The development and validation of a classification system for biliary complications following orthotopic liver transplantation

Amy Anne Neville, MD

Department of Epidemiology, Biostatistics and Occupational Health

McGill University

Montréal, Québec, Canada

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List of Abbreviations

AL	Anastomotic leak
AS	Anastomotic stricture
CCA	Choledocho-choledochoal anastomosis
CDS	Common duct stricture
ERCP	Endoscopic retrograde cholangiopancretography
ESLD	End stage liver disease
FD	Filling defect
HAT	Hepatic Artery Thrombosis
HJA	Hepaticojejunostomy anastomosis
HIV	Human immunodeficiency virus
ICD	International Classification of Disease
HIS	Intra-hepatic stricture
IVC	Inferior vena cava
MELD	Model for End Stage Liver Disease
MRCP	Magnetic resonance cholangiopancreatography
NAL	Non-anastomotic leak
OLT	Orthotopic liver transplantation
PTC	Percutaneous transhepatic cholangiography

ABSTRACT

Introduction: The estimated incidence of biliary complications after OLT ranges from 10-40% but the absence of a standardized classification system prevents accurate documentation. We propose a structured classification for biliary complications following choledocho-choledochal anastomosis (CCA) at non living-related OLT. The classification is based on 3 major components and anatomic location: strictures (intrahepatic, common hepatic or anastomotic), leaks (anastomotic, non-anastomotic) and filling defects. The initial steps in proposing this classification are to test its reliability and validity.

Methods: The study population consisted of OLT recipients from the McGill University Health Centre who underwent transplantation between 2004-2011. Reliability was determined using formal reliability testing including inter-rater reliability and test-retest reliability. The classification scheme was validated by analysis of the relationship between classification elements and important clinical outcomes (including diagnostic studies, need for revisional surgery, repeat transplantation, number of post-transplant hospital admissions, the total number of hospital admission days and graft and patient survival).

Results: A total of 184 patients, including 76 patients with biliary complications, were included. Both inter-rater reliability and test-retest reliability showed high levels of agreement with kappa statistic greater than 0.8 for all classification elements. The proposed classification components showed a strong relationship with the selected clinical outcomes. Poorer clinical outcomes were observed with strictures when compared to leaks or filling defects. Within the differing types of strictures, increasing severity of the complications was demonstrated with higher level biliary lesions, further supporting validity of our classification method. The relationship between stricture components of the classification and days of hospital admission exemplifies the validation method; adjusted rate ratio (95% confidence interval) for days of hospital admission for anastomotic, common duct and bilateral intra-hepatic strictures was 2.01 (1.84- 2.18), 3.80 (3.42-4.21) and 7.05 (6.46- 7.70) respectively.

Conclusions: The proposed classification of biliary complications shows excellent reliability and good construct validity. The significant difference in clinical outcomes between different classification components demonstrates the appropriateness of the chosen components. The classification components reflect the relative severity of the different complications, further supporting validity. Given small numbers in this preliminary study, larger numbers are needed to further validate the classification

RÉSUMÉ

Introduction: L'incidence estimée de complications biliaires après transplantation hépatique varie de 10-40%, mais l'absence d'un système de classification normalisé empêche une documentation précise. Nous proposons une classification structurée des complications biliaires après anastomose cholédocho-biliaire lors d'une greffe hépatique. La classification est basée sur trois éléments principaux et leur localisation anatomique: les sténoses (intra-hépatique, canal hépatique commun ou anastomose), les fuites (anastomose, non anastomotique) et les débris cannulaires. Les étapes initiales afin d'évaluer cette classification sont d'en mesurer la fiabilité et la validité.

Méthodes: La population étudiée était composée de patients receveurs de greffe hépatique au Centre universitaire de santé McGill qui ont subi une transplantation entre 2004 et 2011. La fiabilité a été déterminée en utilisant des tests de fiabilité formelle, y compris la fiabilité « inter-évaluateurs » et la fiabilité « test-retest ». Le système de classification a été validé par l'analyse de la relation entre les éléments de classification et les résultats cliniques importants (y compris les études diagnostic, les chirurgies de révision, une re-transplantation, le nombre d'admissions à l'hôpital après la greffe, le nombre total de jours d'hospitalisation, et les durées de survie du greffon et du patient).

Résultats: Un total de 184 patients, dont 76 patients présentant des complications biliaires, ont été inclus dans l'étude. La fiabilité inter-évaluateurs et la fiabilité test-retest ont montré des niveaux élevés d'accord avec valeurs de Kappa supérieures à 0,8 pour tous les éléments de la classification. Les composantes de la classification proposée ont montré une forte corrélation avec les résultats cliniques évalués. Les pires issues cliniques ont été observées plus souvent avec des sténoses qu'avec des fuites

biliaires ou des débris dans le canal hépatique. En ce qui concerne la localisation des complications biliaires, une augmentation de la gravité des complications a été démontrée avec un niveau de lésion biliaire cranial, confirmant en sus la validité de la classification proposée. La relation entre les composantes des sténoses de la classification et le nombre de jours d'hospitalisation confirme la validation; les rapports de taux ajusté (intervalle de confiance à 95%) pour les jours d'hospitalisation quant à la localisation au niveau de l'anastomose, du canal hépatique commun ou en intra hépatique bilatéral: respectivement de 2,01 (1,84 à 2,18), 3,80 (3,42 à 4,21) et de 7,05 (6,46 à 7,70).

Conclusions: La classification proposée des complications biliaires montre une excellente fiabilité et une très bonne validité. La différence significative entre les résultats cliniques reliés aux différentes composantes de la classification démontre la pertinence des composantes choisies. Ces composantes de la classification reflètent la gravité relative des différentes complications, ce qui soutient par surcroit la validité de la classification. Compte tenu du petit nombre de patients dans cette étude préliminaire, un plus grand nombre de patients sera nécessaire afin de valider d’avantage la classification.

Chapter 1: Introduction

1.1. Brief History of Liver Transplantation

Following many years of research, experimentation and attempts at liver transplantation in dogs, the first human liver transplantation was attempted in 1963 by Dr Thomas Starzl in Denver, Colorado. Starzl and his team performed 3 orthotopic liver transplants (OLT), with the longest surviving recipient living only 22 days. These, and failed attempts in Boston and Paris around the same time, resulted in a worldwide moratorium on liver transplantation for the subsequent 3 years. Later, following further advances in transplantation research, Dr Starzl and colleagues performed the first successful liver transplant in 1967 (1). Despite this achievement, success rates remained dismal throughout the 1960's and1970's and mortality in transplant recipients was greater than 50% in the first year following transplantation. However, liver transplantation would begin to gain wider acceptance with the development of improved immunosuppressive medications in the late 1970's. Combined with ever improving surgical technique, these medications dramatically increased graft and patient survival (2). This success prompted the National Institutes of Heath Consensus Development Conference in 1983 to declare that liver transplantation was no longer an experimental procedure and state that the use of OLT in treating acute and chronic liver disease in clinical practice should be expanded (3).

From these early beginnings, liver transplant has become the gold standard treatment for liver failure. Today, patient survival rates are estimated to be 80-85% at one year (4, 5), In 2011, 381 adult deceased donor liver transplants were performed in Canada (6) and more than 6010 were performed in the United States in 2012 (7).

1.2 Clinical Application of Liver Transplantation

1.2.1 The Basics of Liver Transplantation

Orthotopic liver transplantation is a procedure in which an individual's diseased liver is removed and replaced with a donor liver. Liver transplants performed in humans are referred to as 'orthotopic' as the new liver is placed in the same anatomic location as the native liver. Compatibility between a donor and a recipient is determined by a number of factors. The most important of these is compatible ABO blood groups and an approximate size match between the donor and recipient livers (estimated by the height and weight of the individuals). There are two potential sources of donor organs. The first is a deceased donor. These donors are individuals who meet the criteria for organ donation, have been certified as having experienced brain death, and who have consented to organ donation (either personally through wishes expressed prior to death or by the patient's family at the time of death). The second type of donor is a live donor. Live donors are individuals compatible with the transplant recipient, most often members of the immediate or extended family, which consent to the removal and donation of a portion of their liver. Deceased donors are substantially more common in Canada, representing 85% of transplanted livers (6).

1.2.2 Indications and Contraindications

The most common indications for OLT are end stage liver disease (ESLD) and malignancy. End stage liver disease refers to a liver that is severely and irreversibly damaged resulting in impaired function. ESLD is the end result of cirrhosis, a degenerative disease of the liver caused by repeated injury to hepatocytes and subsequent fibrosis and scar tissue formation. The etiologies of cirrhosis are numerous and are listed in table 1. An end-stage liver is unable to perform its usual functions including protein production and metabolism of hormones, nutrients and medications. The diagnosis of ESLD is based on clinical findings of inadequate hepatic synthetic function manifested as impaired coagulation, low serum albumin and hypoglycemia. Portal hypertension, a result of impeded portal blood flow through the scarred liver, is another manifestation of ESLD. Clinical findings of portal hypertension include ascites, esophageal varices, encephalopathy and thrombocytopenia (8). Certain primary malignancies of the liver are also considered indications for OLT. In the appropriate clinical context these include hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma, hepatoblastoma and hemangioendothelioma. Less common indications for liver transplantation include metabolic disorders causing severe extrahepatic disease (for example glycogen storage disease or amyloidosis), miscellaneous conditions (Budd Chiari syndrome, polycystic liver disease) and retransplantation for graft failure (9).

While most liver transplants are performed in the setting of chronic liver disease, liver transplant is also indicated for fulminant (acute) liver failure. Fulminant liver failure is characterized by rapid deterioration of hepatic function. Although fulminant liver disease is considered potentially reversible, transplantation is indicated in severe, life threatening cases. The most common causes of such an acute liver failure include viral hepatitis, drug reactions, toxic insults and metabolic disorders (10, 11).

As post-transplant outcomes continue to improve due to progress in surgical technique, perioperative care and immunosuppressive medications, the contraindications to liver transplantation have evolved over time. Clinical conditions formerly considered absolute contraindications to OLT, such as human immunodeficiency virus (HIV), cholangiocarcinoma and portal vein thrombosis, are now considered relative contraindications. Other relative contraindications include advanced age, previous malignancy and active psychiatric disease. Absolute contraindications to liver transplantation include extrahepatic malignancy, diffuse hepatic malignancy, active sepsis or uncontrolled infection, severe cardiopulmonary disease, active drug or alcohol use, psychosocial factors that would prevent recovery and compliance with medication regimes (untreated psychiatric disease, strong history of non-compliance for medical therapies, etc), brain death, and technical factors precluding transplantation(12-14).

1.2.3 Technique

A brief discussion of the liver transplant procedure facilitates understanding of the potential complications that arise following this complex surgical procedure. Intra-operative management of the OLT recipient requires very involved anesthetic care to manage and correct the metabolic derangements and altered fluid and electrolyte balance associated with liver failure. Considerable hemodynamic shifts and coagulopathy are common in ESLD and must be appropriately managed during surgery (15). The liver transplant procedure begins with removal of the diseased liver. This requires identification, dissection and division of venous and arterial inflow to the liver (portal vein, hepatic artery) as well as the venous (infrahepatic inferior vena cava (IVC), suprahepatic IVC) and biliary (common bile duct) outflow. The native liver can then be removed. The time between removal of the native liver and implantation of the graft liver is referred to as the "anhepatic" phase and the patient is especially prone to hemodynamic and metabolic derangements during this period. Implantation and proper function of the graft liver involves a number of vascular anastomoses including portal vein, IVC and hepatic artery. A number of techniques and variations in techniques exist for this part of the transplant procedure but are beyond the scope of the present discussion. The common bile duct connects the biliary tract within the liver to the patient's intestinal tract and this continuity must be restored during the transplant procedure. This can be done in two different ways. The most common technique is choledocho-choledochoal anastomosis (CCA), meaning the common bile duct of the graft liver is connected to the remaining segment of the patient's common bile duct. The surgeon may choose to do a simple anastomosis or to sew the anastomosis over a stent. Stents may be entirely internal or may have an internal portion and a portion externalized via the skin (called a t-tube). Use of an internal stent to "bridge" the anastomosis is dictated by surgeon preference at the present time. T-tubes have generally fallen out of use in OLT due to a high incidence of t-tube related complications (to be discussed in section 1.4.2). Less commonly, a roux-Y hepaticojejunostomy anastomosis (HJA) is performed. HJA is a connection between the graft common bile duct and a recipient loop of intestine. HJA is often used in patients with sclerosing cholangitis, where all of the native duct must be excised due to an elevated risk of malignancy, or because of technical factors such as a large size discrepancy between the graft and native ducts. At the end of the OLT procedure, adequate control of bleeding is ensured and the patient is brought to the intensive care unit for monitoring (8, 16).

Immunosuppression to prevent rejection of the allograft is started during surgery. Rejection occurs when the body recognizes the transplanted liver as "foreign" and mounts an immune response against the graft, resulting in graft damage and dysfunction. Immunosuppressive medications blunt the body's immune response to the graft. These medications must be continued for life in transplant recipients (8).

1.3 Overview of Complications Following Liver Transplantation

Liver transplantation is a complex surgical procedure with significant risk of both immediate and long-term complications. Despite these risks there is a clear survival benefit of transplantation in patients with ESLD; transplant recipients have an estimated 79% lower risk of mortality at one year than transplant candidates awaiting a graft on the transplant waiting list (17). Patient survival following OLT approaches 85% at one year and 75% at five years (5, 13). Long-term survival is good with an estimated actuarial survival of 48% at eighteen years (4).

1.3.1 Non-surgical Complications

Infection is a common complication in liver transplant recipients. In the immediate postoperative period pneumonia, urinary tract infections, cholangitis, and wound infections are common. The incidence and severity of postoperative infections are exacerbated due to immunosuppression. Despite prophylactic therapy, transplant recipients are at risk of a number of opportunistic infections in the short and long term including cytomegalovirus, Epstein barr virus, pneumocystis carinii and invasive fungal infections (18).

Other long-term complications in OLT recipients include diabetes, hypertension and osteoporosis (19, 20). Hyperlipidemia develops in 30% of patients and 40% of patients become obese within the first two years following transplantation (13). Impaired renal function following transplantation is a significant concern with 18% of OLT recipients developing chronic renal failure. Post transplant renal dysfunction results not only in a significant incidence of end stage renal disease requiring dialysis (9.5% of OLT recipients) but also a 4-fold increased risk of death from renal failure (21, 22). These complications are multifactorial but strongly associated with long-term immunosuppression. Disease recurrence in the new liver, especially in the case of viral hepatitis and particularly hepatitis C, is a concern throughout the life of a transplant recipient (13).

Another complication of long-term immunosuppression is malignancy. The overall estimated incidence of this dreaded complication following liver transplant is 4.7% - 15.7%, significantly higher than the risk of cancer in the general population. Non-melanoma skin cancers are the most commonly occurring tumors with an estimated incidence of 15% in liver transplant recipients (representing up to 10%-70% of observed post transplant malignancies). Post-transplant lymphoproliferative disease, which includes leukemia and lymphoma, accounts for up to 30% of malignancies in liver transplant recipients (23, 24).

Finally, rejection of the allograft is a potentially serious complication following OLT. While the timeframe (acute versus chronic) and the immunologic basis (antibody mediated versus cell mediated) of rejection episodes may vary, advances in immunosuppressive medications have greatly facilitated the treatment of rejection. Allograft rejection may lead to graft dysfunction but graft failure due to chronic rejection is rare, occurring in only 1%-2% of OLT patients (25).

1.3.2 Surgical Complications

OLT is one of the most technically challenging operations performed by surgeons today. Surgical complications are common and up to 35% of patients undergoing OLT will require an additional surgical intervention in the same hospital admission (26, 27). Surgical complications can be divided into vascular complications, biliary complications and less common miscellaneous complications. Vascular complications have the potential to impact the biliary system and will be briefly discussed below. As the focus of this study, biliary complications will be discussed separately in section 1.4.

Vascular complications include bleeding, stenosis, thrombosis, aneurysm or obstruction of the arterial or venous systems related to the liver. In general these complications are technical in nature. Postoperative bleeding is common because of the underlying coagulopathy and the presence of large collateral vessels due to portal hypertension. Bleeding is one of the most common reasons for re-operation (28). Hepatic artery thrombosis (HAT) is worthy of special mention. This particularly devastating complication has an estimated incidence of 4.4%, most often during the same hospitalization. HAT results in impaired blood flow to the graft liver and particularly the biliary system of the graft liver. The graft biliary tract derives its blood supply mainly from the hepatic artery and HAT is a well-recognized risk factor for severe biliary complications. While HAT can occur later in the post-transplantation period, early HAT (within 2 months of transplantation) is particularly devastating. Early HAT results in re-transplantation in 50% of patients and carries an overall mortality of 33% (29)

1.4 Biliary Complications Following Liver Transplantation

Biliary complications have long been considered the “Achilles heel” of liver transplantation (30). Despite advances in surgical technique over the last 20 years, biliary complications remain an important source of postoperative complications following OLT and cause significant morbidity (31). While graft loss due to biliary complications is uncommon (1-3% of OLT recipients), it is estimated that 2.8%-10% of post transplant deaths can be directly or indirectly attributed to biliary complications (32-35).

1.4.1 Description and Definitions

Biliary complications include any complication related to the biliary system of the donor liver, the donor or recipient common bile duct and the anastomosis between these ducts. The different types of complications are briefly detailed below.

Stricture: Stricture is the most commonly occurring biliary complication (36). A biliary stricture is defined as a narrowing of a segment of the biliary tree. Strictures occurs most frequently at the anastomosis between donor and recipient ducts but can occur anywhere along the course of the biliary tree including within the graft liver (intrahepatic) and the donor or recipient common bile duct.

Leaks: A biliary leak is defined as leakage of bile from the biliary ductal system. These leaks can occur at the level of the biliary anastomosis, typically as a result of inadequate technique or ischemia. Leakage can also occur away from the anastomosis, such as from the cystic duct stump (where the gallbladder is routinely removed from the graft) or intrahepatic ducts that leak through damaged liver parenchyma. Leaks may also be secondary to T-tube removal and the defect in the duct that remains after the tube is removed.

Filling defects: Filling defects refer to any obstructive lesion within the biliary tree. These obstructions are typically due to stones or biliary casts. Biliary casts are deposits of hard, dark material composed of "biliary sludge" (37).

Miscellaneous: Rare biliary complications include cystic duct mucocele and sphincter of Oddi dysfunction. A cystic duct mucocele is an abnormal dilation of the cystic duct stump that becomes engorged with mucinous material. This technical complication results from obstruction of the cystic duct stump with an incidence of approximately 2% post OLT (38). Sphincter of Oddi dysfunction is defined as impaired relaxation of the Sphincter of Oddi (the sphincter between the common bile duct and the duodenum) resulting in increased intraductal pressure and impaired biliary outflow leading to cholestasis. This ill-characterized complication occurs in 3-5% of OLT recipients (32).

1.4.2 Predisposing Factors

Biliary complications after OLT can be attributed to a number of technical and non-technical factors. Technical factors pertain to surgical technique and include improper suture placement, creation of a narrowed anastomosis, excessive tension on the anastomosis, excessive dissection of the donor common bile duct leading to ischemia, bleeding from the cut ends of the duct and use of electrocautery on the duct ends (34, 39). Technical complications related to the blood supply of the bile ducts, in particular hepatic artery complications and hepatic artery thrombosis, lead to biliary complications secondary to ischemia of the ductal system.

The use of T-tubes as stents across the biliary anastomosis has been a subject of considerable debate over the years. T-tubes were previously thought to decrease biliary complications. T-tubes, as described earlier, are small plastic stents that bridge across the choledocho-choledochal anastomosis and have an arm that is exteriorized to the skin, providing drainage and permitting easy access to the biliary tree for imaging in the post-operative period. Early retrospective and observational studies questioned the use of T-tubes after suggesting these may actually increase biliary complications, with incidences as high as 50%. In particular, leak at the T-tube site is reported to occur in 5-33% of patients upon tube removal (32, 40-43). Randomized trials have reported conflicting data. While some trials showed no significant difference in complications with and without T-tube (44, 45), T-tubes led to an increase in cholangitis, peritonitis and fistula formation in one large randomized trial (46). Three recent meta-analyses have suggested that the use of T-tubes should be abandoned in OLT due to high rates of T-tube associated complications (47-49).

Non-technical factors associated with biliary complications include reperfusion injury, graft quality and ischemia time, graft rejection and cytomegalovirus infection. Patients whose primary disease is primary sclerosing cholangitis are also at increased risk of biliary complications following OLT (50-52).

1.4.3 Diagnosis and Imaging

Biliary complications manifest as a number of different symptoms including fever, right upper quadrant pain, abnormal liver enzyme and liver function tests, cholangitis or leakage of bile from post-operative drains or incisions (53). Any of these findings raises the clinical suspicion that a biliary complication is present and further investigation is warranted. Typically this begins with an ultrasound to look for obvious signs of biliary complications such as dilation of the intrahepatic biliary tree suggestive of obstruction or peri-hepatic fluid collections suggestive of leak. The absence of these findings on ultrasound does not exclude a biliary complication but ultrasound is also critical to rule out a vascular problem, such as hepatic artery thrombosis, as vascular complications are associated with severe concomitant biliary complications (52). When a biliary complication is diagnosed on ultrasound, or is strongly suspected on a clinical basis, additional imaging studies are necessary to further define the relevant anatomy, extent and severity of the problem. This is done using direct cholangiography (either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC)), or noninvasive cholangiography (magnetic resonance cholangiopancreatography (MRCP)).

ERCP is an invasive test that combines endoscopy and fluoroscopy to visualize the biliary tract. A flexible endoscope is used to cannulate the biliary system and a cholangiogram is performed. As an invasive test, ERCP carries a risk of complications including bowel perforation, bleeding, pancreatitis, infection and complications related to sedation given to perform the procedure. Complications occur in up to 10% of patients undergoing ERCP with an associated mortality of 0.5% (54, 55). ERCP is a user-dependent test and relies on the ability of the endoscopist to cannulate the biliary system (56). Despite these risks, ERCP is the gold standard in the diagnosis of biliary complications. ERCP also has an important role in therapy and is the treatment of choice for the majority of biliary complications (57-59). This will be further discussed in section 1.4.5.

PTC is an alternative method of direct cholangiography. It provides the same accuracy and advantages as ERCP but accesses the biliary system percutaneously. This technique is used in patients with roux-Y hepaticojejunostomy anastomosis. Reconstruction with roux-Y hepaticojejunostomy precludes ERCP as the biliary system is re-implanted into a loop of jejunum and this is not accessible by endoscopy. PTC is also used when ERCP fails due to technical difficulties. PTC is an invasive test that carries a small risk of bleeding and cholangitis (60).

MRCP is a newer, non-invasive test that utilizes magnetic resonance imaging to visualize the biliary tree. As MRCP is non-invasive there is little risk of complications to the patient. The use of MRCP in evaluation of the biliary tree is well described in the transplant population. However, some limitations do exist. A potential limitation is the frequent use of metal clips during the transplant surgery. Metal creates artifact that can render MRCP images potentially difficult and occasionally impossible to interpret (56). Despite these concerns, MRCP has been shown to have high sensitivity (94-96%) and specificity (89-94%) in diagnosing biliary complications after liver transplant when compared to ERCP as the gold standard (61, 62). Although MRCP is increasingly recognized as a useful and accurate diagnostic test, a recent meta-analysis by Jorgensen et al looking at MRCP to diagnose biliary obstruction concluded that more high quality data is needed before recommending MRCP as the diagnostic test of choice in transplant patients (60, 61). At the present time, ERCP remains the standard of care.

Endoscopic ultrasound (EUS) is a newer technology that uses an ultrasound probe mounted on an endoscope to visualize the biliary tree and pancreas. While the diagnostic accuracy of EUS for biliary obstruction due to a number of etiologies (choledocholithiasis, malignancy, benign stricture) is excellent in non-transplanted patients (63), there is little evidence to date regarding the utility of this diagnostic test in patients who have undergone liver transplantation. Endoscopic ultrasound has some therapeutic potential, including pancreatic and lymph node biopsies, but has no therapeutic role in relief of biliary obstruction.

1.4.4 Incidence

Biliary complications tend to occur early in the post transplant period, with two thirds occurring in the first 3 months and the majority of complications (80%) occurring within 6 months. Late biliary complications are rare and less than 4% occur after the first post-transplant year (33, 36).

There is considerable discrepancy in the reported incidence of biliary complications in the current literature (table 2). Estimates of the incidence of these complications vary anywhere from 2.6% to 50% (31, 40-44, 46, 49, 51, 64-85). Estimates of incidence are difficult to interpret due to variable timing of outcome measurement; while most complications occur within the first year post-transplantation incidence rates are reported within highly variable time frames (post-transplantation weeks/months, years and up to a decade after transplantation) (40). Further confounding interpretation of these estimates is the fact that many studies report incidences that combine the two different types of biliary anastomoses, CCA and HJA (31, 41, 51, 66-71, 74, 75, 82, 83). These two different anastomoses are used in different clinical scenarios and are associated with different potential complications. Many studies also combine patients who receive grafts from deceased donors with those who receive live donor grafts (42, 70, 74, 75). Similarly, these two different techniques have very different complication rates. Living donors are associated with a significantly greater incidence of biliary complications (40). Looking at estimates of incidence that combine different types of anastomoses and different surgical procedures are the transplant equivalent of comparing apples and oranges.

Reporting of biliary complications in the liver transplant literature also lacks standardization and clearly stated definitions. While variation in the incidence of complications between studies is certainly a reflection of many potential factors including variations in surgical technique, heterogeneous patient populations and differing graft quality, non-standardized definitions likely account for some of the variation in the estimated incidence. Many studies report complications using only broad encompassing and non-specific terms such as "stricture" or "leak" without differentiation between the different potential locations (anastomotic, donor common duct, intrahepatic, etc). Many studies include additional diagnoses such as cholangitis, sphincter of oddi dysfunction and hemobilia which certainly impact the estimated incidence of biliary complications (31, 43, 66, 69, 73, 74, 77, 78, 80, 82). Without standardized nomenclature it is impossible to know which specific types of strictures, leaks or other complications authors may have included in the estimated incidence. Furthermore, biliary complications generally lie along a spectrum of severity and in the absence of a clearly stated definition it is impossible to determine if complications of differing severities were included. Some studies that provided definitions only included complications where intervention was required for treatment (66, 83, 86) and at least one study ignored complications deemed "insignificant" (87).

To complicate interpretation of the literature even further, only a minority of studies clearly state how individual biliary complications were diagnosed (40, 43, 44, 49, 66, 73, 80, 83). As discussed, biliary complications can be diagnosed in a number of ways including diagnosis based on clinical findings, ultrasound imaging or cholangiography. Estimated incidence of complications may vary depending on what methods are used to investigate suspected biliary complications. Overall, inconsistent reporting without clearly defined outcomes across varied populations makes it difficult to interpret the incidence of biliary complications after OLT from the published literature.

1.4.5 Treatment

The treatment of biliary complications following OLT varies according to a complex mix of the type and severity of complication as well as patient factors. The majority of biliary complications occurring at the choledocho-choledochal anastomosis are treated by endoscopic means with ERCP. ERCP treatments such as stent placement, sphincterotomy and balloon dilation provide effective therapy for a number of post-OLT complications including leaks and many strictures. The success rate of endoscopic therapy is generally high with a reported 70-100% of leaks and anastomotic strictures responding to endoscopic therapy. ERCP may have to be repeated several times to achieve resolution of the problem, with most patients requiring 3-5 treatments (60). Recurrences are not uncommon and approximately 20% of patients will require additional therapy (57, 60, 88). The need for re-transplantation and surgical intervention are uncommon except for rare circumstances, which include failure of repeated endoscopic attempts of treatment. Certain biliary complications are less amenable to ERCP therapy and more likely to require more aggressive therapy including large biliary leaks and non-anastomotic strictures. The latter are successfully managed by ERCP alone in only 50-70% of cases (60, 80, 81). Further discussion of the treatment of these potentially complex complications is beyond the scope of this study and this discussion is meant only to highlight the basic tenets of treatment.

1.5 Tables:

Table 1: Etiologies of liver cirrhosis (89)

Viral	Hepatitis B
	Hepatitis C
	Hepatitis D
Fatty liver diseases	Alcoholic liver disease
	Non-alcoholic steatohepatitis (NASH)
Autoimmune	Autoimmune hepatitis
	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	IgG4 cholangiopathy
Storage Diseases	Hemochromatosis
	Wilson disease
	Alpha-1 antitrypsin deficiency
Cardiovascular	Budd-Chiari syndrome
	Right heart failure
Chronic biliary disease	Recurrent bacterial cholangitis
	Bile duct stenosis
Rare causes	Medication related
	Porphyria

Table 2: Estimates of the incidence of biliary complications

Author	**Location**	**Year**	**Review**	**n**	**Anatomosis**	**Population***	**Incidence (%)**
Abdullah	Saudi Arabia	2005	No	184	CCA, HJA	A, P	17.4
Abouljoud	USA	2001	No	161	CCA, HJA	A	18-50
Akamatsu	Japan	2011	Yes	11,547	CCA, HJA	A	5-12
AlSharabi	Poland	2007	No	200	CCA, HJA	A	11.0-17.0
Amador	Spain	2005	No	1000	NS	A, P	25-39.5
Barkun	Canada	2005	No	396	CCA, HJA	A	30.7-35
Buczkowski	Canada	2007	No	77	CCA	NS	2.6-26
Castaldo	USA	2007	No	100	CCA	NS	13.5-17.1
Duailibi	Brazil	2010	Yes	2,227	CCA, HJA	NS	15.5
Elola-Olaso	Spain	2005	No	100	NS	NS	16
Fleck	Brazil	2002	No	157	NS	A	15.3
Gantxegi	Spain	2011	No	300	CCA, HJA	A	9-20
Gomez	Spain	2001	No	412	CCA	A	18
Haberal	Turkey	2006	No	127	CCA, HJA	A, P, L	8.1-25
Khuroo	Saudi Arabia	2005	No	220	CCA, HJA	A, P, L	18.2
Lin	China	2007	No	104	CCA	NS, L	10.0-17.0
Mosca	Italy	2000	No	136	CCA	A	12.5
Nemec	Czech Republic	2001	No	118	CCA	NS	27.9
Paes-Barbosa	Brazil	2011	Yes	NS	CCA	NS	21.4-33
Patowski	Poland	2003	No	193	CCA, HJA	NS	18.7
Pfau	USA	2000	No	260	CCA	NS	24.6
Qian	Hong Kong	2004	No	241	CCA, HJA	A, P, L	20.7
Rerknimitr	USA	2002	No	367	CCA	NS	25
Salahi	Iran	2005	No	140	CCA, HJA	NS	10
Sanna	Italy	2009	No	1634	CCA, HJA	A	24.6
Scatton	France	2001	No	180	CCA	A	33.3
Shimoda	USA	2001	No	147	CCA	A	15.5-32.9
Thethy	UK	2004	No	379	CCA, HJA	A	14.6
Thuluvath	USA	2003	No	423	CCA	A, P	18.6
Weiss	Germany	2009	No	194	CCA	A	27-50

* Cadaveric donors unless otherwise specified

Legend: *CCA* choledochocholedochal anastomosis; *HJA* hepaticojejunostomy; *NS* not specified; *A* adult; *P* pediatric; *L* living

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Chapter 2: Classification Systems

2.1 Definition

A classification system is defined as "the systematic arrangement of similar entries on the basis of certain differing characteristics (1)." In medicine, classification systems typically fall into two main categories: statistical or nomenclature. Statistical classifications group similar diseases, diagnoses or clinical concepts into like groups. These classifications standardize reporting and facilitate statistical analysis. A well-recognized example is the International Classification of Disease (ICD) by the World Health Organization. Classifications may also have prognostic or other clinical significance. The second category of classification is nomenclature systems, which provide an agreed upon naming scheme and a name or title for every disease or clinical entity (little or no grouping of concepts). These systems do not follow any set classificatory principles and mainly serve to provide a common language for reporting and communication (2).

Classification schemes are governed by a number of general principles. The first is that there are "consistent, unique classificatory principles in operation (2)." In medicine such principles include classification of a given disease or clinical concept according to diagnosis (eg Todani classification of the different types of choledochal cysts (3)), treatment required (eg Clavien classification of postoperative complications (4)) or severity (eg Balthazar severity index for classifying acute pancreatitis (5)). Another guiding principle of classification systems is that categories within the system be mutually exclusive such that every entity can be easily classified into a single category or class. Finally, classification systems should be complete such that its classes encompass all entities of a given clinical concept. While these principles provide the basis upon which classification systems are built, rarely does a given classification perfectly satisfy all of these principles in real practice (2).

2.2 Postoperative Outcomes and Classification Systems

Reporting of post-operative complications is an important outcome measure and quality indicator. However the use of postoperative complications as a measure of quality is limited by two main factors. The first is the reliability of the methods and systems in place to capture and record complications. The second is how complications are defined. The use of standardized, valid and reliable definitions is necessary to ensure accurate reporting of post-operative outcomes (6, 7). Previous studies evaluating the reporting of postoperative complications in other areas of general surgery have found that variable definitions and classification of complications are a major limitation in interpretation of outcome data (8, 9).

The quality of post-operative complication reporting is improved by classification systems. First, classifications increase uniformity of reporting and allow for the comparison of outcomes in a single center over time or between differing centers. A well-designed classification system is essential for "unequivocal and uniform" reporting of complications (6). Secondly, classification systems facilitate the study of postoperative complications by allowing for easy application of statistical methods, including meta-analysis. For this to occur, the classification system needs to be standardized and broadly applied. This facilitates evaluation and comparison of alternate therapies or different surgical techniques. Finally, standardized definitions and reporting are important building blocks in the development of potential preoperative risk scores or prognostic scores (10).

In transplantation, quality assessment is particularly important to ensure optimal and appropriate use of limited donor organs (11). Reporting of postoperative outcomes allows clinicians to ensure a given transplant program meets recognized standards and can potentially flag adverse trends in outcomes. This allows for problematic areas to be quickly identified and remedied. Ongoing quality assessment requires reliable monitoring of post-operative complications.

Despite all the positive attributes of classification systems, such schemes have potential disadvantages. There is a perception that classification systems impart "objectivity, truth and reason" to diagnosis (12), however this assumption depends largely on whether the classification has been tested for reliability and validated (which many classifications are not). Classifications may also lead to loss of important details regarding individual circumstances as clinical data is funneled into a single class. There may also be difficulty in classifying patients with unusual or rare diseases, symptoms, etc. Finally, classifications are generally descriptive and are generally not treatment guidelines (12). Assuming or interpreting classifications as guiding therapy may be perilous until the classification is specifically tested and validated to this effect.

2.3 A Classification System for Biliary complications

2.3.1 The Clinical Need

A classification system of biliary complications following orthotopic liver transplant is needed to standardize reporting of these frequently occurring complications. Standardization would allow for easier comparison of differing surgical techniques and improved quality assessment of transplant programs. Such a classification system could potentially provide the necessary high quality data for development of preoperative risk and prognostic scoring systems, neither of which exists to date. The transplant community has recognized the lack of standardized reporting and some authors have called for more accurate and uniform classification of complications following OLT (13, 14).

Biliary complications as a group are arguably the most common complication after liver transplantation, and carry a potential for significant morbidity. As such, a classification specific to biliary complications after liver transplantation is necessary to improve reporting and facilitate quality indicators in liver transplant.

2.3.2 Previous Classifications

Classification systems of postoperative complications do exist and are frequently used in general surgery. The most commonly used classification is one proposed and validated by Clavien et al. This classification scheme has greatly facilitated reporting of postoperative complications and was cited more than 200 times between its description in 2004 and 2009 (15). It is a general classification system that does not apply only to a specific surgical discipline or specific type of surgical complication. The system classifies postoperative complications according to the type of therapy (eg medications or intervention) required to treat or manage the complication. Classes range from grade 1 which requires no specific intervention to grade 5 complications that result in patient death (4). While the Clavien classification has provided much needed uniformity to the reporting of postoperative complications, it is difficult to apply such a classification to biliary complications. This classification is based on therapy required for treatment but the vast majority of biliary complications are treated in a similar fashion using ERCP techniques. Despite the similarities in treatment of differing biliary complications, these complications are associated with different prognoses with respect to number of treatments required, success of endoscopic therapy and effect on the graft and graft survival. A recent report of biliary complications by Gantxegi et al (16) classified complications using the Clavien classification and in this report 70% of complications were classified as grade IIIa or IIIb (requiring radiographic intervention without (IIIa) or with (IIIb) general anesthesia). A classification system with finer discrimination is needed for the classification of biliary complications after OLT.

At the present time, there exists no universally accepted or widely used classification of biliary complications occurring after OLT. Some authors have described various ways in which these complications could potentially be classified, including dividing complications based on anatomic location (17-21), the presence or absence of a bile leak (22) or by suspected etiology (23). Lee et al

(24) proposed a classification of non-anastomotic intra-hepatic strictures however this classification only addresses a subset of complications which is the most uncommonly occurring subset. This classification, like the others described above, was not tested for reliability or validity. To date no author has attempted to propose and justify a formal, all encompassing classification of biliary complications and to determine its reliability and validity.

2.3.3 Description of the Proposed Classification System

The proposed classification system provides a structured description and classification of biliary complications following deceased donor OLT with choledocho-choledochoal anastomosis (CCA). The classification includes the three main types of biliary complications (stricture, leak, filling defect) seen after transplantation on radiographic testing and subdivides each of these elements based on anatomic locations (Table 1). The classification was developed based on review of the available literature and expert consensus, as described below.

The available evidence suggests that complications at these differing locations have different clinical implications. This appears to be true with respect to both strictures and leaks. Non-anastomotic strictures are regarded as having a different clinical significance than anastomotic strictures (25). Non-anastomotic strictures are typically located in either the donor common hepatic duct or the graft intrahepatic ducts and occur with an incidence of 5-15% in OLT (26). They are frequently associated with vascular complications and are typically considered ischemic in nature; hepatic artery compromise is present in 50% of patients with non-anastomotic strictures. Treatment of these strictures is very different as interventional ERCP techniques are less effective than with anastomotic strictures (29% vs 75%). Non-anastomotic strictures are regarded as having an overall poorer prognosis with worse graft survival at one year when compared to anastomotic strictures (69% vs 88%). Approximately 25-50% of patients with non-anastomotic strictures will either die or require re-transplantation due to this complication (27-30). Reports specifically examining the intra-hepatic subset of non-anastomotic strictures have shown differences in outcome between patients who have unilateral or bilateral strictures. Those patients presenting with bilateral strictures have higher mortality rates (50% vs 1%) as well as higher graft failure rates of up to 70% (24, 31). As such, and at the suggestion of the expert panel, these entities were classified separately.

Similar to strictures, there appear to be clinical differences between anastomotic and non-anastomotic leaks. Non-anastomotic leaks are those arising from the cystic duct stump, liver parenchyma or accessory ducts of Lushka. Anastomotic leaks are considered “more hazardous” as they tend to reflect ischemia to the anastomosis and are more likely to cause harm to the patient than non-anastomotic leaks (30). Leaks from non-anastomotic sites can typically be managed conservatively by ERCP while leaks from the anastomosis may require more aggressive measures if the anastomotic disruption is significant, including potential re-operation (32).

After development of the proposed classification it was presented to a group of experts consisting of 4 experienced liver transplant surgeons at the

McGill University Health Centre. Expert consensus was that the proposed classification would meet the clinical need and was acceptable based on principles of classification. The system classified complications based on type and location as the guiding classificatory principles. The expert panel agreed such a classification would be intuitive to clinicians and appeared easy to apply in everyday clinical practice. It is recognized that a given patient can have more than one complication at the same time or over time. Thus a given patient may be diagnosed as having more than one biliary complication using the proposed classification. While this does not satisfy the second principle of classification (each diagnosis fits into a single class), this is the nature of biliary complications following liver transplantation. Using the classification to assign more than one complication reflects the real world situation. Finally, the experts felt that the classification system was complete and captured the clinical entities of importance. Rare complications such as cystic duct mucocele and sphincter of oddi dysfunction occur in less than 2% of patients and typically are late diagnoses. The expert panel felt there was little clinical relevance for including such entities as they are rarely seen in clinical practice and have a totally different prognosis.

The following definitions are used to define biliary complications. All complications are diagnosed using direct cholangiography (ERCP or PTC). Stricture is defined as a distinct area of visually significant narrowing of any part of the biliary system by 50% or more of the duct diameter. Differences in donor and recipient duct size are not considered to be strictures as this size mismatch does not appear as a distinct area of narrowing but rather a consistent size mismatch between the two ducts. Leak is defined as extravasation of contrast outside the biliary tree. Filling defects are defined as any area of non-opacification of the biliary tree at cholangiography consistent with stones or casts. Filling defects of the common duct include ONLY defects of the recipient duct as these represent a primary process. Stones and casts of the donor duct are generally a secondary process related to strictures and outflow obstruction lower down in the biliary tree.

2.5 Tables

Table 1: Proposed Classification

1. Stricture	
	a) Anastomotic
	b) Donor Common Hepatic Duct
	c) Intra-hepatic (unilateral)
	d) Intra-hepatic (bilateral)
2. Leak	
	a) Anastomotic
	b) Non-anastomotic (Cystic duct, parenchymal or duct of Lushka)
3. Filling Defect	
	a) Common Duct (recipient)
	b) Intra-hepatic

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Chapter 3: Study Rationale and Objectives

3.1 Study Rationale

There is a clinical need for a classification system of biliary complications after orthotopic liver transplant to ensure standardized and reliable reporting of these common post-transplant complications.

3.2 Study Objectives

1- To propose a classification system for biliary complications after orthotopic liver transplant based on literature review and expert consensus

2- To demonstrate reliability of the proposed classification using formal testing to ensure it will meet the clinical need of consistent and reproducible reporting of biliary complications.

3- To validate the proposed classification by demonstrating the individual components of the classification relate to patient outcomes and provide clinically meaningful differentiation between biliary complications.

Chapter 4: Manuscript One
& Additional Comments

4.1 Preface

This chapter contains a manuscript prepared for submission to a clinical journal. The manuscript is presented as submitted with minor changes made to formatting. Additional comments and discussion not considered appropriate for this concise, clinical manuscript are contained in Section 4.3.

4.1.2 Author Contributions

Dr Amy Neville, MSc candidate and first author, was involved in study design and defining the elements of the proposed classification. She was responsible for carrying out the literature review, data collection, statistical analysis and writing of the manuscript. She also served as a rater for reliability testing.

Dr Jeffrey Barkun, thesis co-supervisor, oversaw the project as a whole. He was responsible for study design and proposal of the classification, interpretation of results and critical review of the manuscript. He also served as a rater for reliability testing.

Dr Elham Rahme, thesis co-supervisor, contributed to data analysis, interpretation of the study results and critical review of the manuscript.

Dr Marylise Boutros, surgical resident, contributed to data collection and critical review of the manuscript.

4.1.3 Ethics

This study was approved by the McGill University Health Centre Institutional Review Board (#12-349-SDR)

4.2 Manuscript

The Development of a Classification System for Biliary Complications following Orthotopic Liver Transplantation: Determining Reliability

Amy Neville MD[1], Marylise Boutros MD[1], Elham Rahme PhD[2], Jeffrey S Barkun MSc, MD[1]

[1] Department of Surgery, Multi-Organ Transplant Program, McGill University Health Centre, Montreal, Canada

[2] Departments of Epidemiology and Biostatistics, McGill University, Montreal Canada

Please address correspondence to:

Jeffrey S Barkun, MSc, MD
Royal Victoria Hospital
687 Pine Ave West Suite S9.30
Montreal QC
H3A 1A1

ABSTRACT:

Introduction: Biliary tract complications remain a significant source of morbidity following orthotopic liver transplantation (OLT). No universally accepted classification system of these complications exists at present. As such, descriptions of biliary complications after OLT in the literature lack consistency and clarity, which limits evaluation and comparison of post-transplantation outcomes. As the initial step in the proposal of a structured classification for biliary complications, reliability of the components will be determined. The classification divides complications into three main classes (strictures, leaks and filling defects) and further subdivides each class by anatomic location of the complication based on appearance at Endoscopic Retrograde Cholangio Pancreatography (ERCP).

Methods: Patients having undergone OLT with choledochocholedochal anastomosis at the McGill University Health Center from 2003-2010 and who had at least one contrast cholangiogram post-operatively were candidates for the study. Patients who experienced hepatic artery thrombosis or who died within 10 days of operation were excluded. Biliary complications diagnosed after the initial transplant admission were identified based on their appearance on contrast cholangiography and classified by two independent reviewers according to the proposed classification system. Inter-rater reliability and test-retest reliability were determined. Kappa statistic was used to test interobserver agreement.

Results: One hundred thirty contrast cholangiography films of 35 patients were reviewed. Overall inter-rater reliability (percent agreement) among reviewers was 88.5% (95% confidence interval 81.4% - 93.2%) on specific elements of the classification scheme (leak, stricture, filling defect). There was moderate to almost perfect agreement with kappa values ranging from 0.49 to 0.94. Test-retest reliability, when the same reader reinterpreted films at 3 months, was high with 86.9% (95% confidence interval 79.6% - 92.0%) agreement. Kappa values for individual classification elements were high and ranged from 0.53 to 0.92.

Conclusion: The proposed classification system demonstrated adequate reliability and allows for consistent interpretation and reporting of biliary complications following OLT.

Introduction

Biliary tract complications have long been considered the "Achilles heel" of liver transplantation (1). Despite refinements in surgical technique over the years since the advent of orthotopic liver transplant (OLT), postoperative biliary complications remain a significant source of morbidity (2-5). Although graft loss is rare (1-3% of cases), most affected patients will require numerous interventions for management and treatment including repeated invasive procedures such as endoscopic biliary stenting, etc (6-8).

The estimated incidence of biliary complications following OLT varies widely, ranging from 6% to 40% (9, 10). Differing surgical techniques, individual recipient characteristics and variable graft quality may be responsible in part for the wide range. However some of this considerable variation may only be due to differences in the definitions of biliary complication, and the non-standardized reporting of these complications in different series (11). Many studies report these complications using broad encompassing and non-specific terms such as "stricture" or "leak" without differentiation between the different potential locations (anastomotic, common hepatic duct, intra-hepatic, etc). There is also considerable variation in the kinds of complications reported. While stricture, leak and obstruction/filling defects are commonly reported; many studies also include a variable and heterogeneous number of additional diagnoses such as cholangitis, sphincter of oddi dysfunction and hemobilia (12-14).

At present there exists no universally accepted classification system for biliary complications following OLT. Such a classification system is essential so that outcomes may be reported in a standardized and reproducible manner, and possible prophylactic or therapeutic approaches compared. Post-operative outcomes are an important quality measure and their usefulness as such depends on clearly stated definitions and consistent classification (11, 15, 16).

We propose to evaluate a structured classification system for commonly encocuntered biliary complications following choledocho-choledochostomy at OLT. The classification is based on two components: the type of biliary complication after transplantation (strictures, leaks, filling defects,) and the anatomic location (Table 1). The decision to divide each complication by anatomic location was based on review of the literature and agreed upon by an expert panel of transplant surgeons at our institution. Available case series suggest different biliary complications at differing anatomic locations have diverse clinical implications. One year after OLT, strictures above the anastomosis (either donor common duct or intra-hepatic) exhibit a poorer prognosis with worse graft survival when compared to strictures at the anastomosis (69% vs 88%): approximately 25-50% of patients with non-anastomotic strictures will either die or require re-transplantation (6, 17-19). Moreover, patients presenting with bilateral hepatic duct strictures have lower survival rates at 5 years (40% vs 75%) than those without intrahepatic strictures, and 5-year graft failure rates of up to 70% are reported (20, 21). The significance of biliary leaks also differs based on location: anastomotic leaks are considered “more hazardous” as they may reflect ischemia to the anastomosis and are more likely to cause harm than non-anastomotic leaks (6). Leaks from non-anastomotic sites can typically be managed conservatively by ERCP while leaks from the anastomosis may require surgical intervention if the disruption is significant (22, 23).

We examined the reliability of the proposed classification system and examined whether it may be potentially recommended as a standardized measure of this post-transplantation outcome.

Methods:

Patients

A prospectively maintained multi-organ transplant database was used to identify potential study patients. Patients who underwent orthotopic liver transplantation with choledocho-choledochal anastomosis at the McGill University Health Center between January 2003- December 2010 were considered eligible for this study if they had at least one postoperative contrast study of the biliary tree. Contrast cholangiography was indicated in patients with clinical and/or biochemical suspicion of cholestasis or clinical suspicion of a biliary complication (eg bile present in post-operative drains). As live donor liver transplantation is not performed at our institution, only cadaveric graft recipients were considered. Patients with hepatic artery thrombosis were excluded as biliary complications in these patients represent a specific etiology and pattern of injury which is well described and requires treatment of the underlying vascular cause (24, 25). Patients who lost their graft within 10 days of transplantation or who died were also excluded as most biliary complications do not manifest so early following transplantation and patient or graft demise so early in the postoperative course is typically unrelated to biliary complications (5). Some patients in this cohort underwent repeat transplantation for graft failure. For these patients, each graft (as well as the respective follow-up time following each transplantation) was considered separately.

Only patients whose imaging could be reviewed online (via electronic radiographic records) were included in the study. Patients were followed from the date of surgery until death, loss to follow-up or December 2010 (whichever occurred first).

Definitions

Biliary complications considered in this study were strictures, leaks and filling defects. Stricture was defined as a distinct area of visually significant narrowing of any part of the biliary system by 50% or more of the duct diameter. Differences in donor and recipient duct size may occur and are not considered to be strictures when this size mismatch does not appear as a focal area of narrowing but rather as a consistent size mismatch between the two ducts. Leak was defined as extravasation of contrast anywhere outside the biliary tree (peritoneum or skin). Filling defects were defined as any area of non-opacification of the biliary tree at cholangiography consistent with stones or casts. Filling defects were divided based on location (intrahepatic ductal system and common bile duct). The intrahepatic ductal filling defects also included defects of the donor common duct. This division reflects the postulated differences in etiology of filling defects in these different locations. Filling defects of the donor system are presumed to be related to ductal ischemia and mucosal sloughing (26) and reflect a more serious pathology than defects of the recipient system. These defects are typically more difficult to treat as well.

Outcome assessment

Biliary complications were identified and classified based on their appearance on contrast cholangiogram, mostly endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Each film in the electronic radiographic file was reviewed in chronological order for patients who underwent more than one contrast study. Two readers independently reviewed images from each contrast study. In order to capture varying levels of clinical experience, one reader was an experienced transplant surgeon and the second was a senior surgical resident with basic experience at reading cholangiograms and an instruction session prior to reading the films. Readers recorded their interpretation of the film based on the classification system and these were subsequently compared for concordance. Agreement on individual elements of the classification was also determined. If there was disagreement on one or more element of the classification system for any given film, the overall interpretation was also considered to be discordant.

Statistical Analysis

Patient characteristics and demographic data are presented using means and standard deviations or median and inter-quartile range as appropriate. We sought to review all imaging of consecutive candidate patients, but ulimately, availability of on-line images determined the sample. Patient characteristics (including demographics, number of contrast studies as well as length of follow-up) of those with online images were compared to all those eligible to verify that this group was a representative sample. Differences between these groups were examined using student t-tests, Mann-Whitney U tests and Fisher's test where appropriate.

Contrast studies were interpreted by the individual reviewers using a binomial outcome (yes/no) for each classification element. Inter-rater reliability was determined by the percent agreement between reviewers as well as the kappa statistic (with 95% confidence intervals (CI)). A single reviewer (the least experienced) re-interpreted all films 3 months after the initial interpretation. Percent agreement and the kappa statistic with 95% CI were used to determine test-retest reliability. The kappa statistic was used in order to correct for chance agreement between the readers.

The majority of patients in this study had more than one contrast study post-operatively and in these patients all studies were interpreted in chronological order. Although this reflects clinical practice, the individual films for a given patient could no longer be considered independent which raised concern that reliability may be over-estimated because interpretation of later films may be influenced by knowledge of the findings of previous films. To address this concern, a sensitivity analysis was preformed including only the first film of every patient, thus eliminating multiple measurements and preserving data independence.

R open source software (version 2.15) was used for all statistical analysis.

Results:

Between June 2004 and June 2007, 120 liver transplants were performed in 109 patients. Of these, 60 transplants were excluded: 24 who did not require post-operative cholangiography, 18 who underwent biliary reconstruction with hepaticojejunostomy, 13 patients with hepatic artery thrombosis and 5 who died within 10 days of transplantation (Figure 1). Note that an individual patient may have satisfied more than one exclusion criterion. Thus the eligible patient population consisted of 60 liver transplants. To determine reliability, a total of 130 films belonging to a convenience sample of 35 individual patients were reviewed. Patient demographics are presented in Table 2. Patient demographics of the patients whose cholangiographic films were reviewed were compared to those whose films were not reviewed using Student t-tests, Mann-Whitney U tests and Fisher's test where appropriate and both groups were found to be comparable. There was a statistically significant difference in body mass index between groups but this small difference is of little clinical significance. Etiology of liver cirrhosis for the patient population is shown in Table 3.

The mean (SD) and median [IQR] number of cholangiograms per patient in the study population was 4.4 (4.8) and 3.0 [2, 5], respectively. A summary of biliary complications observed, based on the proposed classification system, is presented in Table 4. Complications related to the choledocho-choledochal anastomosis, including stricture and leak, were the most commonly observed complications. A total of 10 patients who underwent ERCP for suspected biliary obstruction had films interpreted as normal and without evidence of biliary complications.

Formal tests of Reliability:

Inter-rater reliability: There was overall agreement on 115 out of 130 films, translating to 88.5% (95% CI 81.4%-93.2%) agreement. Agreement on each individual element of the classification was also determined (Table 5). For these proportions, the numerator was the number of films in which both readers agreed on the presence or absence of the given element. The denominator was the total number of films. Although inter-rater agreement was very high, it is important to note the relatively small number of events observed. Agreement for each of the individual classification components was similar, but certain complications, such as intra-hepatic strictures, occurred only rarely. The kappa statistic for most elements of the classification showed significant agreement. Intra-hepatic filling defect, with a kappa of 0.49, showed only moderate agreement but this was based on only 2 observations out of 130 films. This small number of observed events is reflected in the 95% confidence interval around the kappa statistic (-0.11-1.0), which spans from agreement worse than that expected by chance alone up to perfect agreement

Test-retest: A single reader reviewed all 130 films three months after the initial interpretation (Table 6). The overall percent agreement with the initial interpretation was 86.9% (95% CI 79.6% - 92.0%) for all films. Percent agreement and the kappa statistic showed substantial agreement for all components.

Sensitivity Analysis

In order to account for potential bias due to lack of independence between multiple films belonging to an individual patient, reliability was determined for only the first film belonging to every patient in the series. Analysis in this fashion showed consistent findings with respect to inter-rater and test-retest reliability (Table 5 and 6). When inter-rater reliability was determined for the interpretation of the first film for each patient, percent agreement and kappa statistic was 88.6% (95% CI 72.3% - 96.2%). Test-retest reliability was 85.7% (95% CI 69.0% - 94.6%) when only the first film was considered. Agreement on individual items was high however the limited number of observed complications limited this analysis.

Discussion:

This report describes an important first step in the development of a classification system for biliary complications following liver transplantation. The goal of the classification is to fill the clinical need for a means of standardized reporting of biliary complications. Reliability must be ensured for a classification system to achieve its purpose of providing a standardized and reproducible system for reporting post-operative outcomes (27). Previous reports have suggested that there is potential for considerable discrepancy in the interpretation of ERCP films. Kucera et al demonstrated a nearly 50% discordance rate between endoscopists and radiologists in the interpretation of cholangiograms obtained at ERCP (28). This finding reinforces the need to establish the reliability of a classification system before its dissemination and application. The concordance rate between interpreters in this study was significantly greater than that reported by Kucera. This may be due to the clinical expertise of the readers, but it is our hypothesis that applying a simple yet structured classification system looking for specific elements helped increase concordance between readers. Scoring rubrics are well recognized as increasing inter-rater reliability by formalizing evaluation criteria and guiding evaluation (29). This classification, in essence, provides a scoring rubric for the evaluation of post-operative cholangiographic studies. The high inter-rater and test-retest reliabilities suggest that the current classification system could be consistently applied when used in clinical practice, but more widespread confirmation will of course be required.

The current classification system relies on contrast cholangiography in order to diagnose and classify biliary complications. While MRCP is increasingly being used for diagnosis, our experience with the use of magnetic resonance cholangiopancreatography (MRCP) has not been satisfactory in the OLT population, partly owing to the use of metal clips at surgery that create artifacts and impair interpretation of magnetic resonance images (30). ERCP is readily available in our institution, and is routinely used in the diagnosis of potential or suspected biliary complications following transplantation. ERCP is also our primary therapeutic tool in the treatment of biliary complications, as is the case in most institutions (8, 31, 32).

A need for standardized reporting of biliary complications has been previously highlighted (11, 33) and we chose to devise a biliary-specific classification scheme. This was chosen rather than a generic scheme relating the complication to the necessary therapy, as does the widely used Clavien classification of postoperative complications (27), because the vast majority of biliary complications after OLT are treated in a similar non operative fashion using either endoscopic or percutaneous techniques. Only rarely is a re-operation or re-transplantation necessary. Moreover, different biliary complications appear to have different long-term prognoses and implications for patients and society (likelihood of cure with ERCP, number of treatments required, cumulative cost, etc) which cannot be borne out by a generic classification. Future work on formal validity testing of the proposed classification will aim to document those very implications.

The main limitation of this initial study is the small sample size. While a significant number of films were reviewed, these represent a relatively small number of patients. Adequate numbers of the more common complications (such as anastomotic stricture and common duct filling defects) were seen but more rare complications such as intra-hepatic strictures or filling defects were diagnosed in only a handful of patients. Although reliability appeared adequate for both the common and less frequent complications, further study with a larger sample size should be pursued to verify these findings.

Conclusions:

The need for a reliable and universally applied classification system exists in order to ensure consistency and clarity in reporting of biliary complications after liver transplantation. The proposed classification system has been shown to be reliable in a small series of patients by using formal reliability testing. Rare elements of the classification would benefit from additional reliability testing in a larger population. Validation of the classification system with clinically pertinent outcomes is ongoing.

Tables and Figures:

Table 1: Proposed Classification

1. Stricture	
	a) Anastomotic
	b) Donor Common Hepatic Duct
	c) Intra-hepatic (unilateral)
	d) Intra-hepatic (bilateral)
2. Leak	
	a) Anastomotic
	b) Non-anastomotic (Cystic duct, parenchymal or duct of Lushka)
3. Filling Defect	
	a) Common Duct
	b) Intra-hepatic

Table 2: Patient demographics comparing eligible cohort and selected subgroup of patients whose films were classified according to the proposed classification system

	Included in Study (n=35)	**Eligible not included (n=26)**	**p-value**
Male, n (%)	28 (80.0%)	17 (65.4%)	0.15
Age at OLT, mean years (SD)	55.9 (18.1)	56.5 (16.6)	0.79
BMI, kg/m2 (SD)	31.1 (6.9)	27.3 (5.0)	0.02
Cold ischemia time, mean hours (SD)	7.8 (2.5)	8.1 (2.2)	0.67
Number of ERCPs, median [IQR]	3 [1, 5]	3 [2, 5]	0.78
Graft Loss, n (%)	11 (31.4)	11 (42.3)	0.59
Length of follow-up, mean years (SD)	5.33 (2.7)	4.97 (2.1)	0.55

Data presented as mean (SD) or median [IQR]
SD: Standard deviation
IQR: interquartile range

Table 3: Etiology of cirrhosis in study group

Etiology of Liver Cirrhosis	n (%)
Hepatitis C	12 (34.2%)
ETOH	6 (17.1%)
Non-alcoholic steatohepatitis	5 (14.3%)
Hepatitis B	4 (11.4%)
Cryptogenic	2 (5.7%)
Secondary to right heart failure	2 (5.7%)
Primary Biliary Cirrhosis	1 (2.9%)
Primary Sclerosing Cholangitis	1 (2.9%)
Drug Induced	1 (2.9%)
Other	1 (2.9%)

Table 4: Biliary Complications Observed in Study Cohort

Classification	Element	Patients* n=35 (%)	Films n=130 (%)
Stricture			
	Anastomotic	15 (42.9)	70 (53.8)
	Common Hepatic Duct (recipient)	6 (17.1)	20 (15.4)
	Intra-hepatic (unilateral)	2 (5.7)	2 (1.5)
	Intra-hepatic (bilateral)	2 (5.7)	3 (2.3)
Leak			
	Anastomotic	4 (11.4)	7 (5.4)
	Non-anastomotic (Cystic duct, Parenchymal or Duct of Lushka)	3 (8.6)	4 (3.1)
Filling Defect			
	Common Duct	6 (17.1)	8 (6.2)
	Intra-hepatic	1 (2.9)	1 (0.8)

* Note than an individual patient may have had more than one diagnosis over time

Table 5: Inter-rater reliability

	Per film (n=130)		On first film (n=35)	
Classification Element	**% Agreement (95% CI)**	**Kappa (95% CI)**	**% Agreement (95% CI)**	**Kappa (95% CI)**
Overall Agreement	88.5 (81.4-93.2)	-	88.6 (72.3-96.2)	-
Stricture				
Anastomotic	96.9 (91.8-99.0)	0.94 (0.88-0.99)	97.1 (83.4-99.9)	0.94 (0.83,1)
Donor Common Hepatic duct	96.2 (90.8-98.6)	0.87 (0.75-0.98)	97.1 (83.4-99.9)	0.79 (0.38,1)
Intra-hepatic (unilateral)	99.2 (95.1-99.9)	0.80 (0.40-1)	100 *	*
Intra-hepatic (bilateral)	99.2 (95.1-99.9)	0.85 (0.57-1)	100 *	*
Leak				
Anastomotic	100 †	1 †	100 †	1 †
Cystic duct, parenchymal, duct of Lushka	100†	1 †	100 †	1 †
Filling defect				
Common duct	96.2 (90.8-98.6)	0.86 (0.74-0.98)	91.4 (75.8-97.8)	0.62 [0.23,1]
Intra-hepatic	98.5 (94.0-99.7)	0.49 (-0.11-1)	100 *	*

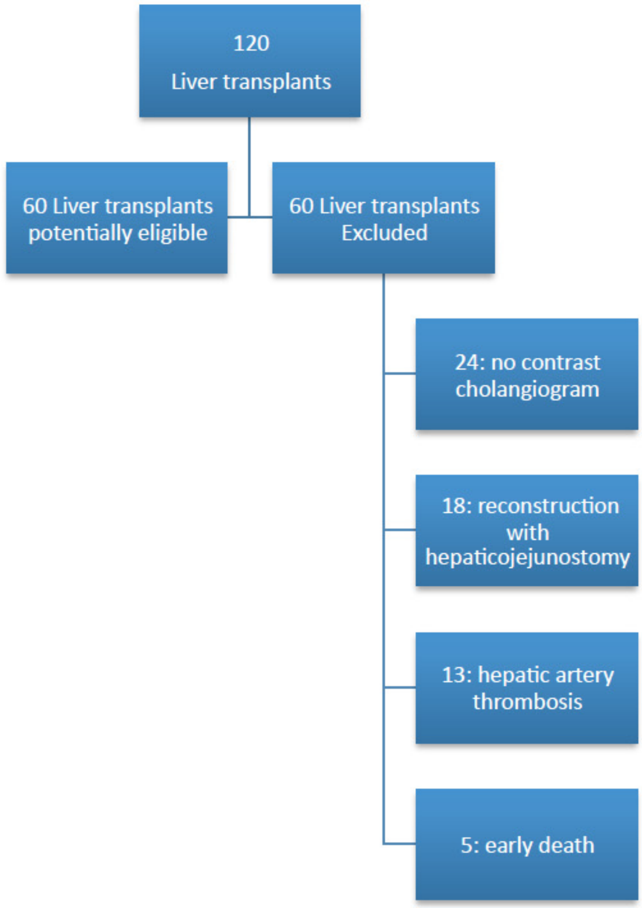
CI: confidence interval
† 95% confidence intervals could not be calculated due to 100% agreement
* no events observed

Table 6: Test-retest reliability

	Per film (n=130)		On first film (n=35)	
Classification Element	**% Agreement (95% CI)**	**Kappa (95% CI)**	**% Agreement (95% CI)**	**Kappa (95% CI)**
Overall Agreement	86.9 (79.6-92.0)	-	85.7 (69.0-94.6)	-
Stricture				
Anastomotic	93.8 (87.8-97.1)	0.88 (0.79-0.96)	91.4 (75.8-97.8)	0.82 (0.62-1)
Donor Common Hepatic duct	97.7 (92.3-99.4)	0.92 (0.82-1)	97.1 (83.4-99.9)	0.78 (0.35-1)
Intra-hepatic (unilateral)	100 †	1 †	100 *	*
Intra-hepatic (bilateral)	100 †	1 †	100 *	*
Leak				
Anastomotic	99.2 (95.2-99.9)	0.92 (0.76-1)	97.1 (83.4-99.9)	0.84 (0.54-1)
Cystic duct, parenchymal, duct of Lushka	99.2 (95.2-99.9)	0.88 (0.66-1)	100†	1 †
Filling defect				
Common duct	96.2 (90.8-98.6)	0.53 (0.16-0.89)	91.4 (75.8-97.8)	0.77 (0.46-1)
Intra-hepatic	100†	1 †	100 *	*

CI: confidence interval
† 95% confidence intervals could not be calculated due to 100% agreement
* no events observed

Figure 1: Flow chart of patient inclusion and exclusion (and reasons for exclusion)



4.3 Additional comments

4.3.1 Measures of Reliability

Reliability refers to the ability of a measurement tool or diagnostic test to yield similar results with repeated application (34). The reliability of an instrument must be established early in its development as this has implications on interpreting study results regarding validity (35). Different types of reliability estimates include inter-rater reliability, test-retest reliability, inter-method reliability and internal consistency reliability. For the purposes of this study, inter-rater reliability and test-retest reliability are the most appropriate reliability tests. Both of these measures are considered consensus measures (35). Inter-rater reliability is a measure of agreement between two independent raters for a given data set at a given point in time. Test-retest measures the differences in responses of a single rater at two different time points. Inter-method reliability assesses agreement when differing methods or instruments are used. In this case there are no other classification systems available for comparison. Internal consistency reliability, which measures consistency across items within a test, is not applicable to this classification system (36).

Both inter-rater reliability and test-retest reliability were determined using percent agreement as well as the kappa statistic. Percent agreement is advantageous as it is intuitive, easy to calculate and easy to explain (35). Percent agreement however does not account for the amount agreement between observers that may be due to chance alone. This weakness is addressed by the kappa statistic, discussed below. Percent agreement may be influenced by prevalence, as very common findings or the absence of very rare findings are more likely to be agreed upon. It is suggested that agreement > 70% represents adequate consensus and demonstrates acceptable inter-rater reliability (35).

4.3.2 Kappa Statistic and its Limitations

Cohen's kappa corrects for chance agreement between two observers and tells the reader how much of the observed agreement is beyond what is expected by chance alone. Chance agreement is not always 50% as this is affected by the prevalence of the condition studied. This is accounted for in the calculation of kappa where the chance agreement is estimated and then the observed agreement beyond chance is compared with the maximal possible agreement beyond chance (37, 38). In general, kappa values from 0.40 to 0.60 are considered to show moderate agreement while anything above 0.61 shows substantial agreement (39). The kappa statistic is most easily applied to discrete variables. A weighted kappa is used in the setting of categorical data where the distance between different categories is thought to be of relevance. For example, differing ratings of normal versus benign may be considered partial agreement while benign versus malignant are considered discordant (40). In the case of this study, a simple kappa statistic was used given the binomial data.

While generally valuable in interpreting inter-rater reliability, the kappa statistic has some disadvantages. One of the disadvantages, and a potential limitation of this study, is that kappa may be influenced by the prevalence of the condition or disease under study. The prevalence effect is present when observer agreement on positive cases differs from agreement on negative cases. When the prevalence of a positive rating is very high or very low, chance agreement is therefore also high and the kappa statistic will be reduced (41). Statistical measures to correct for prevalence effects do exist but many debate their value. Some authors suggest that reporting percent agreement and the kappa statistic, as well as 2x2 contingency tables, is the best way to help readers interpret the data (41). In situations where the percent agreement is high but the kappa statistic is low (for example in the situation of a condition with low prevalence) the reader can better judge the kappa statistic interpretation as ambiguous and not necessarily as poor inter-rater reliability (42).

Another potential disadvantage of kappa is that although it provides a measure of agreement, it does not indicate whether disagreements are random or whether they are due to systematic differences. A consistent pattern of disagreement between observers usually requires further attention in analysis. As such, the data itself must be carefully examined when interpreting a kappa statistic (41).

In this study, the prevalence of some elements of the classification was very low with only a handful of cases in the sample. Overestimation of the percent agreement and underestimation of kappa is possible with data of this nature. While the small sample size and low prevalence is a potential weakness of the study, both percent agreement and the kappa statistic none-the-less showed acceptable agreement. In this preliminary study the classification shows acceptable reliability however further evaluation with a larger sample size is necessary.

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Chapter 5: Manuscript Two & Additional Comments

5.1 Preface

This chapter contains a manuscript prepared for submission to a clinical journal. The manuscript is presented as submitted with minor changes made to formatting.

5.1.2 Author Contributions

Dr Amy Neville, MSc candidate and first author, was involved in study design and defining the elements of the proposed classification. She was responsible for carrying out the literature review, data collection, statistical analysis and writing of the manuscript.

Dr Jeffrey Barkun, thesis co-supervisor, oversaw the project as a whole. He was responsible for study design and proposal of the classification, interpretation of results and critical review of the manuscript.

Dr Elham Rahme, thesis co-supervisor, contributed to data analysis, interpretation of the study results and critical review of the manuscript.

Dr Marylise Boutros, surgical resident, contributed to data collection and critical review of the manuscript.

5.1.3 Ethics

This study was approved by the McGill University Health Centre Institutional Review Board (#12-349-SDR)

5.2 Manuscript

The Development of a Classification System for Biliary Complications following Orthotopic Liver Transplantation: Determining Validity

Amy Neville MD[1], Marylise Boutros MD[1], Elham Rahme PhD[2], Jeffrey ST Barkun MSc, MD[1]

[1] Department of Surgery, Multi-Organ Transplant Program, McGill University Health Centre, Montreal, Canada

[2] Departments of Epidemiology and Biostatistics, McGill University, Montreal Canada

Please address correspondence to:

Jeffrey ST Barkun, MSc, MD
Royal Victoria Hospital
687 Pine Ave West Suite S9.30
Montreal QC
H3A 1A1

ABSTRACT

Introduction: The estimated incidence of biliary complications after orthotopic liver transplantation (OLT) ranges from 10-40% but the absence of a standardized classification system prevents accurate documentation. In this preliminary study, we propose to validate a structured classification, previously shown to be reliable, for biliary complications following choledocho-choledochal anastomosis (CCA) at non living-related OLT. The classification is based on 3 major components and their anatomic location: strictures (intrahepatic, common hepatic or anastomotic), leaks (anastomotic, non-anastomotic) and filling defects (intra-hepatic, common duct).

Methods: OLT recipients from the McGill University Health Centre undergoing choledocho-choledochal biliary anastomosis from 2004-2010 were eligible for the study. Patients with hepatic artery thrombosis were excluded, as were patients who experienced early (within one month) graft loss or death. Validity was determined by analysis of the relationship between classification elements and clinical outcomes in patients who experienced a biliary complication within 3 years following transplant. Clinical outcomes of interest included the number of post-transplant hospital admissions and total number of hospital admission days within the first 36 months post-transplant, the need for an invasive procedure to diagnose and/or treat biliary complications, surgical revision of the biliary anastomosis, repeat transplantation, as well as graft and patient survival. Classification components were considered to show good validity if they demonstrated significant associations with clinical outcomes based on regression models, as appropriate. Validity was further supported if the outcomes relative to different anatomic locations of each component showed clinically significant differences, indicating a meaningful sub-classification.

Results: A total of 184 patients were included and 76 had biliary complications. In general, the proposed classification components showed a strong relationship with most of the selected clinical outcomes. Poorer clinical outcomes were observed with strictures when compared to leaks or filling defects. Within the differing types of strictures, increasing severity of the complications was demonstrated with higher level biliary lesions, further supporting the validity of our classification method. The relationship between stricture components of the classification and days of hospital admission exemplifies the validation method; adjusted rate ratio (95% confidence interval) for days of hospital admission for anastomotic, common duct and bilateral intra-hepatic strictures was 2.01 (1.84-2.18), 3.80 (3.42-4.21) and 7.05 (6.46- 7.70), respectively.

Conclusions: The proposed classification of biliary complications after liver transplantation appears to show good construct validity. The classification exhibits the ability to differentiate clinical outcomes between biliary complications of different severities, supporting the clinical significance of the classification. Given the limitations imposed by small numbers in this preliminary study, broader validation is required.

Introduction:

Though outcomes have improved significantly in recent decades, biliary complications remain the "Achilles Heel" of liver transplantation, representing one of the most common post-operative complications (1). Currently there is no accepted, widely used classification to report biliary complications. This lack of standardized definitions and reporting results in variable estimates of incidence and limits the surgeon's ability to critically appraise and evaluate new prophylactic and therapeutic approaches. Previous authors have stated that the lack of standardized and validated means of reporting of postoperative complications in the surgical literature "has hampered proper evaluation of the surgeon's work and possibly progress in the surgical field" (2). The need for standardized reporting of complications in the field of liver transplantation has been specifically highlighted (3). Furthermore, the occurrence of post-operative complications remains an important quality measure in liver transplantation and the use of post-operative complications such as biliary complications to serve as quality indicators depends heavily on consistent definitions (4, 5). A validated classification system is necessary to ensure standardized and reliable reporting of these common yet clinically significant complications (3).

We propose a classification scheme of biliary complications following deceased donor OLT with choledocho-choledochal anastomosis (Table 1). This structured classification is based on the type of complication (stricture, leak and filling defect) and its anatomic location (anastomotic, common duct / non-anastomotic or intrahepatic). The classification was previously shown to exhibit good reliability on formal evaluation (6). Validation of the proposed classification is a critical step in its development. Validation assures that the classification correctly captures and reports biliary complications in not only a standardized but clinically meaningful fashion. The goal of the present study is to formally assess the utility of the proposed classification in differentiating clinical outcomes, as well as the utility of its individual components, to ensure its validity as a standardized reporting tool.

Methods:

Inclusion and exclusion criteria

Consecutive patients who underwent deceased donor OLT with choledo-chocholedochal anastomosis between August 2003 and August 2010 at the McGill University Health Centre (MUHC) were considered eligible for the study. Patients who died from non-biliary complications or experienced graft failure within 30 days of transplantation were excluded as they do not have an adequate follow-up time to meaningfully contribute to the validation exercise (7). Hepatic artery thrombosis or stenosis at any time following transplantation was also considered an exclusion criteria as this complication often requires urgent re-transplantation when this complication occurs early after OLT and biliary complications related to the resulting vascular compromise represent a specific etiology and pattern of biliary injury (8, 9). The study period began with transplantation and ended at the time of death, repeat transplantation or at a maximum of 3 years following transplantation.

All patients who underwent contrast cholangiogram studies (either percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatogram (ERCP)) were identified and these studies were reviewed. Biliary complications were classified using the classification scheme as described in the introduction (Table 1). Study patients were separated into two groups, those with a biliary complication were considered part of the study group and those whose contrast cholangiograms were read as normal or who did not undergo a contrast cholangiogram within the first 3 years post-operatively were considered part of the normal (no biliary complication) group. Contrast studies are not performed routinely in our centre. The decision to perform such a study is made on a clinical basis when the suspicion of a biliary complication arises including bile drainage from post-operative drains, abnormal liver enzymes, jaundice or fever suggestive of cholangitis.

Data Collection:

Patient demographics including age, sex, body mass index (BMI), etiology of liver disease, severity of liver dysfunction (as measured by Model for End Stage Liver Disease (MELD) score), cytomegalovirus (CMV) status, cold ischemic time and the use of biliary endoprostheses were extracted from the prospectively maintained McGill University Health Centre Multi-Organ Transplant Database. Temporary biliary endoprostheses were placed intraoperatively at the time of OLT according to surgeon preference. Graft and patient survival data were also collected from the Transplant Database.

Post-transplant admissions to hospital and post-transplant imaging (contrast cholangiography) were extracted from the patient's electronic medical chart. All admissions occurring after the diagnosis of the biliary complication until the end of the study period were recorded. This time frame was chosen because most admissions attributable to biliary complications occur early in the post-transplant period. Less than 4% of biliary complications are diagnosed more than a year post-transplant (7, 10). However it was felt that only analyzing outcome data at one year post-transplant would fail to capture important clinical outcomes that result from biliary complications, such as repeat transplantation, as these typically occur months to years following the diagnosis of the complication. Qualitative analysis of our data suggested most complications were resolved (either cured by endoscopic or radiological procedures, surgical treatment, or repeat transplantation) by 3 years. Also, as specific cause of admission was not discernable from this retrospective data set and all causes of admission were considered, it was felt that studying patients over a longer follow-up period than three years is more likely to erroneously attribute hospitalization to the biliary complication when independent factors may be at play (long term side-effects of immunosuppressive medications, unrelated medical illness, etc).

Outcome measures

Outcomes of interest include number of hospital admissions per 100 patient-year follow-up, number of days admitted to hospital per 100-patient-year follow-up, and the number of invasive procedures (endoscopic retrograde cholangiopancreatogram (ERCP) and/or percutaneous transhepatic cholangiogram (PTC)) per 100-patient-year follow-up required during the course of treatment. Although ERCP and PTC are frequently performed on an outpatient basis, they are invasive procedures requiring sedation and post-procedure observation. As such, each ERCP or PTC was counted as a one-day admission (the same way any day surgery would be considered as a one-day admission). Other outcome measures of relevance include surgical procedures such as revision of the biliary anastomosis and the need for repeat transplantation. Finally, graft and patient survival were assessed.

Definitions of biliary complications

All complications were classified retrospectively based on direct cholangiography images (ERCP or PTC). The following definitions were used to define biliary complications included in the classification (stricture, leak and filling defect). Stricture was defined as a distinct area of visually significant narrowing of any part of the biliary system by 50% or more of the duct diameter. Donor and recipient duct mismatch were not considered to be strictures as this difference in sizes does not appear as a distinct area of narrowing but rather as a consistent size mismatch between the two ducts. Leak was defined as extravasation of contrast outside the biliary tree from any area of the biliary ductal system or liver parenchyma. Filling defects were defined as any area of non-opacification of the recipient biliary tree consistent with stones or casts. Intra-hepatic filling defects were considered to be any filling defect consistent with a stone or case within the intra-hepatic biliary tree or proximal donor ducts. Filling defects of the recipient common bile duct represent a primary pathologic process akin to primary or secondary biliary stones in the non-transplant setting (11).

Following OLT an individual patient may have more than one biliary complication either at one time (for example an anastomotic stricture as well as intrahepatic strictures) or over time following transplantation (for example an anastomotic leak that resolves but is followed by the development of an anastomotic stricture). Similar to the most widely used classification system of surgical complications, the Clavien-Dindo classification (12), a patient with more than one complication (either at one point in time or over time) was ultimately "classified" under the most severe complication they experienced in the defined follow-up period. The most severe complication is the complication most likely to drive the clinical outcome. In constructing the current classification, a relative severity of complications was proposed based on previous descriptions of biliary complications in the transplant literature. The hierarchical severity of complications, listed in order of decreasing severity, is as follows: intrahepatic stricture, common hepatic stricture, anastomotic stricture, anastomotic leak, non-anastomotic leak, and isolated filling defect. In general, strictures were regarded as more serious than leaks as the majority of leaks are self-limited while strictures frequently require prolonged treatment (11, 13); isolated filling defects were considered the least severe complication. If a patient had more than one complication over the course of follow-up, clinical outcomes (admissions, invasive procedures, etc) were measured from the time of symptom onset (ie the first diagnosis) in order to capture the true clinical burden of having a biliary complication(s).

Statistical Analysis and Validation

Adjusted comparison using logistic regression was used to compare baseline patient demographics between patients with and without biliary complications. Number of admissions, days of admission, and number of invasive tests were assessed and reported as rate per 100-patient years. Additional surgical procedures required, graft and patient survival were also assessed.

Although patients were only classified as having the most severe complication experienced, multiple complications were possible. In order to further understand the impact of such a classification, the inter-relationship between different classification components was examined using the Pearson correlation coefficient for binary variables (Phi correlation) to look for common or strong associations between components diagnosed in concert.

Rate ratio with 95% confidence interval was obtained through Poisson regression models to assess the relationship between the various classification components and rates of hospital admissions per 100 patient -year, number of days of hospital admission per 100 patient -year and the rates of invasive tests required per 100 patient -year. Cox proportional hazard regression models were used to assess the relationship between biliary complications and graft survival. The proportional hazards assumption was verified using Schoenfeld's global test. All biliary complications except non-anastomotic leak and intra-hepatic filling defect (given these classifications were present in one and zero patients respectively) were included in the regression models. Appropriate model selection was verified using Akaike Information Criterion (AIC).

Kruskall-Wallace one-way analysis of variance was used to assess for differences in outcomes between the anatomic divisions (anastomotic, intra-hepatic, etc) of each complication type. R open source software (version 2.15) was used for all statistical analysis.

Results:

Between August 2003 and December 2010 a total of 314 liver transplants were performed at the MUHC. One hundred thirty liver transplants were excluded: 59 who underwent primary biliary reconstruction with hepaticojejunostomy, 25 diagnosed with hepatic artery thrombosis and 26 who died or experienced graft failure within 30 days of transplantation from causes other than biliary complications. An additional 20 patients whose ERCP films were unavailable for review were excluded. Therefore a total of 184 patients were included in the study (Figure 1). Patient demographics are presented in Table 2. Patients who developed a biliary complication had similar baseline characteristics to those who did not with the exception of more frequent use of intra-operative endobiliary stents. The underlying etiology of cirrhosis for patients with and without biliary complications is presented in Table 3.

The breakdown of biliary complications observed in the study population is presented in Table 4. Strictures were the most commonly occurring complication, with anastomotic strictures occurring most frequently (40 patients). Anasomotic leaks were relatively uncommon with only 3 patients being classified with this complication. A total of four patients were diagnosed with non-anastomotic leak but three of these patients also experienced another more serious biliary complication, leaving non-anastomotic leak to be the principal diagnosis in only one patient. Of note, this patient is a significant outlier with respect to clinical course and outcomes. The patient was admitted to the intensive care unit for more than a year after transplantation and eventually died during the same hospital stay of disseminated fungal infection and sepsis. Analysis of the non-anastomotic leak component was therefore not possible. Similarly, no patient had a final diagnosis of isolated intra-hepatic filling defect and therefore no further analysis was possible.

Relationship between Classification Components

Although patients were classified under only the most severe diagnosis they experienced, multiple diagnoses were possible for any given patient. In order to better understand the possible implications of such a classification, the relationship between the different components of the classification were explored to look for common or strong associations. Overall, there were 31 patients who had more than one different biliary complication diagnosed in the follow-up period. For this analysis, patients were not restricted to being classified under the most severe complication experienced (Table 5). Anastomotic leak and anastomotic stricture showed a weak statistically significant correlation

(correlation coefficient 0.29 (95% CI 0.1-0.4)) Anastomotic strictures showed an even weaker correlation with the presence of intra-hepatic strictures (correlation coefficient 0.17 (95% CI 0-0.3)), while common hepatic duct strictures showed a moderate correlation (correlation coefficient 0.38 (95% CI 0.1-0.6)) with intra-hepatic strictures. Otherwise, no components showed strong correlation to any other individual component, suggesting the hypothesized individual components of the classification represent separate entities (and are less likely to be a progression of the same complication).

Intra-hepatic filling defects were uncommon and did not occur in isolation of other biliary complications. This complication showed weak to moderate correlation with the presence of common hepatic duct strictures and bilateral intra-hepatic strictures. No conclusions can be drawn regarding the significance of this finding given the small number of patients who experienced this complication.

Validation using clinical outcomes

Strictures: Having a biliary stricture was associated with a statistically significant increase in the rate of hospital admissions and number of days spent in the hospital (Table 6). The number of hospital admissions increased as strictures went from the presumed least severe location (anastomotic strictures, 78.6 admissions per 100 patient-years) to more severe (common duct stricture, 141.3 admissions per 100 patient-years) to most severe (bilateral intrahepatic strictures, 228.5 admissions per 100 patient-years). The association between both the number of days of admission and the number of invasive tests (ERCP and PTC) performed over the period of follow-up with stricture severity showed a similar pattern. Adjusted rate ratios (Poisson regression) further confirmed these findings (Table 6).

Non-parametric, one-way analysis of variance supports our hypothesis that the three stricture components reflect a true difference in clinical outcome with respect to number of admissions ($p<0.001$), total days of admission ($p<0.001$) and number of invasive procedures ($p<0.001$).

When considering intra-hepatic strictures, this study found a trend towards lower rate of admissions (46.5 versus 228.5 admissions per 100 patient-years, $p=0.02$) and days of admission (2263 versus 6329 days of admission per 100 patient-years, $p<0.01$) for patients with unilateral strictures when compared to those with bilateral strictures. The adjusted rate ratio for both these outcomes were consistent with this trend. While the number of invasive procedures required for patients with these two diagnoses was similar (480 procedures per 100-patient years and 487 procedures per 100-patient years), the adjusted rate ratio was higher for unilateral intra-hepatic strictures (rate ratio 36 vs rate ratio 23). However, there was significant overlap between the 95% confidence intervals.

Cox Proportional hazard models (Table 7) for graft failure demonstrated that bilateral intra-hepatic strictures are the only classification component that significantly impacts on graft death (hazard ratio 8.12, 95% confidence interval 3.82- 17.26). In fact, model selection revealed the best model for predicting graft survival in patients with biliary complications was one containing only bilateral intra-hepatic strictures.

Leaks: Small patient numbers limited studying of the effect of biliary leaks on clinical outcomes. It does not appear that anastomotic leaks increase the rate of hospital admission or number of days spent in hospital when compared to patients who did not experience a leak. Anastomotic leak was however associated with an increased incidence of invasive procedures (rate ratio 8.20, 95% confidence interval 3.31- 17.57). Anastomotic leak was not associated with an increase in repeat transplantation, graft or patient death. No definitive conclusions can be drawn regarding non-anastomotic leaks.

Filling defects: Filling defects were associated with a small but significant increase in hospital admissions (RR 1.96) as well as stronger increase in invasive procedures required (RR 6.03) than patients who did not experience this complication. There was no increase in repeat transplantation, graft death or patient death.

Discussion

The goal of this study was to validate a classification of biliary complications by demonstrating its clinically relevant relationship with clinical outcomes. Many of the components of the classification system performed as hypothesized. The presence of a stricture increased hospital admissions and length of hospital stay, as well as the need for invasive procedures. Strictures of the higher biliary tree were appropriately found to be associated with worsening clinical outcomes; the division of stricture complications into different components based on anatomic location provided not only statistically significant but also clinically significant associations with hospital admissions extending from 78.6 per 100 patient-years, 141.3 per 100 patient-years and 228.5 per 100 patient-years for anastomotic, common duct and bilateral intra-hepatic strictures respectively.

Bilateral intra-hepatic stricture is the only classification component that was associated with increased risk of graft loss. This finding is consistent with previously published literature regarding intra-hepatic strictures (14). The ability to differentiate complications with severe outcomes (such as these) from those with a more benign course is a key feature of the classification. Patients who experience complications strongly associated with very poor clinical outcomes need to be identified in a systematic fashion as they potentially merit different consideration with respect to treatment, including the timing of re-listing for transplant. Most importantly, these findings highlight that not all strictures are the same and therefore should not be lumped together in the reporting of biliary complications as occurs commonly in the OLT literature (15-18).

Previous studies have suggested that unilateral and bilateral intrahepatic strictures should potentially be considered as separate clinical entities as the clinical outcomes associated with these complications may be different. Unilateral strictures have important clinical consequences (such as recurrent episodes of cholangitis) but the clinical manifestations of these strictures appear to not be as severe as bilateral strictures, which almost universally lead to graft loss (19, 20).

Rates of admission were less for unilateral versus bilateral strictures, while invasive procedures can be considered similar between both groups. Furthermore, the data from this study shows only bilateral strictures were associated with an increase in repeat transplantation and graft loss. Given the differences in clinical outcomes, and the obvious severity of graft loss, dividing intra-hepatic strictures into these two groups appears to reflect a clinically relevant distinction.

Isolated anastomotic leaks did not lead to significantly worse outcomes with respect to admissions or invasive procedures, appropriately reflecting their less clinically nature. This is congruent with current clinical practice; once a leak is appropriately drained little intervention is required and the leak typically will heal after endoscopic treatment (sphincterotomy). Therefore repeated contrast studies are typically not needed.

In this classification, leaks were divided into anastomotic and non-anastomotic. This division carries good face value as the literature suggests that anastomotic leaks are generally considered more hazardous and likely to require potential surgical intervention than non-anastomotic leaks. Non-anastomotic leaks are more likely to respond to conservative management measures such as short-term drainage and ERCP (13). The construct validity of this sub-categorization was impossible to evaluate in our study because only one patient in the study group experienced a non-anastomotic leak.

Although considered a minor complication, there were a significant number of invasive procedures performed for patients who developed filling defects due to stones, casts, etc. As such, common duct filling defects were associated with a significant increase in the rate of hospital admissions, highlighting the burden of such complications to the patient as well as the hospital system. Intra-hepatic filling defects were proposed as a potential component of the initial classification but these were not found to be an isolated biliary diagnosis and in this series were always associated with other complications of greater significance. While this may suggest that intra-hepatic filling defects are secondary process related to a primary process (typically strictures), it is difficult to make such a conclusion given small patient numbers. As such, it is hypothesized that this component may be removed from the classification following future validation studies.

Leaks and filling defects appear to be different from strictures in that they both necessitate more invasive procedures but have no significant impact on admissions or graft survival. This is an important distinction in clinical outcomes and reinforces the validity of the classification.

Conclusions:

The proposed classification of biliary complications shows appropriate relationships between most of its components and clinical outcomes following OLT. The classification discriminates well between complications of varying severity. The validity of some classification components could not be determined due to a small number of cases; isolated intrahepatic filling defects and the division of leaks into anastomotic/non aanastomotic components require further study. The validity of the classification should be evaluated in a larger patient population of OLT patients before classification deployment as a standardized reporting tool.

Tables and Figures:

Table 1: Proposed Classification

Stricture	
	a) Anastomotic
	b) Donor Common Hepatic Duct
	c) Intra-hepatic (unilateral)
	d) Intra-hepatic (bilateral)
Leak	
	a) Anastomotic
	b) Non-anastomotic (Cystic duct, parenchymal or duct of Lushka)
Filling Defect	
	a) Common Duct
	b) Intra-hepatic

Table 2: Baseline demographics

	No biliary complication	Biliary complication	Odds Ratio (95%CI)
Number of patients	108	76	
Male, n (%)	70 (64.8)	51 (67.1)	1.09 (0.56-1.10)
Age at OLT, mean years (SD)	56.2 (10.1)	57.5 (7.9)	1.05 (0.79-1.40)
BMI (kg/m^2), mean (SD)	27.8 (5.8)	30.0 (7.2)	1.27 (0.96-1.69)
MELD score, mean (SD)	20.7 (7.3)	20.1 (6.9)	0.99 (0.75-1.31)
Cold ischemic time, mean (SD)	7.1 (2.2)	7.6 (2.4)	1.16 (0.87-1.54)
CMV positive (patient or donor), n (%)	92 (85.1)	68 (89.5)	1.18 (0.46-3.25)
Intra-operative stent, n (%)	26 (24.1)	24 (31.6)	2.27 (1.13-4.63)*
Overall length of follow-up, mean years (SD)	2.5 (0.84)	2.4 (0.95)	0.77 (0.53-1.10)

SD: standard deviation
BMI: Body Mass Index
MELD: Model for End-Stage Liver Disease
CMV: Cytomegalovirus
*Odds Ratio and 95% confidence interval determined by logistic regression

Table 3: Etiology of cirrhosis

	No Biliary Complication n (%)	**Biliary Complication n (%)**
Total number of patients	**108**	**76**
Hepatitis C	38 (37.1)	24 (31.6)
Alcohol induced cirrhosis	19 (17.7)	16 (21.1)
Non-alcoholic steatohepatitis	15 (13.3)	10 (13.2)
Hepatitis B	13 (11.5)	7 (9.2)
Primary Biliary Cirrhosis	4 (3.5)	4 (5.5)
Cryptogenic	3 (2.7)	6 (7.9)
Fulminant hepatitis	2 (1.8)	3 (3.9)
Drug induced	2 (1.8)	0
Secondary to right heart failure	1 (0.9)	2 (2.6)
Alpha-1 antitrypsin deficiency	1 (0.9)	0
Polycystic liver disease	1 (0.9)	0
Budd Chiari syndrome	0	1 (1.3)
Primary Sclerosing Cholangitis	0	1 (1.3)
Autoimmune hepatitis	0	1 (1.3)
Other	9 (8.0)	1 (1.3)

Table 4: Biliary Complications Observed

Classification	**Component**	**N (%)**
Stricture		
	Anastomotic	40 (52.6)
	Donor Common Hepatic Duct	12 (15.8)
	Intra-hepatic (unilateral)	3 (3.9)
	Intra-hepatic (bilateral)	10 (13.2)
Leak		
	Anastomotic	3 (3.9)
	Non-Anastomotic	1 (1.3)
Filling Defect		
	Common Duct	7 (7.2)
	Intra-hepatic	0

Table 5: Relationship between classification elements: Correlation coefficient (95% confidence interval)

	AS	CDS	UIHS	BIHS	AL	NAL	CD FD	Intra-hepatic FD
AS	-	0.09 (-0.1, 0.3)	0.15 (-0.02, 0.2)	0.17 (0,0.3)	0.29 (0.1, 0.4)	- 0.01 (-0.1, 0.2)	0.06 (-0.1, 0.2)	0.11 (-0.04, 0.25)
CDS	-	-	0.19 (-0.01, 0.9)	0.38 (0.1, 0.6)	0.22 (0.02, 0.5)	0.07 (-0.1 ,0.3)	0.04 (-0.1, 0.3)	0.38 (0.25, 0.50)
UIHS	-	-	-	0.13 (-0.03, 0.5)	0.10 (-0.04, 0.4)	-0.02 (-0.02, 0.5)	-0.04 (-0.04, 0.3)	-0.02 (-0.16, 0.13)
BIHS	-	-	-	-	0.10 (-0.04, 0.4)	0.13 (-0.03, 0.5)	0.03 (-0.1, 0.3)	0.54 (0.43,0.63)
AL	-	-	-	-	-	-0.04 (-0.04, 0.3)	-0.001 (-0.01, 0.3)	0.12 (-0.03, 0.26)
NAL	-	-	-	-	-	-	-0.04 (-0.04, 0.3)	-0.02 (-0.16, 0.12)
CD FD	-	-	-	-	-	-	-	0.12 (-0.01, 0.27)

Legend: *AS* anastomotic stricture; *CDS* common duct stricture, *UIHS* unilateral intra-hepatic stricture, *BIHS* bilateral intra-hepatic stricture, AL anastomotic leak, *NAL* non-anastomotic leak, *CD FD* common duct filling defect, *FD* filling defect

Table 6: Admission data and invasive procedures according to biliary complication

	Number of admissions*	Rate Ratio (95%CI)	Total days admission*	Rate Ratio (95%CI)	Invasive procedures*	Rate Ratio (95%CI)
No BC	43.0	-	456.9	-	10.3	-
AS	78.6	1.85 (1.39-2.45)	269.0	2.01 (1.84-2.18)	78.6	17.14 (11.92-25.51)
CDS	141.3	3.16 (2.17-4.51)	1580.5	3.80 (3.42-4.21)	367.1	34.84 (23.69-52.78)
Unilateral IHS	46.5	0.92 (0.23-2.42)	2263.6	4.12 (3.47-4.88)	465.0	36.33 (22.03-59.93)
Bilateral IHS	228.5	2.75 (1.81-4.04)	6329.0	7.05 (6.46-7.70)	487.1	23.21 (15.29-36.01)
AL	11.1	0.31 (0.02-1.36)	66.67	0.17 (0.07-0.34)	77.8	8.20 (3.31-17.57)
CD FD	81.4	1.96 (1.10-3.25)	662.3	1.48 (1.22-1.77)	65.2	6.03 (2.97-11.43)

* Data presented as rate per 100 person-years (follow-up from time of complication up to a maximum of 3 years post-transplantation)

Rate ratio and 95% confidence interval as determined by Poisson regression (all complications except NAL were included in model)

† No analysis was attempted for non-anastomotic leaks and intrahepatic filling defects

Legend: *BC* biliary complication, *AS* anastomotic stricture; *CDS* common duct stricture, *IHS* intra-hepatic stricture, *AL* anastomotic leak, *CD FD* filling defect, *RR* rate ratio

Table 7: Surgical interventions (duct revision and repeat transplantation), graft and patient survival according to biliary complication

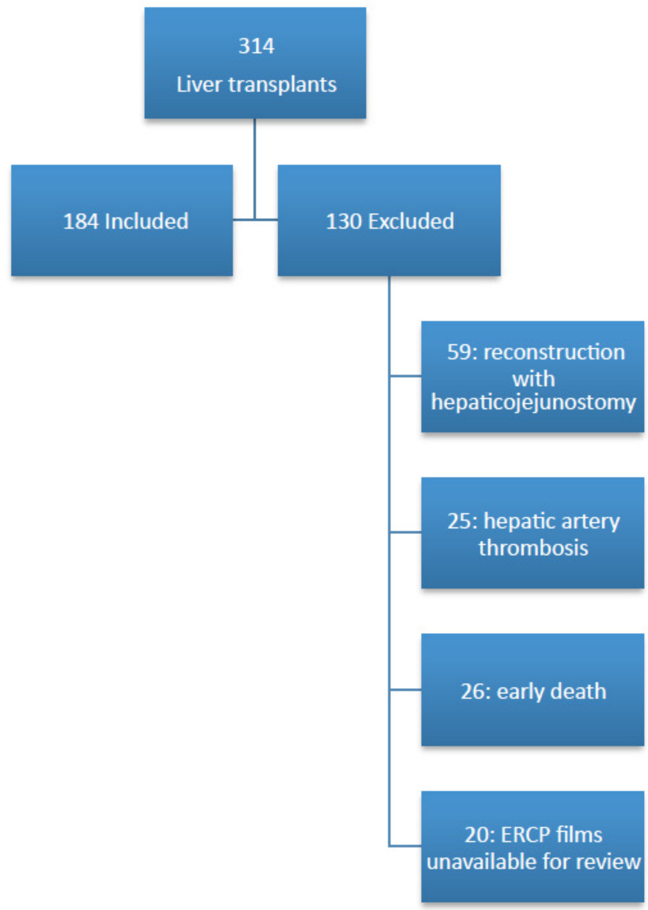
	Duct revised (n)	**Rate per100 -py**	**Redo OLT (n)**	**Rate per100 -py**	**Graft death (n)**	**Rate per100 -py**	**Hazard ratio (95%CI)***	**Patient death (n)**	**Rate per100 -py**
No BC	0	0	3	1.1	25	9.0	-	22	7.9
AS	4	1.14	1	0.3	11	3.13	1.17 (0.58-2.36)	9	2.6
CDS	2	6.42	1	3.2	3	9.64	1.26 (0.38-4.15)	2	6.4
Unilat IHS	0	0	0	0	1	15.5	1.62 (0.22-11.92)	1	15.5
Bilat IHS	0	0	6	45.7	10	76.2	8.12 (3.82-17.26)	4	30.5
AL	0	0	0	-	0	-	-	0	-
CDFD	0	0	0	-	1	5.4	-	1	5.4

† No analysis was attempted for non-anastomotic leaks and intrahepatic filling defects

*Hazard ratio as determined by Cox proportional hazards regression

Legend: *OLT* orthotopic liver transplant, *py* patient years, *BC* biliary complication, *AS* anastomotic stricture; *CDS* common duct stricture, *IHS* intra-hepatic stricture, *AL* anastomotic leak, *NAL* non-anastomotic leak, *CDFD* common duct filling defect, *IRR* incidence rate ratio

Figure 1: Flow chart of patient inclusion and exclusion (and reasons for exclusion)



5.2 Additional Comments

5.2.1 Validity

The origin of the term "validity" comes from the Latin *validus,* which means potent or strong. The dictionary presents several definitions of the word validity, including "well-grounded or justifiable: being at once relevant and meaningful" and "being logically correct" (21). In the epidemiology, validity refers to the degree to which data measures what it intends to measure (22). In the case of this classification development, validity ensures the clinical relevance, and ultimately the utility of the classification.

There are numerous different types of validity. Some examples include face validity, content validity, internal validity and external validity. In validating a clinical classification such as this one, construct and criterion validity are the most appropriate types of validity to consider. Construct validity is present to the extent that the measurement in question (in this case the classification components) is related to other measures believed to be part of the same phenomenon (in this case clinical outcomes) (22). Criterion validity is present to the extent that the measurement (classification component) predicts a directly observable phenomenon (clinical outcomes) (22).

5.2.2 Validation of Classification Systems

There is no standardized method used to assess the validity of new classification systems in the medical literature. In part this is due to the heterogeneous nature of classifications and the variety of purposes they serve. New classifications are commonly proposed on the basis of face validity (whether the classification subjectively appears to measure what it intends to measure) or based on the treatment required (12). Currently, many classifications do not undergo formal validity testing. For example, numerous classifications of bile duct injuries after cholecystectomy (gall bladder removal) have been described (including the Bismuth classification, Stewart-Way classification, Strasberg classification and Hannover classification) but none have been formally validated (23). Determining higher levels of validity (including construct and criterion validity) strengthens the classification and affirms it's utility as a standardized reporting system.

It is important to note that the validity of a scale or classification is not a black and white concept. In general, it cannot be stated that validity is present or absent. Instead a case to support the validity of the classification in question must be built (22).

5.2.3 Examples from the Surgical Literature

Described below are two examples of classification systems of post-operative complications (one general and one specific) that have been formally validated. Both of these classifications are in widespread use in the surgical literature.

The Clavien classification of postoperative complications is the most commonly used classification of its kind (24). It is a general classification that addresses all postoperative complications (not only those specific to a certain surgical procedure or disease pathology). The classification grades complications based on the treatment required to manage the complication. Dindo et al first tested reliability by asking an international sampling of surgeons to "classify" a series of complications (based on description of a clinical scenario) according to the proposed classification. Reliability was established when the classification demonstrated a high level of agreement between surgeons. The classification was then validated using a cohort of more than 6000 surgical patients by correlating the differing grades of complications with length of hospital stay (based on the assumption that more severe complications resulted in longer length of hospitalization). The validation study found a clinically and statistically significant relationship between the grade of complication and hospital stay, thus confirming validity. This classification is now commonly used to report and describe postoperative complications in surgical trials and studies. In a follow-up to their original study, the authors found their classification had been used in more than 200 surgical papers between 2004 and 2009 (24).

The “International Study Group of Pancreatic Fistula (ISGPF) Classification” is another example of a validated classification of post-operative complications. Unlike the more general Clavien classification, this classification pertains to a specific type of postoperative complication (25). Pancreatic fistula is a complication that may occur after pancreatic surgery. The classification grades pancreatic fistulas based on increasing severity. Validation of this classification was “accomplished through analysis and comparison of clinically relevant parameters.” The authors examined the relationship between their classification and length of hospital stay, ICU stay, blood transfusions and complications to determine that the classification reflected clinically relevant differences in clinical outcomes. As worsening clinical outcomes were associated with increasing grades, the classification was considered to be valid. Although relatively new (described in 2007) it has become the recognized standard with which to report pancreatic fistulas after pancreatic surgery (26-28).

Both of these classifications are excellent examples of validated, commonly used classification schemes for surgical complications. Although validation of our proposed classification was limited by small numbers and will require ongoing validation, our methods are similar to these widely accepted classifications and preliminary results are encouraging.

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Chapter 6: Concluding remarks

6.1 Discussion

The development of a novel classification system entails numerous steps including defining the scope of the classification, proposing the specific elements of the classification, establishing reliability and finally validating the proposed scheme. In our attempt to develop a classification of biliary complications we have gone through each of these steps. Establishing reliability and determining validity of the proposed classification is the major strength of this study.

6.1.1 Study Limitations and Potential Biases

The main limitation of this study was small patient numbers. Although the McGill University Health Centre has one of the largest liver transplant programs in Canada, the number of transplants performed yearly (40-50 per year) combined with the relatively low incidence of biliary complications resulted in a small sample size. Reliability testing was not greatly affected by the size of the study population as the number of contrast cholangiogram studies on which the reliability testing was based greatly outnumbered the number of study patients. However, small patient numbers had a more significant impact on the validation of the classification. As such, no firm conclusions could be drawn regarding the validity of some classification components, including the non-anastomotic leaks and intra-hepatic filling defects.

A potential bias affecting this study is differential loss to follow-up. As liver transplantation is a specialized area of surgery that requires care by highly specialized physicians, it is expected that after OLT patients will continue to be followed in a dedicated transplant center. Due to the high degree of specialization required, there are only two centers in the province of Quebec (both situated in Montreal) that care for transplant patients. This means that many patients come from considerable distance across the province for transplantation and related follow-up at the MUHC. Patients with biliary complications are not likely to be lost to follow-up as these patients require close follow-up, and often admission, for management of these potentially complex complications. In contrast, patients who do well post transplantation and who do not have serious complications may be less likely to return with the same frequency to the transplant center. These patients may receive a reasonable amount of their care, included admissions for minor problems, in the "community." As all cause admissions were considered, this may have affected the rates of admission and days of admission for the comparator ("normal" or no biliary complication) group in this study. If such a differential loss to follow-up is present, it would make the effect of biliary complications on clinical outcomes such as admissions and days spent in hospital appear falsely elevated.

6.2 Future Directions

Further validation is required before broad application of the classification can be considered. Validation with a large, external data set would strengthen and confirm the findings of this preliminary study. Larger patient numbers would also allow for validation of less common biliary complications, including non-anastomotic leak, that this study lacked power to clearly validate.

This study validated the proposed classification using biliary complications diagnosed using ERCP. However, biliary complications may also be diagnosed using magnetic resonance cholangiopancreatography (MRCP). The properties of the test are different than those of ERCP, including sensitivity and specificity (see chapter 1 for a more complete discussion regarding MRCP). Additional validation of the classification using complications diagnosed with MRCP would further ensure broad applicability of the classification.

Similarly, this classification was validated using patients who underwent transplantation using grafts from deceased donors. Living related donors represent a small but growing number of liver transplant performed in North America (1, 2). While biliary complications in this population are very similar, validation of the classification for use in this specific population would also increase its applicability.

6.3 Conclusions

The proposed classification of biliary complications shows excellent reliability and good preliminary validity. The significant difference in clinical outcomes between different classification components demonstrates the appropriateness of the chosen components. The classification components reflect the relative severity of the different complications, further supporting validity. Given small numbers in this preliminary study, larger numbers are needed to further validate the classification.

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