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A Single-Center Experience and Review of the Literature

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ABSTRACT

Severe hepatic trauma is a rare indication for liver transplantation (LT). We report our single-center experience of LT for hepatic trauma. Four new cases are discussed in the light of a literature review in order to depict the pathways leading from hepatic trauma to LT and to assess the outcomes of this practice. LT is generally indicated in case of uncontrollable hemorrhage, acute liver failure, or post-traumatic late sequelae. Hepatic vessels thrombosis, sepsis, major hepatic resections and a late referral are factors associated with the progression towards irreversible liver failure. Considering all reported cases, early patient and graft survival reached 68% and 62%, respectively, but in the last decade both have improved to 84%. LT after severe hepatic trauma is a sustainable practice considering the current good outcomes and the ineluctable death of these patients without LT.

Keywords: hemorrhage, liver failure, liver transplantation, sepsis, thrombosis

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FIGURE LEGENDS:

Figure 1. (Case 1) A. Contrast-enhanced computed tomography showing severe dilatation of intra-hepatic bile ducts of the liver remnant after right hepatectomy (arrow) and B. Portal vein thrombosis (arrow) and inferior vena cava dilatation (arrowhead).

Figure 2. (Case 4) Contrast-enhanced computed tomography showing the severely swollen and inhomogeneous liver remnant after right hepatectomy.

Figure 3. Clinical scenarios of LT for hepatic trauma

INTRODUCTION

Liver is the most frequently injured abdominal organ (1). The treatment of blunt hepatic trauma has significantly evolved over the last three decades with the introduction and wide acceptance of the concepts of nonoperative management, damage control surgery and the use of interventional radiology (2-6). Nowadays, nonoperative management is the preferred strategy in hemodinamically stable patients (6-9) but surgery, alone or in association with interventional radiology, still plays a major role in the management of severe liver injuries (grade IV and V according to the American Association for the Surgery of Trauma Organ Injury Score) (10), which remains extremely challenging even in experienced hands (11, 12). The main causes of death in these patients are exsanguinating hemorrhage and liver failure leading to multiorgan failure (13). Both these conditions, in principle, can be treated by a timely liver transplantation (LT).

Nevertheless, severe hepatic trauma is a peculiar albeit rare indication for orthotopic LT. LT has been most frequently performed for an uncontrollable hemorrhage requiring a total hepatectomy, or for an acute liver failure (ALF) developing after the first treatment.

Although salvage LT for hepatic trauma represents a well-established practice in all major liver transplant centers, a comprehensive literature review analyzing the different scenarios in which LT becomes the last possible therapeutic option after hepatic trauma has not been carried out so far. Furthermore, the short and long-term results of this practice have not been thoroughly assessed.

In this article we report four more cases of patients who underwent LT at our institution following a severe hepatic trauma; we focused our case reports on the initial trauma management and on how LT eventually resulted as the only viable therapeutic solution. Afterwards, based on our experience and on an accurate review of the literature, we depict the clinical scenarios in which a liver injury can eventually lead to LT and assess the outcomes of this practice. Finally, we highlight some specific factors linked to the indication for LT in these extreme situations.

CASE REPORTS

CASE 1

In June 2002 a 15-year-old female suffered a grade IV right liver injury as a consequence of a horse kick. She was first referred to a peripheral hospital, where she underwent a right hepatectomy. Her postoperative course was complicated by progressive liver failure, portal vein and inferior vena cava thrombosis, biliary leak-related sepsis, and acute renal failure (Figure 1). She was then transferred to our institution on postoperative day (POD) 14, where a relaparotomy was performed in order to drain the bile collections and to assess the hepatic vessels permeability. At reoperation, we observed a complete portal vein and hepatic artery thrombosis, the latter due to some surgical stitches from the previous operation, and a biliary leak coming from the left bile duct, which had been completely severed. The biliary leak was treated by placing a drain into the left bile duct stump, but the portal vein thrombosis invariably recurred after two successive attempts of surgical thrombectomy. Forty-eight hours later, she developed hepatic failure and coagulopathy and became hemodinamically unstable as a result of massive abdominal hemorrhage. The bleeding was only partially controlled by liver packing. She was then placed on the national waiting list for an urgent liver transplantation for acute liver failure. Despite massive fresh frozen plasma transfusions due to ongoing bleeding, her Model for End-stage Liver Disease (MELD) score was 23. Transplantation was carried out two days later (19 days after the trauma) with resection of the retro-hepatic inferior vena cava that was occluded by a thrombus. The post-transplant course was uneventful and she was discharged home on POD 18. More than 10 years after, she is alive and well with a normal hepatic function.

CASE 2

In March 2003 a 20-year-old female with a previous medical history of Thalassemia Major suffered an abdominal trauma from a motorway accident. She underwent an explorative laparotomy in a

peripheral hospital, where a 5-cm-deep parenchymal tear involving segment 8 was treated by hepatorrhaphy. Due to persistent bleeding and respiratory failure she was transferred to our department on POD 1, where a decision for a re-laparotomy was taken after a CT-scan revealed a large hematoma of the right liver lobe, a dilatation of the bile ducts of the right liver segments and an abundant peritoneal fluid collection. During the operation, we observed a huge hematoma of the right hepatic lobe and a large tear of the right hepatic vein. Hemostasis was achieved through a right hepatectomy. Postoperatively, the patient developed progressive liver failure, acidosis and a systemic inflammatory response syndrome. After having received the pathological report that revealed a severe hepatic iron overload and fibrosis, iron-chelation with desferoxamine was started but could not reverse the deterioration of the hepatic function, which was characterized by hyperbilirubinemia, ascites and encephalopathy. She was placed on the national list for an urgent LT with a MELD score of 32 and was transplanted six days after, i.e. fifteen days after the trauma. Unexpectedly, a previously unrecognized portal vein thrombosis was observed during transplantation. The postoperative course was uneventful except for a transitory early graft dysfunction. She is still alive and well 10 years after the trauma.

CASE 3

In September 2002 a 4-year-old female was rammed by a car and suffered a grade III blunt liver trauma. She was first referred to another institution where, since she was hemodinamically stable, a nonoperative management was initially attempted, in spite of the presence of abundant abdominal effusion. Due to persistent abdominal distension and fever, a percutaneous ultrasound-guided drainage of a bile collection was performed a month later. As the fistula persisted, an explorative laparoscopy was carried out showing a complex injury of the main bile ducts at the hilar plate. Two drains were placed in the hepatic hilar region with the hope of a spontaneous healing of the biliary fistula, but without any positive result. She was eventually treated by a double

hepaticojejunostomy. In the early postoperative period, she developed several episodes of *Enterococcus Faecium* cholangitis and a moderate liver function impairment. She was finally discharged home and was in good health for the following two years, until she presented a sudden upper gastrointestinal bleeding from large esophageal varices. Biliary ducts dilatation and portal vein thrombosis were ruled out by Doppler ultrasonography and CT-scan, which showed signs of portal hypertension and liver cirrhosis. A liver biopsy was consistent with secondary biliary cirrhosis. She subsequently developed thrombocytopenia and presented several episodes of cholangitis, with blood tests revealing a marked cholestasis. The indication for LT was based on the reiterate episodes of cholangitis in the setting of an established cirrhosis complicated by variceal bleeding, thrombocytopenia and growth delay. LT was carried out in February 2005 using a whole liver allograft. The postoperative course was uneventful and she was discharged home on POD 8. Eight years after LT she is well and attending school regularly.

CASE 4

In August 2006, during a motorcycle accident, a 22-year-old male suffered a grade IV liver injury of the posterior right liver segments associated with a grade V lesion of the right kidney. He was initially referred to a peripheral hospital where a right nephrectomy and a liver packing were performed. The packing was removed on POD 3, after which the patient presented a biliary leak exteriorized by the surgical drains, complicated by sepsis and renal failure. Due to the worsening of his conditions despite a broad-spectrum antibiotic therapy he was transferred to our department on POD 11. On arrival, he presented hypotension, tachycardia, fever and anuria. He underwent an explorative laparotomy during which an abundant bile collection was washed out. The liver was oedematous, brown-coloured, and presented a deep necrosis of the right posterolateral segments, the origin of the biliary leak, which was treated by a debridement right hepatectomy. In the postoperative period, we observed a mild but continuous bleeding from the drains and a

progressively worsening coagulopathy. Five days later he underwent a further laparotomy during which an abundant hemoperitoneum was observed and the abdomen was packed to secure hemostasis; at that moment, the liver remnant was severely swollen and cholestatic (Figure 2). As the hemorrhage was not completely controlled despite the peri-hepatic packing, this had to be re-positioned three times during three subsequent operations, but could not achieve a complete hemostasis because of the underlying coagulopathy. Finally, on POD 27, the patient became hemodinamically unstable as a result of the liver failure, so we decided to perform a total hepatectomy associated with a porto-caval shunt and place him on the national list for an emergent LT. An AB0-compatible donor was available the same day, limiting the duration of the anhepatic phase to 19 hours, during which he was treated with continuous veno-venous hemodialysis and infusion of calcium gluconate and glucose. After LT, the abdominal wall closure was achieved with a multistep approach using a Gore-Tex® dual-mesh and the vacuum-assisted closure device (VAC® Therapy). The postoperative course was complicated by an oropharingeal *Rizhomucor* infection, cytomegalovirus infection, an acute rejection, biliary and urinary tract infections by *Enterococcus* and *Pseudomonas Aeruginosa*. He was discharged home 85 days after LT but, six months later, he developed a pharyngeal B-cell lymphoma, which was treated with Rituximab and an immunosuppression switch from Tacrolimus to Everolimus. One year after LT, he presented several episodes of cholangitis in the setting of bilateral intra-hepatic ischemic-type biliary lesions. We considered retransplantation unfeasible due to the previous surgical and medical history, so he underwent several percutaneous dilatations. Recurrent cholangitis was complicated by pneumonias that led to the development of bronchiectasis colonized by multi-resistant *Pseudomonas Aeruginosa*. The latter episode of pneumonia was complicated by an untreatable respiratory failure leading to the patient's death in December 2010, 49 months after LT.

METHODS A systematic interrogation of the PubMed database was performed on December 1 2012 using the terms "hepatic trauma", "liver trauma" and "liver transplantation". Articles reporting recipients of a liver transplantation as a consequence of hepatic trauma were reviewed. References from each article were cross-checked to identify additional articles. Articles reporting cases of multivisceral transplantation, autotransplantation or with insufficient patients' data were excluded. According to Ringe et al. (14), a 2-stage procedure was defined as a LT procedure in which total hepatectomy is performed urgently when a liver allograft is not yet available and a temporary porto-caval shunt is performed to avoid splanchnic congestion. While waiting for an allograft, the patient remains anhepatic; when the two stages are completed, the anhepatic phase is followed by the implantation of the liver allograft. Cases in which the patient died before graft implantation were excluded. The data collected were patients demographics, type of injury (blunt or penetrating), Glasgow Coma Scale score, American Association for the Surgery of Trauma Liver Injury Score, indication for transplantation, timing of transplantation, number and type of previous operations, surgical technique, length of follow-up, patient and graft survival and causes of death or re-transplantation. A particular effort was made to gather information about factors possibly associated with the need for LT, like portal vein or hepatic artery thrombosis or occlusion, sepsis or major hepatic resection (i.e. resection of three or more Couinaud's segments). Early LTs were defined as those performed as a direct consequence of the injury or for an ALF arising after the initial treatment. All other cases were defined as late LTs. Postoperative mortality and graft loss were defined as those occurring within 30 days after LT or during the hospital stay. Data from the literature were pooled with those of the patients in our series. An analysis was performed comparing patients transplanted with a standard versus a 2-stage procedure and according to different indications. The groups were compared by two-sided Fisher's exact test or Mann-Whitney test, as appropriate.

RESULTS After excluding a case of auto-transplantation (15), six double reports (13, 14, 16-22) and a case for which no information about the management was provided (23), 30 patients were identified (17, 24-40) and pooled with the four patients in our series, for a total of 34 patients. Table 1 shows a synopsis of the present series. Table 2 summarizes the literature review, which has been split in two periods, 1987 – 2001 and 2002 - 2012. Median age of LT recipients was 24 years (range 4 – 68) and in 76% of the cases LT was performed after a blunt hepatic injury. The indication for LT was ALF and hemorrhage in 59% and 26% of patients, respectively. Concerning risk factors for acute liver failure, fourteen (41%) patients underwent a major hepatectomy during the first management of injury and 9 (26%) developed a sepsis thereafter; fifteen (44%) patients presented a thrombosis or an occlusion of the portal vein or the hepatic artery which was considered significant in determining the indication for LT. Median length of follow up was 6 months (range 1 – 156 months) and in only 15 (48%) cases long-term follow up (i.e. ≥ 12 months) was reported. In the whole series, postoperative patient and graft survival rate was 68% and 62%, respectively. For patients transplanted in the last decade, postoperative and long-term patient survival significantly improved to 84% and 79%, respectively. In 9 (26%) cases LT was performed as a 2-stage procedure. Overall, a 2-stage procedure was attempted in 13 patients, four of whom (31%) died before the second stage completion (i.e. graft implantation) and another four (31%) died in the early post-LT period, leading to a procedure-specific 38% survival rate. The most frequent cause of early death was sepsis. Seven patients required re-transplantation and one patient was transplanted three times (38). Death with a functioning graft and primary non function were the most frequent causes of graft loss. No significant difference between early and late LT was observed concerning the rates of postoperative patient survival (67% vs 71%, p = 1) and graft survival (59% vs 71%, p = 0.68). An analysis comparing standard versus 2-stage procedure was performed (Table 3): a 2-stage procedure was carried out most frequently in case of uncontrollable hemorrhage; no difference in patient survival was observed but patients undergoing a 2-stage procedure showed a trend towards a decreased graft survival (72% versus 33%; p = 0.057). Finally, patients were regrouped according

to the indication for LT (Table 4). Patients transplanted for an uncontrollable hemorrhage were more likely to undergo a 2-stage procedure; in this group postoperative graft survival was 27%.

DISCUSSION

As hemodynamic stability is the main factor determining the treatment, roughly 85% of liver trauma are managed nonoperatively (41). Unstable patients requiring an emergent laparotomy usually present more severe injuries that can be managed with a combination of surgical techniques including bimanual compression, Pringle maneuver, resectional debridement, hepatic resection and liver packing (1). Along with surgical procedures, angiography with transcatheter embolization is a mainstay in liver trauma management, either as a nonoperative hemostasis technique or as an adjunct hemostasis following damage control surgery (42, 43).

The most frequent cause of death after severe hepatic trauma is an exsanguinating hemorrhage from a disrupted liver or an acute liver failure consequence of the injury itself or to the operative procedures used to achieve hemostasis. Although both of these conditions are ideally treatable by LT, only 34 cases have been reported. In 1987, Esquivel et al. reported the first case of post-traumatic LT in a patient with a complex vascular and biliary lesion 66 days after a motor vehicle accident (29). In 1988 (44), Ringe et al. described the two-stage procedure, which was used in this context to treat an injury beyond repair by an expeditious total hepatectomy, in the hope of a readily available liver donor.

Subsequent reports have described a variety of clinical situations that can be grouped in three distinct clinical scenarios (Figure 3). The emergency indication for LT is represented by a massive hemorrhage arising from an injured liver that can be controlled only with a total hepatectomy. In this case, LT is carried out as a two-stage procedure. The longest anhepatic phase mentioned in the literature lasted 66 hours (45) and there are several reports in which an anhepatic period lasting more than 30 hours was tolerated (25, 27). However, it must be noted that survival rate of patients in whom a 2-stage procedure was attempted was 38% and that a reduced postoperative graft survival and a trend towards an increased postoperative mortality were observed in patients reaching the second step. In the second scenario the urgent indication for LT is ALF. As the clinical

picture deteriorates quickly, clinicians have the choice to list the patient for an urgent LT with the standard technique, or to opt for a two-stage procedure with the aim of improving the hemodynamic state through immediate removal of a toxic liver. As the efficacy of such a strategy is not clear (28), the choice to perform a two-stage procedure in this situation should be carefully evaluated on a case-by-case basis. Finally, the third setting refers to the patients with late post-traumatic sequelae, mostly complex vascular and biliary injuries that are not amenable to a surgical repair or lead to a secondary biliary cirrhosis, in which LT is carried out electively (30).

Although LT was frequently performed in desperate situations, early patient and graft survival rate was 68% and 62%, respectively, increasing to 84% in the last decade. This improvement can be explained by the fact that in comparison with the 1987 – 2001 period, in the last decade the indication for LT was less frequently an uncontrollable hemorrhage and consequently a 2-stage technique was more rarely used. As performing a total hepatectomy to fix an otherwise uncontrollable hemorrhage clearly represents an extreme clinical situation, it is not surprising that a trend towards a reduced postoperative patient and graft survival was observed in this setting (Table 4 and 5).

Our experience reflects the heterogeneity of the scenarios depicted above: patients reported in case 1 and 2 were transplanted for an ALF presenting after a major hepatic resection and favored in one case by sepsis and in the other by an underlying liver disease; case 3 is an example of LT carried out for the late consequences of a traumatic injury to the biliary ducts and of the repair procedure; in case 4 ALF was complicated by reiterate hemorrhage and hemodynamic instability, leading to the need for a 2-stage procedure.

Our results highlight some common features associated with the progression towards hepatic failure and the need for LT.

In the whole series, a major hepatic resection was performed prior to LT in 41% of the cases. Our patients who finally required LT for an ALF had undergone a major hepatic resection, one as the first treatment and two during a subsequent laparotomy. There is no doubt that there are situations

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in which performing a formal hepatic resection is unavoidable and this can yield good results in centers where an experienced hepatobiliary surgeon is readily available (23). Nevertheless, in the trauma setting, performing a major hepatic resection is associated with an increased mortality and morbidity (46, 47), and several Authors claim that it should be avoided as much as possible. For example, it could be argued that a liver packing followed by angiography would have probably been a more sound approach for our patient in case 1. Based on our results, it could be suggested that also in the "second look" operations viable liver parenchyma should be preserved as much as possible, because the hepatic functional reserve could be reduced as a result of hypovolemic shock, sepsis and previously unknown hepatic disease.

Another frequent finding in patients requiring LT for ALF was the presence of a portal vein or hepatic artery thrombosis, which was observed in 26% and 35% of the patients, respectively (Table 2). It is well known that an abrupt interruption of the hepatic arterial inflow can favor the progression towards irreversible ALF, even in a non-traumatic setting (48), and this should be taken into account in case of angiographic embolization, if the arterial supply to large portions of hepatic parenchyma is interrupted (42). Concerning portal vein thrombosis, this can be either one of the factors precipitating ALF, or one of its effects. Portal vein thrombosis can result from the vessel injury itself or from the surgical maneuvers to achieve hemostasis, or be favored by the pro-coagulating state which results from the activation of the inflammatory pathways after trauma. Alternatively, it can be caused by sinusoidal congestion that has been observed after major hepatic resection in association with liver failure (49) as it was probably the case for our patient in case 3. Finally, sepsis was documented in 26% of the cases. The presence of an inflammatory response in patients with ALF is a negative prognostic factor and, when it is associated with sepsis, the progression towards encephalopathy is more probable (50). The presence of a bile leak clearly represents a predisposing factor for an abdominal sepsis and ALF, as it has been observed after elective hepatic resections (51) and in the trauma setting (37).

The analysis of the factors linked to the progression towards ALF stresses once more the mainstay importance of the first surgical management and of a timely referral to a center where a whole surgical expertise and all therapeutic means, including LT, are available. Every effort should be made not to get to a desperate situation in which LT remains the only possible therapeutic mean.

In conclusion, despite the widespread ongoing problem of organ shortage, the indication for LT after hepatic trauma has to be considered sustainable, in the light of both the current good early survival (utilitarian approach) and the virtual 100% mortality of these patients without LT (survival benefit approach). Three different scenarios characterized by different degrees of urgency and surgical strategy are possible. As a trend towards a reduced patient and graft survival has been observed in patients transplanted for an uncontrollable hemorrhage undergoing a 2-stage procedure, the indication for LT in this setting should be carefully evaluated. Sepsis, hepatic vessels thrombosis and major hepatic resections may favor the progression towards liver failure. Early referral to a specialized center should aim primarily at avoiding the need for LT and the consequent possible complications and secondarily at allowing LT to be performed in a timely fashion when it remains the only therapeutic option.

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Liver Transplantation after Severe Hepatic Trauma: a Sustainable Practice.

A Single-Center Experience and Review of the Literature

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ABSTRACT

Severe hepatic trauma is a rare indication for liver transplantation (LT). We report our single-center experience of LT for hepatic trauma. Four new cases are discussed in the light of a literature review in order to depict the pathways leading from hepatic trauma to LT and to assess the outcomes of this practice. LT is generally indicated in case of uncontrollable hemorrhage, acute liver failure, or post-traumatic late sequelae. Hepatic vessels thrombosis, sepsis, major hepatic resections and a late referral are factors associated with the progression towards irreversible liver failure. ~~Considering all reported cases, early patient and graft survival rate reaches 68% and 62%, respectively, but in the last decade postoperative results have improved to 84% patient and graft survival rate.~~ Considering all reported cases, early patient and graft survival reached 68% and 62%, respectively, but in the last decade both have improved to 84%. LT after severe hepatic trauma is a sustainable practice considering the current good outcomes and the ineluctable death of these patients without LT.

Keywords: hemorrhage, liver failure, liver transplantation, sepsis, thrombosis

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FIGURE LEGENDS:

Figure 1. (Case 1) A. Contrast-enhanced computed tomography showing severe dilatation of intra-hepatic bile ducts of the liver remnant after right hepatectomy (arrow) and B. Portal vein thrombosis (arrow) and inferior vena cava dilatation (arrowhead).

Figure 2. (Case 4) Contrast-enhanced computed tomography showing the severely swollen and inhomogeneous liver remnant after right hepatectomy.

Figure 3. Clinical scenarios of LT for hepatic trauma

INTRODUCTION

~~The liver~~ Liver is the most frequently injured abdominal organ (1). The treatment of blunt hepatic trauma~~–~~ has significantly evolved over the last three decades with the introduction and wide acceptance of the concepts of nonoperative management, damage control surgery and the use of interventional radiology (2-6). Nowadays, nonoperative management is the preferred strategy in hemodinamically stable patients (6-9) but surgery, alone or in association with interventional radiology, still plays a major role in the management of severe liver injuries (grade IV and V according to the American Association for the Surgery of Trauma Organ Injury Score) (10)~~)~~, which remains extremely challenging even in experienced hands (11, 12).The main causes of death in these patients are exsanguinating hemorrhage and liver failure ~~evolving~~ leading to multiorgan failure (13).~~,~~ Both these conditions ~~that~~, in principle, can be treated by a timely liver transplantation (LT).

Nevertheless, severe hepatic trauma is a peculiar albeit rare indication for orthotopic LT. LT has been most frequently performed for an uncontrollable hemorrhage requiring a total hepatectomy, or for an acute liver failure (ALF) developing after the first treatment.

Although salvage LT for hepatic trauma represents a well-established practice in all major liver transplant centers, a comprehensive literature review analyzing the different scenarios in which LT becomes the last possible therapeutic option after hepatic trauma has not been carried out so far. Furthermore, the short and long-term results of this practice have not been thoroughly assessed.

In this article~~,~~ we report four more cases of patients who underwent LT at our institution following a severe hepatic trauma; we focused our case reports on the initial trauma management and on how LT eventually resulted as the only viable therapeutic solution. Afterwards, based on our experience and on an accurate review of the literature, we depict the clinical scenarios in which a liver injury can eventually lead to LT and assess the outcomes of this practice. Finally, we highlight some specific factors linked to the indication for LT in these extreme situations.

CASE REPORTS

CASE 1

In June 2002, a 15-year-old female suffered a grade IV right liver injury as a consequence of a horse kick. She was first referred to ~~another~~ a peripheral hospital, where she underwent a right hepatectomy. Her postoperative course was complicated by progressive liver failure, portal vein and inferior vena cava thrombosis, biliary leak-related sepsis, and acute renal failure (Figure 1). She was then transferred to our institution on postoperative day (POD) 14, where a relaparotomy was performed in order to drain the bile collections and to assess the hepatic vessels permeability. At reoperation, we observed a complete portal vein and hepatic artery thrombosis, the latter due to some surgical stitches from the previous operation, and a biliary leak coming from the left bile duct, which had been completely severed. ~~.~~ The biliary leak was treated by ~~draining exteriorly~~ placing a drain into the left bile duct stump, but the portal vein thrombosis invariably recurred after two successive attempts of surgical thrombectomy. Forty-eight hours ~~after~~ later, ~~as a consequence of~~ she developed hepatic failure and coagulopathy, and ~~she~~ became hemodinamically unstable ~~and developed~~ as a result of massive abdominal hemorrhage. The ~~B~~bleeding was only partially controlled by liver packing. She was then placed on the national waiting list for an urgent liver transplantation, ~~the indication being~~ for acute liver failure. Despite massive fresh frozen plasma transfusions due to ongoing bleeding, her Model for End-stage Liver Disease (MELD) score was 23. Transplantation was carried out two days later (19 days after the trauma) with resection of the retro-hepatic inferior vena cava that was occluded by a thrombus. The ~~P~~post-transplant course was uneventful and she was discharged home on POD 18. More than 10 years after, she is alive and well, with a normal hepatic function.

CASE 2

In March 2003, a 20-year-old female with a previous medical history significant forof Thalassemia Major suffered an abdominal trauma during from a motorway accident. She underwent an explorative laparotomy in a peripheral hospital, where a 5-cm-deep parenchymal tear involving segment 8 was treated by hepatorrhaphy. Due to ongoing persistent bleeding and respiratory failure she was transferred to our department on POD 1, where a decision for a re-laparotomy was taken after a CT-scan revealed a large hematoma of the right liver lobe, a dilatation of the bile ducts of the right liver segments, and an abundant peritoneal fluid collection. During the operation, we observed a huge hematoma of the right hepatic lobe and a large tear of the right hepatic vein. Hemostasis was achieved through a right hepatectomy. Postoperatively, the patient developed progressive liver failure, acidosis and a systemic inflammatory response syndrome. After having received the pathological report that revealed a severe hepatic iron overload and fibrosis, iron-chelation with desferoxamine was started but could not reverse the deterioration of the hepatic function, which was characterized by hyperbilirubinemia, ascites and encephalopathy. She was placed on the national list for an urgent LT with a MELD score of 32 and was transplanted six days afterlater, i.e. fifteen days after the trauma. Unexpectedly, a previously unrecognized portal vein thrombosis was observed during transplantation. The postoperative course was uneventful except for a transitory early graft dysfunction. She is currently still alive and well, 10 years after the trauma.

CASE 3

In September 2002, a 4-year-old female was rammed by a car and suffered a grade III blunt liver trauma. She was first referred to another institution where, since she was hemodinamically stable, a nonoperative management was initially attempted, in spite of the presence of abundant abdominal effusion. One month later, dDue to the persistence persistent of abdominal distension and fever, a percutaneous ultrasound-guided drainage of a bile collection was performed a month later. As the

fistula persisted, ~~Due to the persistence of the biliary leak,~~ an explorative laparoscopy was carried out showing a complex injury of the main bile ducts at the hilar plate. Two drains were placed in the hepatic hilar region with the hope of a spontaneous healing of the biliary fistula, but without any positive result. ~~As the biliary leak persisted, s~~She was eventually treated by a double hepaticojejunostomy. In the early postoperative period, she developed several episodes of *Enterococcus Faecium* cholangitis and a moderate liver function impairment. She was finally discharged home and was in good health for the following two years, until she presented a sudden upper gastrointestinal bleeding from large esophageal varices. Biliary ducts dilatation and portal vein thrombosis were ruled out by Doppler ultrasonography and CT-scan, which showed signs of portal hypertension and liver cirrhosis. A liver biopsy was consistent with secondary biliary cirrhosis. She subsequently developed thrombocytopenia and presented several episodes of cholangitis, with blood tests revealing a marked cholestasis. The indication for LT was based on the reiterate episodes of cholangitis in the setting of an established cirrhosis complicated by variceal bleeding, thrombocytopenia and growth delay. LT was carried out in February 2005 using a whole liver allograft. The postoperative course was uneventful and she was discharged home on POD 8. Eight years after LT, she is well and ~~regularly~~ attending school regularly.

CASE 4

In August 2006, during a motorcycle accident, a 22-year-old male suffered a grade IV liver injury of the posterior right liver segments associated with a grade V lesion of the right kidney. He was initially referred to a peripheral hospital where a right nephrectomy and a liver packing were performed. The packing was removed on POD 3, after which the patient presented a biliary leak exteriorized by the surgical drains, complicated by sepsis and renal failure. Due to the worsening of his conditions despite a broad-spectrum antibiotic therapy he was transferred to our department on POD 11. On arrival, he presented hypotension, tachycardia, fever and anuria. He underwent an

explorative laparotomy during which an abundant bile collection was washed out. The liver was

oedematous, brown-coloured, and presented a deep necrosis of the right posterolateral segments, the

origin of the biliary leak, which was treated by a debridement right hepatectomy. In the

postoperative period, we observed a mild but continuous bleeding from the drains and a

progressively worsening coagulopathy. Five days later he underwent a further laparotomy during

which an abundant hemoperitoneum was ~~evacuated~~ observed and the abdomen was packed to

secure hemostasis; at that moment, the liver remnant was severely swollen and cholestatic (Figure

2). As the hemorrhage was not completely controlled despite the peri-hepatic packing, this had to be

re-positioned three times during three subsequent operations, but could not achieve a complete

hemostasis because of the underlying coagulopathy. Finally, on POD 27, the patient became

hemodinamically unstable as a result of the liver failure, so we decided to perform a total

hepatectomy associated with a porto-caval shunt and place him on the national list for an emergent

LT. An AB0-compatible donor was available the same day, limiting the duration of the anhepatic

phase to 19 hours, during which he was treated with continuous veno-venous hemodialysis and

infusion of calcium gluconate and glucose. After LT, the abdominal wall closure was achieved with

a multistep approach using a Gore-Tex® dual-mesh and the vacuum-assisted closure device (VAC®

Therapy). The postoperative course was complicated by an oropharingeal *Rizhomucor* infection,

cytomegalovirus infection, an acute rejection, biliary and urinary tract infections by *Enterococcus*

and *Pseudomonas Aeruginosa*. He was discharged home 85 days after LT but, six months later, he

developed a pharyngeal B-cell lymphoma, which was treated with Rituximab and an

immunosuppression switch from Tacrolimus to Everolimus. One year after LT, he presented several

episodes of cholangitis in the setting of bilateral intra-hepatic ischemic-type biliary lesions. We

considered retransplantation unfeasible due to the previous surgical and medical history, so he

underwent several percutaneous dilatations. Recurrent cholangitis was complicated by pneumonias

that led to the development of bronchiectasis colonized by multi-resistant *Pseudomonas*

Aeruginosa. The ~~last~~ latter episode of pneumonia was complicated by an untreatable respiratory

failure leading to the patient's death in December 2010, 49 months after LT.

METHODS A systematic interrogation of the PubMed database was performed on December 1, 2012, using the terms "hepatic trauma", "liver trauma" and "liver transplantation". Articles reporting recipients of a liver transplantation as a consequence of hepatic trauma were reviewed. References from each article were cross-checked to identify additional articles. Articles reporting cases of multivisceral transplantation, autotransplantation or with insufficient patients' data were excluded. According to Ringe et al. (14), a 2-stage procedure was defined as a LT procedure in which total hepatectomy is performed urgently when a liver allograft is not yet available and a temporary porto-caval shunt is performed to avoid splanchnic congestion. While waiting for an allograft, the patient remains anhepatic; when the two stages are completed, the anhepatic phase is followed by the implantation of the liver allograft. Cases in which the patient died before graft implantation were excluded. The data collected data were patients demographics, type of injury (blunt or penetrating), Glasgow Coma Scale score, American Association for the Surgery of Trauma Liver Injury Score, indication for transplantation, timing of transplantation, number and type of previous operations, surgical technique, length of follow-up, patient and graft survival, and causes of death or re-transplantation. A particular effort was made to gather informations about factors possibly associated with the need for LT, like portal vein or hepatic artery thrombosis or occlusion, sepsis, or major hepatic resection (i.e. resection of three or more Couinaud's segments). Early LTs were defined as those performed as a direct consequence of the injury or for an ALF arising after the initial treatment. All other cases were defined as late LTs. Postoperative mortality and graft loss were defined as those occurring within 30 days after LT or during the same hospital stay. Data from the literature were pooled with those of the patients in our series. An analysis was performed comparing patients transplanted with a standard versus a 2-stage procedure and according to different indications. The Ggroups were compared by two-sided Fisher's exact test or Mann-Whitney test, as appropriate.

RESULTS After excluding a case of auto-transplantation (15), six double reports (13, 14, 16-22) and a case for which no information about the management was provided (23), 30 patients were identified (17, 24-40) and pooled with the four patients in our series, for a total of 34 patients. Table 1 shows a synopsis of the present series. Table 2 summarizes the literature review, which has been split in two periods, 1987 – 2001 and 2002 - 2012. Median age of LT recipients was 24 years (range 4 – 68) and in 76% of the cases LT was performed after a blunt hepatic injury. The indication for LT was ALF and hemorrhage in 59% and 26% of patients, respectively. Concerning risk factors for acute liver failure, fourteen (41%) patients underwent a major hepatectomy during the first management of injury and 9 (26%) developed a sepsis thereafter; fifteen (44%) patients presented a thrombosis or an occlusion of the portal vein or the hepatic artery which was considered significant in determining the indication for LT. Median length of follow up was 6 months (range 1 – 156 months) and in only 15 (48%) cases long-term follow up (i.e. ≥ 12 months) was reported. In the whole series, postoperative patient and graft survival rate was 68% and 62%, respectively. For~~In~~ patients transplanted in the last decade, postoperative and long-term patient survival significantly improved to 84% and 79%, respectively. In 9 (26%) cases LT was performed as a 2-stage procedure. Overall, a 2-stage procedure was attempted in 13 patients, four of whom (31%) died before the second stage completion (i.e. graft implantation) and another four (31%) died in the early post-LT period, leading to a procedure-specific 38% survival rate. The most frequent cause of early death was sepsis. Seven patients required re-transplantation and one patient was transplanted three times (38). Death with a functioning graft and primary non function were the most frequent causes of graft loss. No significant difference between early and late LT was observed concerning the rates of postoperative patient survival (67% vs 71%, p = 1) and graft survival (59% vs 71%, p = 0.68). An analysis comparing standard versus 2-stage procedure was performed (Table 3): a 2-stage procedure was carried out most frequently in case of uncontrollable hemorrhage; no difference in patient survival was observed but patients undergoing a 2-stage procedure showed a trend towards a decreased graft survival (72% versus 33%; p = 0.057). Finally, patients were regrouped according

to the indication for LT (Table 4). Patients transplanted for an uncontrollable hemorrhage were

more likely to undergo a 2-stage procedure; in this group postoperative graft survival was 27%.

DISCUSSION

As hemodynamic stability is the main factor determining the treatment, roughly 85% of liver trauma are managed nonoperatively (41). Unstable patients requiring an emergent laparotomy usually present more severe injuries, ~~which~~ that can be managed with a combination of surgical techniques including bimanual compression, Pringle maneuver, resectional debridement, hepatic resection and liver packing (1). Along with surgical procedures, angiography with transcatheter embolization is a mainstay in liver trauma management, either as a nonoperative hemostasis technique, or as an adjunct hemostasis following damage control surgery (42, 43).

The most frequent cause of death after severe hepatic trauma is an exsanguinating hemorrhage from a disrupted liver or an acute liver failure ~~consequent to~~consequence of the injury itself or to the operative procedures used to achieve hemostasis. Although both of these conditions are ideally treatable by LT, only 34 cases have been reported. In 1987, Esquivel et al. reported the first case of post-traumatic LT in a patient with a complex vascular and biliary lesion 66 days after a motor vehicle accident (29). In 1988 (44), Ringe et al. described the two-stage procedure, which was used in this context to treat an injury beyond repair by an expeditious total hepatectomy, in the hope of a readily available liver donor.

Subsequent reports have described a variety of clinical situations that can be grouped in three distinct clinical scenarios (Figure 3). The emergency indication for LT is represented by a massive hemorrhage arising from an injured liver that can be controlled only with a total hepatectomy. In this case, LT is carried out as a two-stage procedure. The longest anhepatic phase mentioned in the literature lasted 66 hours (45) and there are several reports in which an anhepatic period lasting more than 30 hours was tolerated (25, 27). However, ~~I~~it must be noted~~, however,~~ that survival rate of patients in whom a 2-stage procedure was attempted was 38% and that ~~, in patients reaching the second step,~~ a reduced postoperative graft survival and a trend toward_s_ an increased postoperative mortality were observed in patients reaching the second step. In the second scenario the urgent

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indication for LT is ALF. As the clinical picture deteriorates quickly, clinicians have the choice to list the patient for an urgent LT with the standard technique, or to opt for a two-stage procedure with the aim of improving the hemodynamic state through immediate removal of a toxic liver. As the efficacy of such a strategy is not clear (28), the choice to perform a two-stage procedure in this situation should be carefully evaluated on a case-by-case basis. Finally, the third setting refers to the patients with late post-traumatic sequelae, mostly complex vascular and biliary injuries that are not amenable to a surgical repair or lead to a secondary biliary cirrhosis, in which LT is carried out electively (30).

Although LT was frequently performed in desperate situations, early patient and graft survival rate was 68% and 62%, respectively, increasing to 84% in the last decade. This improvement can be explained by the fact that , compared toin comparison with the 1987 – 2001 period, in the last decade the indication for LT was less frequently an uncontrollable hemorrhage and, consequently, a 2-stage technique was more rarely used. As performing a total hepatectomy to fix an otherwise uncontrollable hemorrhage clearly represents an extreme clinical situation, it is not surprising that a trend towards a reduced postoperative patient and graft survival was observed in this setting (Table 4 and 5).

Our experience reflects the heterogeneity of the scenarios depicted above: patients reported in case 1 and 2 were transplanted for an ALF presenting after a major hepatic resection and favored in one case by sepsis and in the other by an underlying liver disease; case 3 is an example of LT carried out for the late consequences of a traumatic injury to the biliary ducts and of the repair procedure; in case 4 ALF was complicated by reiterate hemorrhage and hemodynamic instability, leading to the need for a 2-stage procedure.

Our results highlight some common features associated with the progression towards hepatic failure and the need for LT.

In the whole series, a major hepatic resection was performed prior to LT in 41% of the cases. Our patients who finally required LT for an ALF had undergone a major hepatic resection, one as the

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first treatment and two during a subsequent laparotomy. There is no doubt that there are situations in which performing a formal hepatic resection is unavoidable and this can yield good results in centers where an experienced hepatobiliary surgeon is readily available (23). Nevertheless, in the trauma setting, performing a major hepatic resection is associated with an increased mortality and morbidity (46, 47), and several Authors claim that it should be avoided as much as possible. For example, it could be argued that a liver packing followed by angiography would have probably been a more sound approach for our patient in case 1. Based on our results, it could be suggested that also in the "second look" operations viable liver parenchyma should be preserved as much as possible, because the hepatic functional reserve could be reduced as a result of hypovolemic shock, sepsis and previously unknown hepatic disease.

Another frequent finding in patients requiring LT for ALF was the presence of a portal vein or hepatic artery thrombosis, which was observed in 26% and 35% of the patients, respectively (Table 2). It is well known that an abrupt interruption of the hepatic arterial inflow can favor the progression towards irreversible ALF, even in a non-traumatic setting (48), and this should be taken into account in case of angiographic embolization, if the arterial supply to large portions of hepatic parenchyma is interrupted (42). Concerning portal vein thrombosis, this can be either one of the factors precipitating ALF, or one of its effects. Portal vein thrombosis can result from the vessel injury itself or from the surgical maneuvers to achieve hemostasis, or be favored by the pro-coagulating state which results from the activation of the inflammatory pathways after trauma. Alternatively, it can be caused by sinusoidal congestion that has been observed after major hepatic resection in association with liver failure (49), as it was probably the case for our patient in case 3. Finally, sepsis was documented in 26% of the cases. The presence of an inflammatory response in patients with ALF is a negative prognostic factor and, when it is associated with sepsis, the progression towards encephalopathy is more probable (50). The presence of a bile leak clearly represents a predisposing factor for an abdominal sepsis and ALF, as it has been observed after elective hepatic resections (51) and in the trauma setting (37).

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(46, 47)The analysis of the factors linked to the progression towards ALF stresses once more the mainstay importance of the first surgical management and of a timely referral to a center where a whole surgical expertise and all therapeutic means, including LT, are available. Every effort should be made not to get in to a desperate situation in which LT remains the only possible therapeutic mean.

In conclusion, despite the widespread ongoing problem of organ shortage, the indication for LT after hepatic trauma has to be considered sustainable, in the light of both the current good early survival (utilitarian approach) and the virtual 100% mortality of these patients without LT (survival benefit approach). Three different scenarios characterized by different degrees of urgency and surgical strategy are possible, characterized by different degrees of urgency and surgical strategy. As a trend towards a reduced patient and graft survival has been observed in patients transplanted for an uncontrollable hemorrhage undergoing a 2-stage procedure, the indication for LT in this setting should be carefully evaluated. Sepsis, hepatic vessels thrombosis and major hepatic resections may favor the progression towards liver failure. Early referral to a specialized center should aim primarily at avoiding the need for LT and the consequent possible complications, and secondarily at allowing LT to be performed in a timely fashion when it remains the only therapeutic option.

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Table 1. Synopsis of the present series

Pt	Mechanism of injury	Grade	First treatment	Complications	Secondary treatment	Evolution	Indication for LT	Interval from trauma to LT	Surgical technique	IS	Length of follow-up (years)	Status
1	Horse kick	IV	Right hepatectomy	Biliary leak, sepsis, hepatic artery injury; portal vein and IVC thrombosis, ARF	Portal vein thrombectomy, external biliary drainage	Acute liver failure, hemorrhage requiring repacking	ALF	19 days	1-stage	Tac, steroids	10.5	Alive
2	Motorway accident	III	Hepatorrhaphy	Hemorrhage, ARF, respiratory failure	Right hepatectomy	Acute liver failure, portal vein thrombosis	ALF	15 days	1-stage	CyA, AZA, steroids	10	Alive
3	Motorway accident	III	Nonoperative management	Biliary leak, sepsis	Laparoscopic drainage, hepatico - jejunostomy	Recurrent cholangitis; secondary biliary cirrhosis	Secondary biliary cirrhosis	28 months	1-stage	Tac, steroids	8	Alive
4	Motorcycle accident	IV	Liver packing	Biliary leak, sepsis	Right hepatectomy	Acute liver failure, hemorrhage requiring repacking	ALF	27 days	2-stage	Tac, steroids	4	Dead

Abbreviations: Pt, patient; LT, liver transplantation; IS, immunosuppression; IVC, inferior vena cava; ALF, acute liver failure; ARF, acute renal failure; Tac, tacrolimus; CyA, cyclosporine A, AZA, azathioprine

Table 2. Liver Transplantation after Hepatic Trauma

	Overall n = 34	1987 – 2001 n = 15	2002 – 2012 n = 19	p
Age (years)	24 (4-68)	21.5 (6 – 43)	26 (4 – 68)	ns
Sex				0.019
Male	17 (50%)	8 (53%)	6 (32%)	
Female	14 (41%)	4 (27%)	13 (68%)	
Not specified	3 (9%)	3 (20%)	0	
AAST grade				ns
III	4 (12%)	1 (7%)	3 (16%)	
IV	12 (35%)	3 (20%)	9 (47%)	
V	14 (41%)	7 (47%%)	7 (39%)	
VI	1 (3%)	1 (7%)	0	
Not specified	3 (9%)	3 (20%)	0	
Mechanism of injury				ns
Blunt	26 (76%)	10 (67%)	16 (84%)	
Penetrating	5 (15%)	2 (13%)	3 (16%)	
Not specified	3 (9%)	3 (20%)	0	
Indication				0.007
Acute Liver Failure	20 (59%)	5 (33%)	15 (79%)	
Hemorrhage	9 (26%)	7 (47%)	2 (11%)	
Biliary fistula	2 (6%)	2 (13%)	0	
Secondary biliary cirrhosis	2 (6%)	1 (7%)	1 (5%)	
Liver gangrene	1 (3%)	0	1 (5%)	
Timing				ns
Early	27 (79%)	10 (67%)	17 (89%)	
Late	7 (21%)	5 (33%)	2 (11%)	
Number of previous operation	2 (0 – 8)	2 (0 – 4)	2 (1 – 8)	ns
Packing	20 (59%)	8 (53%)	12 (63%)	ns
Major hepatic resection	14 (41%)	4 (27%)	10 (53%)	ns
Angiographic embolization	6 (18%)	2 (13%)	4 (21%)	ns
Portal vein occlusion	8 (26%)	5 (33%)	3 (16%)	ns
Hepatic artery occlusion	12 (35%)	6 (40%)	6 (32%)	ns
Sepsis	9 (26%)	3 (20%)	6 (32%)	ns
Technique				0.025
1-stage	25 (74%)	8 (53%)	17 (89%)	
2-stage	9 (26%)	7 (47%)	2 (11%)	
Length of follow up (months)*	6 (1 – 156)	1 (1 – 67)	36 (1 – 156)	0.006
Follow up ≥ 12 months*	15 (48%)	2 (17%)	13 (68%)	0.009
Postoperative patient survival	23 (68%)	7 (47%)	16 (84%)	0.03
Postoperative graft survival	21 (62%)	5 (33%)	16 (84%)	< 0.01
Overall patient survival	22 (65%)	7 (47%)	15 (79%)	0.07
Overall graft survival	17 (50%)	4 (27%)	13 (68%)	0.04
Re-transplantation	8 (24%)	5 (33%)	3 (16%)	ns
Cause of death				ns
Sepsis	5 (15%)	3 (20%)	2 (11%)	
Pneumonia	2 (6%)	1 (7%)	1 (5%)	
Bowel ischemia	1 (3%)	1 (7%)	0	
CMV infection	1 (3%)	1 (7%)	0	
Cerebral edema	1 (3%)	0	1 (5%)	
Multi-organ failure	1 (3%)	1 (7%)	0	
Not specified	1 (3%)	1 (7%)	0	
Cause of graft loss				ns
Death with functioning graft	9 (26%)	6 (40%)	3 (16%)	
Primary non function	5 (15%)	4 (27%)	1 (5%)	
Chronic rejection	1 (3%)	0	1 (5%)	
Hepatic artery thrombosis	1 (3%)	1 (7%)	0	
Ischemic-type biliary lesions	1 (3%)	0	1 (5%)	

Data are expressed as number (prevalence) or median (range). Length of follow up was not available in three cases (*). Abbreviations: AAST, American Association for the Surgery of Trauma; CMV, cytomegalovirus. Data in the two periods are compared with Fisher's exact or Mann-Whitney test, as appropriate.

Table 3. 1-stage versus 2-stage procedure

	1-stage (n = 25) N (%)	2-stage (n = 9) N (%)	p
Indication			0.036
Acute Liver Failure	17 (68%)	3 (33%)	
Hemorrhage	3 (12%)	6 (67%)	
Biliary fistula	2 (8%)	0	
Secondary biliary cirrhosis	2 (8%)	0	
Liver gangrene	1 (4%)	0	
Timing			ns
Early	19 (76%)	8 (89%)	
Late	6 (24%)	1 (11%)	
Postoperative patient survival	18 (72%)	5 (56%)	ns
Postoperative graft survival	18 (72%)	3 (33%)	0.057

Data are compared with Fisher's exact test.

Table 4. Surgical technique and outcome according to indication for LT

	ALF (n = 20) N (%)	Hemorrhage (n = 9) N (%)	Other (n = 5) N (%)	p*
Surgical technique				0.008
1-stage	17 (85%)	3 (33%)	5 (100%)	
2-stage	3 (15%)	6 (76%)	0	
Postoperative outcome				
Patient survival	15 (75%)	4 (44%)	4 (80%)	0.27
Graft survival	15 (75%)	2 (22%)	4 (80%)	0.019

(*) Two-sided Fisher exact test. Abbreviations: LT, Liver Transplantation; ALF, Acute Liver Failure.
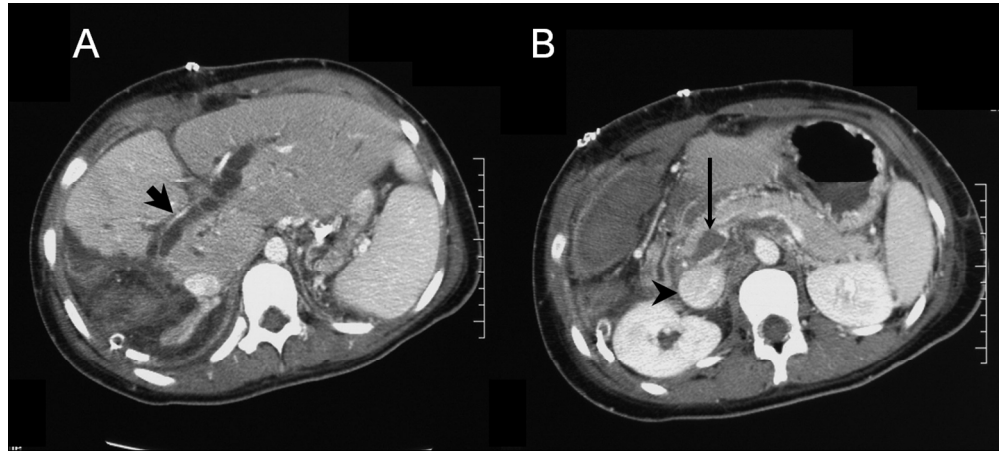
Figure 1. (Case 1) A. Contrast-enhanced computed tomography showing severe dilatation of intra-hepatic bile ducts of the liver remnant after right hepatectomy (arrow) and B. Portal vein thrombosis (arrow) and inferior vena cava dilatation (arrowhead).
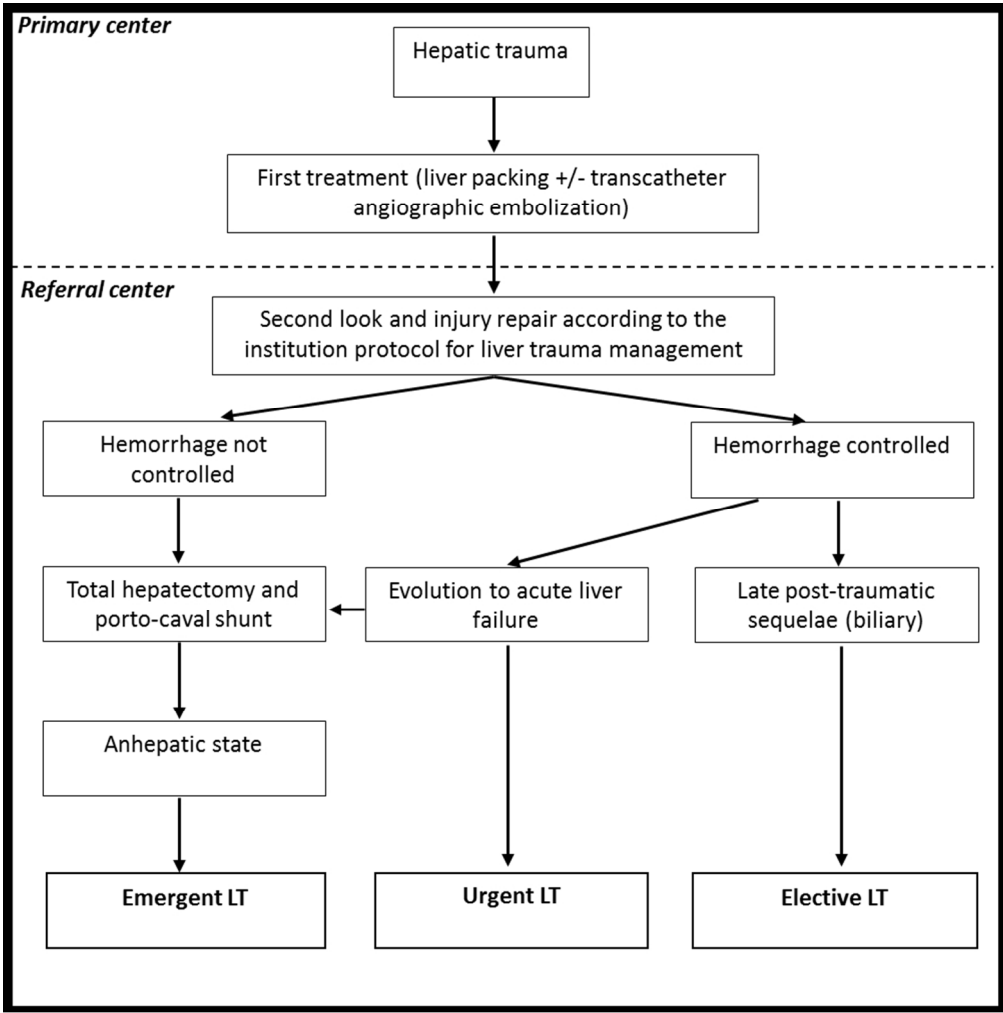249x111mm (150 x 150 DPI)

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Figure 2. (Case 4) Contrast-enhanced computed tomography showing the severely swollen and inhomogeneous liver remnant after right hepatectomy.
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