# "Outcome of Biliary Complications after Living Donor Liver Transplantation"

**Thesis**
Submitted For Fulfillment of MD Degree in Tropical Medicine
Faculty of Medicine
Cairo University

**By**

**Ahmed Abd El-Azeem El-Mikkawy**
(M.B., B.Ch; MSc. Cairo University)
Assisstant Lecturer of Gastroenterology & Hepatology
Theodor Bilharz Research Institute

**Supervisors**

**Prof. Mahasen Abd El-Rahman Mabrouk, MD**

Professor of Endemic Medicine
Faculty of Medicine
Cairo University

**Prof. Ibrahim Mostafa Ibrahim, MD**

Professor of Endemic Medicine
Theodor Bilharz Research Institute

**Prof. Mahmoud Shawky El- Meteini, MD**

Professor of General Surgery
Faculty of Medicine
Ain-Shams University

**Dr. Shereen Shoukry Hunter, MD**

Associate professor of Endemic Medicine
Faculty of Medicine
Cairo University

FACULTY OF MEDICINE
CAIRO UNIVERSITY
2013

# List of Contents

# *ACKNOWLEDGMENT*

**"First and Foremost, Thanks are Due to GOD,
The Beneficent and Merciful of All"**

*It was an honor to work under the supervision of eminent professors, who lent me their whole hearted support and immense facilities as is their usual with their juniors. To them, I owe more than I can record.*

*I would like to express my deepest gratitude and sincere thanks to* ***Prof. Dr. Mahasen Abd El-Rahman,*** *Professor of Endemic Medicine, Faculty of Medicine, Cairo University, for her unlimited support, keen & instructive supervision, continuous guidance, valuable instructions and offering all facilities to complete this work*

*My thanks and appreciation to* ***Prof. Dr. Ibrahim Mostafa,*** *Professor of Tropical Medicine, Theodor Bilharz Research Institute, for his sincere effort , valuable remarks and consistent support which have contributed a lot to the delivery of this work.*

*Many thanks to* ***Prof. Dr. Mahmoud El-Metini,*** *Professor of General Surgery, Faculty of Medicine, Ain Shams University, for his continuous help and valuable suggestions all through the work.*

*Many thanks to* ***Prof. Dr, Shereen Hunter,*** *Associate Professor of Tropical Medicine, Faculty of Medicine, Cairo University, for her continuous help, valuable suggestions, guidance and encouragement during the progress of this work. I would like to thank her for the close and patient revision of the work.*

*Whatever I say or write, I will never be able to express my deep feelings and profound gratitude to* ***Prof. Dr. Mohammed Bahaa,*** *Professor of General Surgery, Ain Shams University, for his support and high sense of profession in the entire development of this thesis. Without*

*his creative thinking, valuable suggestions, data supplmenattion, the completion of this work would have been difficult.*

*I am extremely grateful to* ***Dr. Tarek Mahmoud Diab****, Professor of Parasitology, Theodor Bilharz Research Institute, for his unlimited help in the statistical analysis of the data; he gave me much of his time advice and effort throughout this work.*

*Many thanks to* ***Prof. Dr. Ayman Yosri,*** *Professor and Head of Tropical Medicine Department, Faculty of medicine, Cairo University, and to* ***Prof. Dr. Maged Elghanam,*** *Professor and Head of Tropical Medicine Department, Theodor Bilharz Research Institute, and to the whole staff members and workers in these departments for their support and advice. Many thanks also to the whole staff members and workers in* ***Wady El-Neel Liver transplant centre*** *for their efforts, help and support.*

*Also I am honored by the presence of Prof.* ***Dr. Magdy El-Serafy,*** *Professor of Tropical Medicine, Faculty of Medicine, Cairo University for his acceptance to come here today and that he found time in his busy schedule to discuss my thesis….much obliged sir*

*Also many thanks and my deepest gratitude to Prof.* ***Dr. Motaaz Seyam,*** *Professor of Tropical Medicine, Theodor Bilharz Research Institute, for his kind acceptance to come here today to discuss my thesis…I am honored sir*

*Finally, No words can express my deepest appreciation and gratitude to my family, my wife, and my daughter for their never ending care, support and love.*

*To All Those I say:* جزاكم الله خيراً

*Ahmed El-Mikkawy*
*2013*

# Abstract

Biliary complications continue to be a major cause of morbidity in liver transplant recipients with an incidence of 10–40% following liver transplantation and a mortality rate of up to 5%. Biliary leaks and strictures are the most common encountered complications. Biliary complications may be related to various factors such as hepatic artery patency, preservation injury, cytomegalovirus infection, chronic ductopenic rejection, ABO incompatibility, and technical reasons. The general management guidelines for biliary complications include conservative, endoscopic, percutaneous transhepatic and surgical approaches.

Objectives; we sought to assess and to document the frequency, risk factors, clinical presentation, management and outcome of biliary complications after liver transplantation in patients who underwent LDLT in Wady El-Neel Hospital, Cairo, Egypt.

From November 2001 to December 2008, 150 adult-to-adult living donor liver transplantations (LDLT) were undertaken using right lobe grafts (RLG). Patients were divided into those with and those without biliary complications. Duct-to-duct biliary anastomosis (DD) done in 98% of cases. The overall biliary complication occurred in 52 patients (34.7%), including bile stricture rate of 31.3% and bile leakage rate of 4%. Risk factors associated with biliary complications were prolonged cold ischemia time, multiple donor ducts together with multiple biliary anastomosis. Endoscopic interventions alone were successful in 38/50 patients (76%) and if combined with percutaneous methods (Rendezvous) the success rate becomes higher (96%). Overall patient survival rates at 1, 2, 3 and 4 years were 90.07%, 84%, 80% and 77.30% respectively

We concluded that post-liver transplantation biliary complications were relatively common and most biliary complications after LDLT can be successfully treated with nonsurgical approaches as both endoscopic and percutaneous methods had a satisfactory outcome. ERCP, in particular, has proven to be relatively safe and effective in the management of these complications. The occurrence of biliary complications does not appear to adversely affect the long-term graft and patient survival.

**Key words:**

- Living donor liver transplantation (LDLT)
- Duct-to-duct anastomosis (DD)
- Endoscopic retrograde Cholangiopancreatgraphy (ERCP)

# List of Abbreviations

| | |
|---|---|
| **AIH** | Auto immune hepatitis. |
| **ALP** | Alkaline phosphatase. |
| **ALT** | Alanine transaminase. |
| **AS** | Anastomotic strictures. |
| **AST** | Aspartate transaminase. |
| **BCS** | Budd Chiari syndrome. |
| **CMV** | Cytomegalovirus. |
| **CT** | Computed tomography. |
| **DD** | Duct-to-duct anastomosis. |
| **DDLT** | Deceased donor liver transplantation. |
| **ECG** | Electrocardiogram. |
| **ERC** | Endoscopic retrograde cholangiography. |
| **ERCP** | Endoscopic retrograde Cholangiopancreatgraphy. |
| **ESLD** | End stage liver disease. |
| **ESR** | Erythrocyte sedimentation rate. |
| **EUS** | Endoscopic Ultrasound. |
| **GGT** | Gamma glutamyl transferase. |
| **GI** | Gastrointestinal. |
| **GRWR** | Graft recipient weight ratio. |
| **GV** | Graft volume. |
| **GW** | Graft weight. |
| **HAT** | Hepatic artery thrombosis. |
| **HBS** | Hepatobiliary Scintigraphy. |
| **HCC** | Hepatocellular carcinoma. |
| **HIDA** | Hydroxyl imino-diacetic acid. |
| **HIV** | Human immunodeficiency virus. |
| **ICU** | Intensive care unit. |
| **INR** | International normalizied ratio. |
| **ITBL** | Ischemia-type biliary lesions. |
| **LDLT** | Living donor liver transplantation. |
| **LHA** | Left hepatic aretry. |
| **LHD** | Left hepatic duct. |

| | |
|---|---|
| **MDCT** | Multidetector computed tomography. |
| **MELD** | Model for End-Stage Liver Disease. |
| **MHV** | Middle hepatic vein. |
| **MOF** | Multiple organ failure. |
| **MRC** | Magnetic resonanace cholangiography. |
| **MRCP** | Magnetic Resonance Cholangiopancreatgraphy. |
| **MRI** | Magnetic resonanace imaging. |
| **NAS** | Non-anastomotic strictures. |
| **OLT** | Orthotopic liver transplantation. |
| **PBC** | Primary biliary cirrhosis. |
| **PCR** | Polymerase chain reaction. |
| **PSC** | Primary sclerosing cholangitis. |
| **PTC/D** | Percutaneous transhepatic cholangiography/drainage. |
| **PVT** | portal vein thrombosis. |
| **RE-LTX** | Retransplantation. |
| **RHA** | Right hepatic artery. |
| **RHD** | Right hepatic duct. |
| **RLG** | Right lobe graft. |
| **SEMS** | Self expanding metal stents. |
| **UNOS** | United Network for Organ Sharing. |
| **US** | Ultrasound. |

# List of Tables

# List of figures

# Introduction and Aim of work

## History

The history of liver transplantation began with experimental transplants performed in dogs in the late 1950s. The first deceased donor liver transplant (DDLT), also known as orthotopic liver transplant (OLT), was attempted in humans was in 1963 by Thomas Starzl. The recipient was a 3-year-old boy with biliary atresia who unfortunately died of haemorrhage. The first successful liver transplant was in 1967, again by Starzl at the University of Colorado Health Sciences Center, Denver. Yet, for the next 10 years, liver transplants remained essentially experimental, with survival rates well below 50%. Still, advances in the surgical procedure and in anesthetic management continued to be made during that time ***(Starzl et al., 1977).***

## Overview

Liver transplantation has become a life saving therapy for many types of end stage liver disease ***(Ahmed and Keeffe, 2007).*** This field has undergone remarkable advances in the last two decades. Patient survival at 1 year post transplant has increased from 30% in the early 1980s to more than 85% at present. The major reasons for this dramatic increase include refined surgical and preservation techniques, better immunosuppressive protocols, more effective treatment of infections, and improved care during the critical perioperative period ***(Busuttil et al., 2005).***

However, during the past decade; a critical shortage of cadaveric organs for adults in need of liver transplants has developed. During this time, the waiting period for liver transplantation and the rate of death among patients on waiting lists have been increased. This led to the development of innovative surgical techniques such as split-liver transplants and living donor liver transplants (LDLT), with the first right lobe liver transplant performed in Hong Kong in 1996. Initially these new techniques were mainly applied to pediatric patients because of the difficulty associated with finding appropriate size-matched organs for them. However, as the number of adults on the waiting list grew, these techniques began to be applied for adult recipients as well ***(Lee et al., 2008).***

Therefore, LDLT has become an important tool to treat end stage liver disease due to the lack of such cadaveric donors**.** The use of LDLT progressed at an even more rapid pace in countries such as Japan, where the concept of deceased donor organ donation was not widely accepted ***(Fan et al., 2000).*** In Egypt, the use of Cadaveric donor is still prohibited, forcing some capable patients to seek this service abroad. LDLT is the only possible option for end stage liver disease patients in Egypt (***EL-Meteini et al., 2003).***

Over the past several decades, advances in surgical techniques, organ preservation, immunosuppressive therapy, and early detection of postoperative complications have increased survival rates after liver transplantation ***(Caiado et al., 2007).*** However, a liver transplant remains a major undertaking, with the potential for complications affecting every major organ system ***(Busuttil et al., 2005).***

### Biliary Complications

Despite the great advances in the field of liver transplantation, it is still nonetheless a major surgery for a usually morbid patient. It is accompanied by a wide range of complications. Biliary tract complications after liver transplantation, which represent the "Achilles heel" of liver transplantation ***(Alsharabi et al., 2006),*** continue to be a cause of morbidity and mortality, the incidence of which is still high despite advances in surgical techniques, medical care, immunosuppression, and postoperative management ***(Pascher and Neuhaus, 2005).***

Reports in literature indicate that biliary complications occur in 10 to 40% of all adult cases of liver transplantation though some may not require intervention ***(Gobal et al., 2003, Thethy et al., 2004).*** Biliary tract complications after liver transplantation show a mortality of up to 5% ***(Zoepf et al., 2005).*** It can occur both early and late after transplantation. The majority of biliary complications are bile leaks and biliary strictures, less common but significant biliary complications include retained internal biliar stents, sludge/stones, bile duct necrosis and biliary cast syndrome ***(Buck and Zajko, 2008).***

No uniform algorithm for management of these biliary complications has been adopted by the transplant centers. As experience in the field of transplantation is increasing, so are the treatment options for biliary complications. The trend towards non-surgical therapies is rising, and the results are expected to improve even further ***(Patkowski et al., 2003),*** as transplant patients are both surgically and medically complicated and therefore percutaneous and endoscopic methods for treatment of biliary complications have been used with increasing frequency ***(Buck and Zajko, 2008).***

## Aim of the work

The aim of this study is to assess and to document the frequency, risk factors, clinical presentation, management and outcome of biliary complications after liver transplantation in patients who underwent LDLT in Wady El-Neel Hospital during the period from 2001 till 2008.

# Chapter 1: Living Donor Liver Transplantation

## 1.1- History

From the earliest days of clinical transplantation, the availability of donor organs has been a matter of concern. The use of kidneys from live donors began shortly after kidney transplantation itself and has been accepted worldwide as an important alternative for patients with renal failure. In 2003, 42.7% of kidney transplants in the United States were with organs from living donors. Because the kidneys are paired, and the removal of a kidney is technically relatively simple, donor safety has not been a major concern (estimated donor mortality risk is 0.02-0.05%) ***(Kasiske, 1996).***

By contrast, hepatic resection is a technically demanding procedure, which, despite continual refinement of technique and perioperative care, carries risk that is greater than nephrectomy ***(Pomfret, 2003; Miller, 2004).***

LDLT, driven by the dire shortage of organs for children with liver failure who otherwise would die, was first performed in 1988 ***(Raia, 1989; Broelsch et al, 1991).*** Through the early 1990s, LDLT for children using a graft comprising segments II and III gained popularity. Together with the development of split liver transplantation with organs from deceased donors, LDLT has virtually eliminated the problem of children dying while awaiting transplantation ***(Testa, 2001).***

The typical pediatric transplant candidate has biliary atresia and needs a transplant before age 2; a segment II/III graft is ideally sized for such patients. The anatomy of the liver, with the left portal structures coursing up the umbilical fissure and the small parenchymal bridge connecting segments II and III to the rest of the liver that contains no major vessels, is favorable for the preparation of this graft ***(Otte, 2002).*** Waiting list mortality for adults continued to increase unabated, and the use of left lobes for adult recipients began in Japan in 1993 ***(Hashikura, 1999),*** the first successful transplant using the right lobe from a living donor was reported in 1994 ***(Yamaoka, 1994).*** Since 2001, adult LDLT has been the only available treatment with curative intent for patients with end-stage liver disease (ESLD) in Egypt ***(El-Meteini et al., 2005)***.

## 1.2- Living donor selection

Living donors are usually close family members or spouses, although some transplant programs do accept unrelated "good Samaritan" living donors. ABO blood type compatibility is preferable and donors are usually less than 60 years of age. Only about 14 % of potential donors end up being suitable after the evaluation ***(Valentin-Gamazo et al., 2004).***

**Initial screening process *(Hashikura et al., 1997).***

- Education regarding the risks of donation with morbidity and mortality statistics.
- A thorough psychosocial assessment is performed.
- Confirm that consent is informed and willing with no external pressures.
- Donor has adequate time to contemplate the risks of the procedure.