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Rescue liver transplantation for post-hepatectomy liver failure- single center retrospective analysis

Łukasz Masior[1*], Maciej Krasnodębski[1], Piotr Smoter[1], Marcin Morawski[1], Konrad Kobryń[1], Wacław Hołówko[1], Wojciech Figiel[1], Marek Krawczyk[1], Tadeusz Wróblewski[1] and Michał Grąt[1]

Abstract

Introduction Liver transplantation (LT) is a well-established method applied for the treatment of various liver diseases, including primary and secondary malignancies, as well as acute liver failure triggered by different mechanisms. In turn, liver failure (PHLF) is the most severe complication observed after liver resection (LR). PHLF is an extremely rare indication for LT. The aim of the present study was to assess the results of LT in patients with PHLF.

Methods Relevant cases were extracted from the prospectively collected database of all LTs performed in our center. All clinical variables, details of the perioperative course of each patient and long-term follow-up data were thoroughly assessed.

Results Between January 2000 and August 2023, 2703 LTs were carried out. Among them, six patients underwent LT for PHLF, which accounted for 0.2% of all patients. The median age of the patients was 38 years (range 24–66 years). All patients underwent major liver resection before listing for LT. The 90-day mortality after LT was 66.7% (4 out of 6 patients), and all patients experienced complications in the posttransplant course. One patient required early retransplantation due to primary non-function (PNF). The last two transplanted patients are alive at 7 years and 12 months after LT, respectively.

Conclusions In an unselected population of patients with PHLF, LT is a very morbid procedure associated with high mortality but should be considered the only life-saving option in this group.

Keywords Liver failure, Rescue liver transplantation, Liver resection, Complications, Outcomes

*Correspondence:
Łukasz Masior
lukasz.masior@wum.edu.pl
[1]Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Banacha Street 1A, Warsaw 02-097, Poland

Introduction

Currently, resection is a standard treatment for various malignant and rarely nonmalignant liver tumors. Due to continuous progress in surgical techniques as well as significant improvements in perioperative care, even major resections can be performed safely, especially when carried out in experienced centers [1, 2]. However, major LR is still a very demanding procedure with benchmark values for severe complications, 90-day mortality and posthepatectomy liver failure (PHLF) reaching ≤ 45.5%, ≤ 5.7% and ≤ 10.2%, respectively [1]. PHLF is a major cause of postoperative mortality after hepatectomy. Grade C PHLF based on the International Study Group of Liver Surgery (ISGLS) definition is associated with a mortality as high as 50% [3]. The risk of clinically relevant liver failure is mostly related to the extent of resection; however, PHLF may complicate even minor resections. Based on the National Surgical Quality Improvement Program (NSQIP) database comprising more than 7000 patients, PHLF after minor resection (less than 3 segments) was diagnosed after 2.7% of the procedures. However, in patients with diseased livers (cirrhosis/steatosis), the risk was elevated to more than 5% [4]. Grade C PHLF requires prompt diagnosis and obligatory treatment in the ICU (intensive care unit (ICU). However, in patients who experience deterioration, salvage liver transplantation becomes only a potentially life-saving treatment. Nevertheless, the application of this strategy raises some ethical concerns, as patients undergoing liver resection for malignancy are often not transplant candidates from an oncological standpoint [5]. Thus, PHLF is an extremely rare indication for LT, and data in the literature are scarce. Herein, we present our own experience with LT in patients with PHLF.

Materials and methods

Patient`s population

This retrospective cohort study included all LTs performed from January 2000 to August 2023. During the study period, 2703 LTs were performed in the Department of General, Transplant and Liver Surgery at the Medical University of Warsaw. Among those, 6 were carried out due to PHLF (0.2%). The study protocol was approved by the Ethics Committee of the Medical University of Warsaw. Due to the retrospective nature of the study, informed consent was not needed.

Data collection

All clinical variables were extracted from the prospectively collected database, which comprises all consecutive LRs and LTs performed at our center.

Treatment strategy

Major LR was defined as the removal of 3 or more segments. Liver volumetry was calculated in cases of planned hemihepatectomies or more extended resections, especially in patients with underlying liver damage; however, this approach was not universally applied during the study period. Liver augmentation strategies were applied when the predicted FLR (future liver remnant) was ≤ 30% and ≤ 40% for healthy and cirrhotic livers, respectively. Portal vein embolization (PVE) was the preferred method for inducing liver growth. The transection method and application of the Pringle manoeuvre were left to the discretion of the operating surgeon. The technique of transplantation and the regimens applied for immunosuppressive treatment were described previously [6]. PHLF is an extremely rare indication for LT, and no formal guidelines exist to support the decision-making process; thus, all patients were analysed individually, and a final decision was made after thorough discussion during multidisciplinary meetings. Two definitions were used for the assessment of the kinetics of certain laboratory values to determine the cause of progressive liver failure. The "50–50" definition based on the seminal study of Balzan et al. was used before 2011 [7], and the ISGLS definition was subsequently applied. The clinical condition of the potential recipient, therapeutic options and prognosis without LT, surgical risk of the procedure, oncological status and ethical issues were taken into consideration to optimize patient outcomes and minimize the impact on the elective waiting list. All LTs were performed by experienced liver transplant surgeons. Every organ was procured from the DBD (donation after brain death) donor. LT with veno-venous bypass was applied in all but one patient, in whom the piggy-back technique with a temporary porto-caval shunt was used. Machine perfusion was not used during the study period.

Statistical analysis

Qualitative variables are presented as numbers and percentages, while quantitative variables are presented as medians and ranges. The primary outcome measures were 5-year survival and 90-day postoperative mortality. Long-term survival was defined as survival beyond 90 days after surgery. Overall survival was calculated from the date of transplantation until patient death, irrespective of cause, and censored at 5 years posttransplantation or the last follow-up visit. Due to the small sample size, regression analysis could not be conducted to determine specific risk factors. The statistical analyses were performed with STATISTICA version 13.3 (TIBCO Software, Inc., Palo Alto, CA, USA).

Table 1 Characteristics of the study cohort

	Median (range) lub *n* (%)
Recipient age (years)	38 (24–66)
Recipient sex (male)	4 (66.7%)
BMI	24.4 (20.1–34.2)
Major liver resection	6 (100%)
Preoperative chemotherapy	1 (16.7%)
TACE before resection*	1 (16.7%)
PVE before resection*	1 (16.7%)
Time between resection and LT (days)	2.5 (1–58)
Technique of LT (classic)	6 (100%)
Retransplantation	1 (16.7%)
AB0 non-compatible LT	2 (33.3%)
Veno-venous by-pass	5 (83.3%)
CIT (minutes)	420 (310–600)
PRBC transfusion during LT	8 (7–18)
FFP transfusion during LT	8 (5–15)
MELD score before LT	25.6 (21-31.7)

Data are presented as median (range) or n (%) TACE- transarterial chemoembolisation, PVE- portal vein embolization, CIT- cold ischemic time, PRBC- packed red blood cells, FFP- fresh frozen plasma, MELD- model for end-stage liver disease, *- TACE and PVE were both applied in one patient

Results

The analysed group consisted of 6 patients, including 2 females (33.3%). Major LR was undertaken in every patient, and 2 of them had simultaneous portal vein reconstruction (33.3%). In all but one patient who underwent massive liver trauma, liver or biliary tumors were indications for hepatectomy. One patient with hepatocellular carcinoma (HCC) underwent transarterial chemoembolization (TACE) and subsequent PVE before LR. The median elapsed time between LR and LT was 2.5 days (range 1–58 days). The median model for end-stage liver disease (MELD) score before LT was 25.6 (range 21-31.7). The detailed characteristics of the study cohort are presented in Table 1. Two patients survived beyond the 90th day after LT, translating into 90-day mortality as high as 66.7% (4 out of 6 patients). One patient who underwent transplantation in November 2016 is alive and disease free for more thn 7 years. The last transplanted patient who underwent LT and early retransplantation in December 2022 is alive and cancer free. Below, we present a granular description of our cohort of individuals who underwent transplantation due to PHLF. Details regarding the perioperative course and relevant complications are summarized in Table 2.

Patient 1

A 31-year-old female patient underwent extended right hemihepatectomy with bilioenteric anastomosis due to colorectal liver metastases. The postoperative course was complicated by the development of left portal vein thrombosis and IVC stenosis. Portal vein thrombosis was related to IVC narrowing and obstruction of the outflow

Table 2 Clinical course of patients who underwent rescue LT for PHLF

Pt	Age (years)	Indication for LR	Time to LT (days)	Year of LT	Postresection complications	Post-LT complications	Alive	Oncologic status (recurrence)
1	31	CRC mets	2	2008	1.Left PV thrombosis and IVC stenosis 2.PHLF	1.Intraabdominal bleeding 2.Biliary Fistula 3. MOF 4.Died on POD 72	No	
2	61	CRC mets	4	2013	1.PV thrombosis 2.Liver necrosis 3.PHLF	1.Died directly after LT	No	
3	44	HCC	2	2013	1.Bleeding, relaparotomy and packing 2.PHLF	1.Myocardial infarction 2.Septic shock and MOF 3.Died on POD 12	No	
4	24	Liver trauma	3	2015	1.PHLF	1.MOF 2.Died on POD 2	No	
5	55	Hilar tumor- inflammatory	58	2016	1.Bleeding, relaparotomy 2.Biliary fistula 3.Wound dehiscence 4.Progressive hiperbilirubinemia 5. PHLF	1. Late stenosis of the bilio-enteric anastomosis with subsequent redo anastomosis 2 years after LT	Yes	No
6	32	Hilar tumor- cancer	1	2022	1.PV thrombosis 2.PHLF	1.PNF and retransplantation on POD 2 2. Biliary fistula 3. Stenosis of the cavo-caval anastomosis with stent placement	Yes	No

LT- liver transplantation, PHLF- posthepatectomy liver failure, CRC- colorectal cancer, HCC- hepatocellular carcinoma, PV- portal vein, IVC- inferior vena cava, MOF- multiorgan failure, POD- postoperative day, SFSS- small for size syndrome, PNF- primary nonfunction

of the left hepatic vein. On postoperative day (POD) 1, she underwent relaparotomy with IVC revision and portal thrombectomy. Due to progressive PHLF on POD 2, the patient underwent AB0 noncompatible LT with the liver recovered from a 50-year-old female DBD donor after traumatic brain injury. Apart from AB0 noncompatibility, no other donor-related risk factors were revealed. During the posttransplant period, she underwent reoperation on POD 4 due to intraabdominal bleeding. A further course was complicated by the development of biliary fistula followed by septic complications. Finally, she experienced multiorgan failure (MOF) and ultimately died on POD 72.

Patient 2

A 61-year-old male patient underwent major LR due to colorectal liver metastases. In addition to bulky liver involvement, portal vein resection and reconstruction were performed to achieve margin clearance. Massive portal vein thrombosis complicated the postoperative course. As a consequence, liver necrosis and subsequent PHLF led to LT on POD 4 using organ procured from 23-year-old male DBD donors after traumatic brain injury. No graft-related risk factors were found. The patient died directly after LT, 30 min after being transferred to the ICU due to intractable MOF.

Patient 3

A 44-year-old male patient was diagnosed with advanced HCC that developed in a noncirrhotic liver. Before LR, two TACE sessions were carried out as downstaging procedures. Subsequently, an unsuccessful attempt to LR was undertaken, and portal vein ligation was performed at this stage to increase the volume of the FLR. In the next step, PVE was applied. After confirming the satisfactory effect of liver augmentation, the patient ultimately underwent a definitive operation. Right hemihepatectomy extended to segment 4 was performed. During the postoperative course, intraabdominal bleeding was diagnosed, which necessitated relaparotomy and packing. Based on the clinical picture of progressive PHLF, the patient was referred for LT and transplantation was carried out on POD 2. An AB0 noncompatible piggy-back LT was performed with a temporary porto-caval shunt. A graft was procured from a 58-year-old male DBD donor after subarachnoid hemorrhage (SAH). Apart from AB0 noncompatibility, no other donor-related risk factors were revealed. The posttransplant period was complicated by myocardial infarction and acute kidney injury (AKI). Subsequently, the patient developed MOF related to septic shock with a fatal outcome on POD 12.

Patient 4

A 24-year-old male patient after blunt abdominal trauma was transferred to our center after urgent laparotomy and liver packing. After hemodynamic stabilization, repacking and right hemihepatectomy were employed. The patient developed PHLF postoperatively, and due to failure of conservative management, he underwent LT on POD 3. The organ we used was obtained from a 31-year-old male DBD donor after SAH. The donor had morbid obesity; thus, the liver was steatotic. Graft steatosis was suspected after analysis of the donor's radiological studies. This was further confirmed during organ procurement based on the macroscopic appearance and liver consistency. The liver was accepted following the clinical assessment and analysis of the laboratory tests; thus, biopsy was not used. Despite technically successful LT, the patient`s clinical condition deteriorated, leading to death 2 days after surgery with the clinical picture of MOF.

Patient 5

A 55-year-old male patient underwent right hemihepatectomy with bile duct resection due to suspicion of a hilar tumor. The postoperative course was complicated by intraabdominal bleeding and relaparotomy. Additionally, biliary fistula and wound dehiscence occurred during the following days, both of which were managed conservatively. Apart from the severe surgical complications, liver function deteriorated, with predominant progressive hiperbilirubienia reaching the level as high as 34 mg/dl. Ultimately, the patient was transplanted on POD 58. The liver was recovered from a 53-year-old female DBD donor after SAH. Apart from the 2 h of profound hypotension before procurement, no other donor-related risk factors were revealed. The patient recovered successfully from the posttransplant period. Final pathology revealed a benign (inflammatory) lesion in the biliary tree, and no cancer cells were found. One year later, stenosis of the hepaticojejunostomy was diagnosed, and both percutaneous and endoscopic procedures were employed with initial success. However, the recurrent nature of the stenosis and unsuccessful minimally invasive treatment led to open redo bilioenteric anastomosis two years after LT. Currently, the patient is alive with good liver function and no signs of biliary stenosis.

Patient 6

A 32-year-old female patient was referred to our center with a suspicion of hilar tumor. Before referral, biliary tree was stented due to jaundice. Endosocopic stenting was complicated by liver hematoma with subsequent laparotomy aimed at controlling bleeding from the liver capsule. After admission to our center, an extensive work-up was initiated, which ultimately confirmed the diagnosis

of a hilar tumor with portal vein invasion. The patient underwent extended right hemihepatectomy (segments 1+4–8) with bile duct resection and portal vein reconstruction. After the procedure, portal vein thrombosis with rapidly progressive PHLF was observed, and she was transplanted on POD 1. A graft was procured from a 63-year-old female DBD donor after SAH. A 2-week ICU stay and initially elevated liver enzymes were highlighted as graft-related risk factors. LT was further complicated by PNF followed by retransplantation 2 days later. Due to the highly controversial nature of this clinical setting, after thorough discussion, we decided to list the patients for retransplantation using organ which was discarded by all liver transplant centers in our country. The liver was obtained from a 54-year-old male with obesity and alcoholism whose liver enzymes and bilirubin concentration were initially markedly elevated (bilirubin concentration above 6 mg/dl). During retransplantation, synthetic mesh was implanted to close the abdomen and avoid liver compression secondary to the mismatch between the donor and recipient livers. The postoperative course was complicated by a biliary fistula and further by stenosis of the cavo-caval anastomosis, which led to stent placement into the inferior vena cava (IVC). The patient is cancer free over a year after the procedure.

Discussion

PHLF is the most serious complication after liver resection and is a single major driver of postoperative mortality even at the population-based level [8]. In addition to increased mortality, even Grade A PHLF translates into a greater number of complications, and in those with Grade B/C PHLF, major complications occur in almost 80% of patients [9]. Conservative treatment with typical organ support is the mainstay of therapy aimed at successful liver regeneration [10]. Despite some promising data regarding the application of MARS (molecular adsorbent recirculating system) in patients with PHLF, it cannot be recommended as a standard of treatment [11]. Thus, in progressive liver failure, LT is the only life-saving option [4, 10].

Herein, we present our group of 6 patients who underwent transplantation due to PHLF for more than 20 years. In our previous analysis of intraoperative injuries during 1005 liver procedures, liver failure, which ultimately led to death, was diagnosed in 7 patients (0.7%), which represents the pool of potential candidates for rescue LT [12]. Our results mirror the experiences of other centers that emphasize that PHLF remains an extremely rare indication for LT [5]. In our own material, this procedure accounted for just 0.2% of all LTs performed during the study period. However, contrary to the results of single-center analyses conducted by other centers and one systematic review that has been published thus far, our data highlight extremely high 90-day mortality, reaching more than 60%. First, due to the scarcity of data, fair comparisons of perioperative results are almost impossible. In the systematic review comprising 8 publications, half of them were case reports involving one patient in each study [11]. The largest cohort was published by Sparrelid et al. and included 10 patients from 5 liver transplant centers in Europe [5]. In their series, no 90-day mortality was noted, and 80% of patients were alive after a median follow-up of 49 months. However, the median time to decide whether to list patients for LT was 14 days, which might serve as an indirect sign against rapidly progressive PHLF. In our cohort, the median time to LT was 2.5 days, and the median MELD score at the time of listing was greater than 25. In addition, two patients underwent AB0 noncompatible procedures. The main reasons for receiving rescue LT were progressive deterioration of clinical status, biochemical signs of liver failure and ongoing MOF. All patients underwent major hepatectomy (hemihepatectomies or extended hemihepatectomies), and vascular resection was performed in two patients. We believe that in patients with small/marginal liver remnants and signs of progressive liver failure, especially when the portal vein is severely thrombosed, early LT is often the only curative option. However, in select groups of patients, surgical thrombectomy may be successful after liver resection complicated by portal vein thrombosis (PVT). In the study by Kuboki et al., PVT was diagnosed in more than 5% of right and extended right-sided resections. In stable patients, early thrombectomy (within 5 days of resection) seems to be a valuable option with a high success rate [13]. We attempted this approach in one patient (patient 1) but with unsatisfactory results, which led to LT rescue the day after procedure.

In our cohort, noncirrhotic patient (patient 3) underwent extended right hemihepatectomy, which is associated with the highest risk of PHLF because of the small FLR, and often, liver augmentation strategies are employed as a first step of treatment. Moreover, early bleeding necessitating relaparotomy and packing in patients with small/marginal FLRs increases the initial risk of PHLF. In particular, the volume of the FLR does not always correspond to the quality of the liver parenchyma. Taken together, these findings suggest that major liver resection even in noncirrhotic livers, especially when severe early complications occur, may still lead to potentially fatal PHLF.

These descriptions highlight extremely urgent clinical scenarios that led us to consider and apply LT as the only life-saving procedure with no real alternative solutions. Under such circumstances, not surprisingly, the median intraoperative transfusion volume of packed red blood cells (PRBCs) was 8 units. We previously published that MELD score and intraoperative transfusion are factors

contributing to worse outcomes in patients undergoing LT [14, 15]. Similarly, AB0 noncompatible LTs are a well-known factor that negatively influences the results of LTs [16].

Most patients in our study underwent LT with veno-venous by-pass. However, in metaanalysis conducted by Pratschke et al. porto-caval shunt during piggy-back LT was associated with reduced blood loss, less hepatic injury and better renal function [17]. Similarly, Rayar et al. confirmed benefits of temporary shunt, especially when ECD (Extended criteria donors) are implanted [18]. Thus, if possible caval preservation might lead to better perioperative outcomes.

It is worth mentioning that 14 years elapsed between the first and the last rescue LT carried out by our liver transplant program, and almost 2000 LTs were performed in the meantime. Thus, greater experience and significant changes in intra- and perioperative management would likely translate into better outcomes in the last two cases, despite the PNF and early retransplantation in the last patients. Moreover, our four unsuccessful attempts led us to modify our policy toward a more critical assessment of potential candidates. We believe that proper selection is a cornerstone of achieving satisfactory outcomes and is mirrored by the history of the two successful rescue LTs performed at our center. Although our results are worse than those of other small series published thus far, we think that our data granularly describe extremely challenging situations that liver transplant teams face in reality when managing unselected populations of patients with PHLF. Thus, we believe that providing real-life data, especially in such challenging cases, should be perceived as a strength of our analysis.

Another important finding that can be drawn from our study regards the applicability of the ISGLS score and other definitions of PHLF commonly used in clinical practice. Most of these methods use postoperative day 5 as a cut-off point at which PHLF can be diagnosed [3, 7]. Our results suggest that in extreme situations, when a prompt decision is crucial, judicious clinical assessment is of utmost importance. It plays a pivotal role, as intractable PHLF must be diagnosed early. Thus, we are able to avoid a situation in which patients are too sick to become LT candidates. This finding mirrors the experience shared by Otsuka et al. from the University of California Los Angeles (UCLA) (19). Their study also underlines the importance of early suspicion of irreversible PHLF based on the laboratory values assessed on POD 2. This, in turn, allows for prompt listing for LT before standard criteria 5 days after resection are ultimately fulfilled, as longer waiting times are often detrimental to otherwise critically ill patients.

The most striking issue regarding rescue LT addresses ethical aspects of the procedure. As the transplant community worldwide is struggling with organ shortages, it is natural that questions about the futility of the procedure arise. Currently, LT can be successfully offered as a standard treatment for HCC in patients with a background of cirrhosis. This approach provides significantly better long-term outcomes than resection [19]. This strategy was successfully adopted, which paved the way for the extension of the benchmark Milan criteria published by Mazzaferro [20]. LT performed based on modestly expanded criteria provides very good long-term results and has been described by various centers [21–23]. Similarly, unresectable metastases of neuroendocrine tumors can be regarded as a well-established indication for LT [24]. Moreover, LT is now efficiently offered to patients with hilar cancer based on treatment methods established in seminal studies published by the Mayo Clinic [25, 26]. Disruptive publications from Norway encouraged many centers to adopt LT for patients with unresectable colorectal liver metastases, and currently, many prospective trials aimed at standardizing eligibility criteria are ongoing [27–29]. Under very strict circumstances, even intrahepatic cholangiocarcinoma can now be considered an indication for transplantation [30]. Despite the rapid development of transplant oncology in recent years, major controversy surrounds the need for rescue LT because most of the considered patients undergo extensive liver resection for tumors, which are often beyond the currently accepted transplant criteria. Accordingly, inferior oncological results are described by most authors and explained mostly by the advanced tumor stage in treated populations [5, 31, 32]. In patients resected for otherwise transplantable disease, the decision about LT is less contentious. For those with greater tumor burdens, Sparrelid et al. suggested rapid pathological assessment before the ultimate decision about listing patients for LT to avoid futile transplantation in those with negative prognostic factors [5]. This approach seems to be a valuable strategy; however, with rapidly progressing PHLF, as was the case in our study, when the time between resection and LT was only 2.5 days, thorough specimen analysis is often not possible.

Due to the lack of unequivocal data that could guide the decision-making process, we believe that considerations about transplantation in patients with irreversible PHLF are still influenced by the general philosophy of the transplant center. We advocate a rather aggressive strategy, especially for younger patients, because the survival benefit is unquestionable, as highlighted by the study of Otsuka et al. In their cohort, the median survival of transplanted patients due to PHLF was greater than 40 months versus less than 2 months in nontransplanted patients [31]. Of course, case-by-case analysis during multidisciplinary meetings is always necessary to balance risk and benefits for the recipient. Concomitant impact

on the other patients from the waiting list should always be carefully assesed to avoid ethical concerns regarding organ allocation.

We and others have shown that rescue LT is an extremely rare indication for LT despite the large number of extensive liver resections, which are routinely performed in many liver centers across the globe. Apart from the technical agility of liver surgeons, this approach is a direct effect of excellent preoperative planning, including quantification of liver volumetry, functional assessment of the FLR and routine application of liver augmentation strategies [33, 34]. Hepatobiliary scintigraphy with mebrofenin is one of the most promising methods of functional assessment according to data published by Olthof et al. This technique shows its greatest potential, especially in patients undergoing the most complex resections due to biliary tumors. In a group with FLR>40% and liver function<8.5%/ min. based on the scintigraphy, PHLF occurred in 30% of patients compared to 6% among those with function above this threshold [35]. Indocyanine green retention test at 15 min (ICG-R15) is another well-known tool to predict PHLF. Study from China revealed that it is more accurate than MELD and Child-Pugh scores in predicting PHLF in patients with HCC undergoing liver resection [36]. Often extensive liver involvement by malignant or benign disease precludes one-stage radical resection. In such case two-stage hepatectomy (TSH) or ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) may be employed to increase FLR. Recent metaanalysis comparing TSH and ALPPS in patient with colorectal cancer metastases showed feasibility and efficacy of both methods with no differences in overall survival when performed in experienced centers. However, further research is needed to draw a more meaningful conlusions [37]. Similarly, ALPPS may be successfully performed in patients with infilitrative, non-malignant diseases e.g. alveoar echinococcosis as described by Akbulut et al. [38]

Despite the implementation of this armamentarium in everyday practice, major liver resection always poses an inherent risk of severe complications [1, 4]. Even living donors may encounter life-threatening complications including PHLF. Onur et al. analyzed their single- center experience of more than 1000 LDLT (Living donor liver transplantation). Severe complications in donors occurred in <3% cases including four PHLF which ultimately neccesitated decased donor LT. Authors emphasis the critical role of meticulous perioperative management and improvements observed with increasing experience in such complex procedures [39]. As mounting data confirming excellent results of LT in various malignant diseases are published every year, we believe that LT, as an ultimate onco-surgical strategy, might be considered useful for well-selected individuals more liberally instead of risky, extremely complex liver resections. However, in the future, less invasive oncologic therapy may change the paradigm of treatment. One of the potential targets is leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5), which is perceived to be a marker of cancer stem cells (CSCs). Lgr5 is crucial for cancer growth, proliferation and metastasis development [40]. Thus, modifying its activity seems to be a very interesting goal of anticancer therapy. Gong et al. presented their experimental study describing the application of dedicated antibody–drug conjugates (ADCs). Specific ADCs were developed by the combination of cytotoxic agents and anti-Lgr5 antibodies. The authors revealed that this strategy has high anticancer potential for various gastrointestinal cancers. Accordingly, further development of this very promising method is encouraged [41].

We noted in our study that the course of PHLF is unpredictable and that rescue LT even at experienced centers is associated with high mortality and morbidity, with oncologic outcomes significantly inferior to those of the selected LT candidates. Nonetheless, we are aware that this more aggressive oncological approach might be difficult to achieve in regions that are struggling with, e.g., inadequate numbers of donors. The donation rate in Poland is 11.76 donations per million inhabitants. In 2022, 435 new patients were registered as recipients, and 38 died (8.73%) while awaiting LT. Despite waiting-list mortality and relatively low donation activity in our country, we believe that, based on the current data, such a shift in oncological approach is beneficial for well-selected patients. On the other hand, the availability of a liver transplant program paves the way for advanced liver resections in patients who are not ideal transplant candidates and who are at high risk of resection and potential subsequent rescue liver transplantation. PHLF is a unique indication for LT, thus personalized approach is mandatory. As mentioned previously, our initial discouraging results led us to change our policy and we believe that meticoluos recipient assessment is of utmost importance. Marginal livers or organs that otherwise could be discarded should be used in this population. With rigorous selection process we are able to avoid any ethical concerns. What`s more, with such approach potential harm to the other recipients from the waiting list is diminished which should be prioritized.

The major limitations of our study are its retrospective nature and the very small sample size, which hamper any formal statistical analysis. Despite the small cohort, this population is still one of the largest groups published thus far, which clearly underlines the paucity of data in this field. On the other hand, we described real-life scenarios highlighting all pitfalls that can be experienced by

liver centers when dealing with irreversible PHLF managed by LT.

Conclusions

PHLF is an exceptional indication for LT. In an unselected cohort, high perioperative mortality and morbidity are linked; however, this approach is the only potentially curable strategy and should be considered in this group of patients.

Author contributions

Concept and design: Ł.M, M.G.Acquisition and analysis data: Ł.M, M.K, P.S, M.M, K.K, W.H, W.FCritical review: M.K, T.W, M.GDrafting of the manuscript: Ł.M. Supervision: M.GAll authors have read and approved the final manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Warsaw.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Patient informed consent was waived by the Ethics Committee of the Medical University of Warsaw (AKBE/290/2023) due to the retrospective nature of the study.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare no conflicts of interest.

Consent to publish

Not applicable.

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