture and allow the liver to regain normal function. Given its potential to provide anti-inflammatory effects and to bind reactive oxygen species (ROS) (173), detoxification of Albumin might increase its anti-oxidative capacity and thus decrease oxidative stress in the regenerating liver. In addition, several effects on cytokines important for liver regeneration have been observed in patients with acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF), e.g., an increase of hepatocyte growth factor (HGF) and decrease of IL-6 and TNF-α (135). Those have been identified as key players of liver regeneration (41), thus modulation of plasmatic concentrations might positively influence the regenerative capacity of the liver (134). Even portal hypertension has been recognized as a major risk factor for PHLF (110). In accordance, the potential of MARS of lowering portal pressure (120, 133) might contribute to improved patient outcome, too.

In summary, we made several observations in this study which, together with findings from other reports, served as background for the development of a treatment protocol to validate safety and feasibility of early MARS treatment in a prospective pilot study. In our opinion, it is essential to start treatment as early as possible, based on the available literature on POD 5 when the Balzan criteria are fulfilled. In order to avoid "under treatment", a minimum of 5 treatment cycles should be applied. Patients with secondary PHLF should not be treated with MARS.

6.3.4 Study IV

In our pilot study, we found early MARS treatment to be safe and feasible in patients with PHLF. In-hospital mortality was considerably lower compared to a historical control group. Half of the patients were alive 1-one year post-hepatectomy without signs of disease recurrence.

In recent years, several studies were aiming to demonstrate survival benefits for patients with acute liver failure. However, MARS could not show a survival benefit in large randomized controlled trials for patients with neither ALF (125) nor AoCLF (124). Regarding the PHLF situation, there were some publications in the early 2000´s, only reporting results not supporting the use of MARS. However, these studies were not performed in homogeneous patient populations, included just a very small number of patients, and there was no standardized treatment protocol (16, 127-129, 168). Thus, our pilot study is to our knowledge the first one with a strict study protocol and a comparable study population.

With regards to safety and feasibility, we observed no major complications. In two patients, there were problems with the central venous line making it necessary to replace lines one and two times, respectively. The MARS filter clotted in one treatment session. As we did not observe any bleeding complication, this illustrates a very good balance between anticoagulation in order to avoid clotting of the MARS filter and hemostasis in the patient to avoid bleeding after major surgery. Using local citrate anticoagulation (139), we did not observe severe disturbance of electrolyte balance either. However, in one patient we observed an unexpected clinical course. Even in this patient, MARS was started according to the protocol. After the first MARS session, we observed a moderate decrease in bilirubin. MARS was continued according to the protocol and there was a slight decrease in bilirubin even after the following treatments. However, the increase in bilirubin in-between the MARS cycles was so massive, that the overall increase of bilirubin ended up with a peak around 1000 micromol/L. Along with the hyperbilirubinemia, there was just a moderate increase of INR and no signs of encephalopathy. Such a response related to MARS has not been described before in the literature ,and the exact mechanism behind remains, despite extensive consultations with specialists in the field, unclear. Regarding feasibility, we experienced minor problems, mainly related to the fact that MARS treatment requires patient transfer to the ICU. As resources are limited, PHLF patients without further indication of ICU treatment than MARS, were conflicting with those patients being in real need of ICU treatment. Thus, 2 treatment cycles had to be interrupted. This did not lead to a protocol violation, but a more

flexible use of MARS could help to avoid this issue in the future and would be highly appreciated. Our study protocol was designed based on our own experience (Paper III) and observations made in patients with different causes of liver failure. For the PHLF situation, it is probably crucial to initiate treatment early and consequently. According to earlier reports, 3 consecutive MARS treatments were considered to be the minimum amount in order to achieve a sufficient treatment result (169, 170). In this pilot study, we definitely want to avoid "under-treatment". This was the reason for a scheduled minimum of 5 treatment cycles and a minimum of 3, if the MARS treatment was interrupted. The time point of treatment onset is another critical question, and in our opinion, it has to be based on a valid risk assessment. However, as liver regeneration starts immediately after liver resection (41), supportive measures probably should be initiated as early as possible. Currently, there is no solid possibility to predict PHLF during the first days after hepatectomy. In clinical practice and according to our historical control group, the 50:50 criteria (100) serves as the best predictive tool in order to predict PHLF related mortality. Thus, until new evidence is available, we suggest these criteria when choosing patients for MARS treatment due to PHLF.

7 CONCLUSIONS

The papers included in this thesis allow the following to be concluded:

Hepatectomies are performed with low mortality and good long-term results even in a population-based setting.

Risk factors for increased mortality include the extent of liver resection and diagnosis primary liver or bile duct cancer.

Re-do resection improves long-term survival in a selected group of patients.

Centralization of cancer surgery implies improved patient outcome.

Post-hepatectomy liver failure is considered to be the cause of death in about 40% of all patients positive for 90-day mortality.

Thus, PHLF is the single most important reason for 90-day mortality following hepatectomy even in a population-based setting.

A great effort is needed to further improve avoidance and treatment of PHLF.

Based on retrospective experience, MARS treatment cannot be recommended as treatment for patients with PHLF in the later course after hepatectomy and in patients with secondary PHLF.

In a prospective cohort study, it was safe and feasible to use MARS in patients with primary PHLF.

Applying a strict treatment protocol, early and frequent MARS treatment improved both short and long-term survival of patients with PHLF compared to a historical control group.

A prospective, randomized trial is highly warranted to evaluate the impact of early MARS treatment on survival in patients with PHLF.

8 FUTURE RESEARCH

Since the national Swedish liver register was introduced in 2009, this register offers new and compelling opportunities for population-based register studies in the future. In recent years there was a shifting trend for hepatectomies, leaving major and extended hepatectomy when possible and performing parenchyma sparing surgery instead. This paradigm shift, along with better and strictly defined standards regarding pre-operative workup before hepatectomy, the incidence and thus the mortality associated with PHLF should decrease. After validation of the national liver register, we plan a follow-up study in order to evaluate incidence and mortality related to PHLF in more recent years. Based on register data, better insights in risk factors and validation of different prognostic models should be possible even in a population-based setting.

Based on the results of paper IV, we have designed a prospective, randomized, controlled multicenter trial in order to evaluate the impact of MARS on short-term mortality and long-term outcome in patients with PHLF. The study was designed together with collaborators from Hospital Clinic, Barcelona. Ethical board approval was already obtained and currently, the application to the approving authorities is prepared. Several centers in Europe have expressed both their interest and willingness to participate.

Successful treatment of PHLF with MARS has raised several scientific questions regarding existing knowledge and understanding of liver regeneration after partial hepatectomy and the pathophysiology of PHLF. Within the RCT, blood samples are going to be collected in order to analyze changes related to MARS treatment of several relevant factors important for liver resection. Volumetric measurements of the future liver remnant will be performed to allow for correlation between liver volume and function.

As avoidance still represents the best treatment of PHLF, results from the RCT hopefully will contribute to an even better pre-operative patient selection and understanding of PHLF in order to minimize the incidence of PHLF. In our department, several translational projects are ongoing regarding pre-operative workup of patients scheduled for liver resection, like evaluation of different techniques to increase future liver remnant, and these collaborations hopefully will continue even in future research projects.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Leverkirurgi anses idag vara standardbehandlingen för de flesta tumörer i lever och gallvägar. Sedan 1990-talet har leverkirurgin genomgått en betydande utveckling. Det finns trots denna utveckling fortfarande en del diagnoser och ingrepp som har sämre prognos och högre risk vid leverkirurgi. En av de mest fruktade komplikationerna efter en leverresektion är postoperativ leversvikt. I vanliga fall fungerar det bra att ta bort upp till 80% av den totala levervolymen. Vissa diagnoser, som exempelvis gallgångscancer, är ofta förknippade med gallstas vilket leder till sämre leverfunktion inför operation. Dessutom kan förbehandling med cellgifter leda till nedsatt leverfunktion. Även andra sjukdomar som hjärtsvikt eller diabetes kan påverka leverfunktionen negativt. I dessa fall är leverns kapacitet att återhämta sig nedsatt och risken för post-hepatektomi leversvikt (PHLF) större. Trots att man känner till flera faktorer som inverkar negativt på leverns förmåga att återbildas drabbas ändå en del patienter av PHLF. När PHLF uppstått finns ingen effektiv behandling mot detta tillstånd. En möjlig behandling mot PHLF är så kallad leverdialys, som renar patientens blod från olika slagg produkter. Tekniken liknar vanlig njurdialys, men är mer effektiv avseende rening av leverspecifika ämnen. Erfarenheterna av leverdialys är nedslående trots att det teoretiskt finns flera effekter av en sådan behandling som skulle kunna bidra till leverns återhämtning. En konsekvent och intensifierad användning av leverdialys hos patienter med PHLF har inte tidigare studerats.

Det här avhandlingsarbetet har som målsättning att studera olika aspekter av leverkirurgi och PHLF. I första och andra arbetet har vi genomförd populationsbaserade studier och undersökt hur överlevnaden ser ut för patienter med olika sjukdomar efter leverkirurgi och vilken betydelse PHLF har för dödlighet inom 90 dagar efter leverkirurgiska ingrepp. Olika register har använts för att samla in data som sedan har analyserats för att kunna besvara de vetenskapliga frågeställningar. Leverkirurgi i Sverige har låg dödlighet och god långtidsöverlevnad, vilket ligger i nivå med tidigare studier. Dödlighet och överlevnad varierar dock kraftigt, beroende på storlek av ingreppet och på bakomliggande diagnos. Centralisering av stor kirurgi till Universitetssjukhus verkar ha positiv effekt på både komplikationer till ingreppet och långtidsöverlevnad. Det finns knappt några populationsbaserade studier i litteraturen. Möjligen kan man ur våra resultat dra slutsatsen av att vi i Sverige varit för restriktiva när det gäller att välja ut patienter för leverkirugiska ingrepp. I det andra arbete har vi kunnat påvisa att PHLF bidrar till eller är själva orsaken till död hos drygt 40% av alla patienter som dör inom 90 dagar efter leverkirurgi. Några riskfaktorer som är kända från tidigare studier har kunnat bekräftas i vår populationsbaserade studie. Det tredje arbetet hade som målsättning att undersöka om leverdialys har en positiv effekt på patienter med PHLF. Retrospektiv analys genomfördes på två universitetssjukhus, Karolinska Universitetssjukhuset Huddinge och Hospital Clinic Barcelona. Totalt identifierades 13 patienter och överlevnaden för dessa patienter var dålig. Vid granskning av detaljer vid behandlingen av dessa patienter har vi dock kunnat identifiera skillnader i överlevnad beroende på behandlingstid och intensitet. Detta gav oss hypotesen för att designa

en prospektiv studie för att undersöka säkerheten och effekten av tidig leverdialys hos patienter med PHLF efter leverkirurgi. Behandlingsprotokollet syftade på en tidig och mer intensiv behandling så snart som möjligt efter leverkirurgi om patienten visade på tydliga tecken för PHLF. Totalt har 10 patienter ingått i studien och behandlats på Karolinska Universitetssjukhuset Huddinge och vi kunde konstatera att det var säkert och effektivt att behandla patienter enligt studiens behandlingsprotokoll. Både 90 dagars dödlighet och långtidsöverlevnad var betydligt bättre jämfört med historiska kontroller från vårt eget sjukhus och med tidigare rapporterade resultat på svår PHLF. Dessa resultat måste dock bekräftas i en större studie där man lottar patienter med PHLF till standardbehandling enbart eller till standardbehandling plus leverdialys.

Sammanfattningsvis har de genomförda arbetena lett till resultat som kommer att ha betydelse för planering av leverkirurgi i Sverige i framtiden och som ger ett visst hopp om en effektiv behandling för patienter med leversvikt efter leverkirurgiska ingrepp.

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