Retrospective Cohort Study

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Vena cava replacement and major hepatectomy for liver tumors: international multicenter retrospective cohort study

Fabrizio Di Benedetto, MD, PhD, FACS[a,*], Paolo Magistri, MD, FACS[a], Francesca Marcon, MD, PhD, FEBS[b], Olivier Soubrane, MD, PhD[c], Felipe Pedreira Mello, MD[d], Joao Santos Coelho, MD[e], Andre Renaldo Fernandez, MS[f], Samuele Frassoni, MBS[k], Vincenzo Bagnardi, PhD[k], Ashish Singhal, MD[h], Fernando Rotellar, MD, PhD[i], Roberto Hernandez-Alejandro, MD[f], Ruslan Alikhanov, MD, PhD[j], Eduardo de Souza M Fernandes, MD[d,g], Francois Cauchy, MD[c], Paolo Muiesan, MD, FRCS, FEBS[b], Stefano Di Sandro, MD, PhD[a], Hugo Pinto Marques, MD, PhD[e]

Introduction: Involvement of the inferior vena cava (IVC) and hepatic veins has been considered a relative contraindication to hepatic resection for primary and metastatic liver tumors. However, patients affected by tumors extending to the IVC have limited therapeutic options and suffer worsening of quality of life due to IVC compression.

Methods: Cases of primary and metastatic liver tumors with vena cava infiltration from 10 international centers were collected (7 European, 1 US, 2 Brazilian, 1 Indian) were collected. Inclusion criteria for the study were major liver resection with concomitant vena cava replacement. Clinical data and short-term outcomes were analyzed.

Results: Thirty-six cases were finally included in the study. Median tumor max size was 98 mm (range: 25–250). A biliary reconstruction was necessary in 28% of cases, while a vascular reconstruction other than vena cava in 34% of cases. Median operative time was 462 min (range: 230–750), with 750 median ml of estimated blood loss and a median of one pRBC transfused intraoperatively (range: 0–27). Median ICU stay was 4 days (range: 1–30) with overall in-hospital stay of 15 days (range: 3–46), postoperative CCI score of 20.9 (range: 0–100), 12% incidence of PHLF grade B-C. Five patients died in a 90-days interval from surgery, one due to heart failure, one due to septic shock, and three due to multiorgan failure. With a median follow-up of 17 months (interquartile range: 11–37), the estimated 5 years overall survival was 48% (95% CI: 27–66%), and 5-year cumulative incidence of tumor recurrence was 55% (95% CI: 33–73%).

Conclusions: Major liver resections with vena cava replacement can be performed with satisfactory results in expert HPB centers. This surgical strategy represents a feasible alternative for otherwise unresectable lesions and is associated with favorable prognosis compared to nonoperative management, especially in patients affected by intrahepatic cholangiocarcinoma.

Keywords: CRLM, extended liver resection, HCC, iCCA, sarcoma, surgical oncology

[a]Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy, [b]HPB Surgery and Liver Transplant, Queen Elizabeth Hospital, Birmingham, UK, [c]Department of HPB and Liver Transplantation, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris and Université de Paris, Clichy, France, [d]Department of Surgery and Abdominal Organ Transplantation – Hospital Adventista Silvestre, Rio de Janeiro, Brazil, [e]Department of Surgery, Hepato-Biliary-Pancreatic and Transplantation Center, Curry Cabral Hospital, Lisbon, Portugal, [f]Department of Surgery, Division of Transplantation and Hepatobiliary Surgery, University of Rochester Medical Center, Rochester, New York, [g]Hepato-Pancreato-Biliary Unit and Transplant – DHR Health, McAllen, Texas, USA, [h]Advanced Institute of Liver and Biliary Sciences, Fortis Hospitals, Delhi, NCR, India, [i]Department of Surgery, HPB and Liver Transplantation Unit, University Clinic, Universidad de Navarra; Institute of Health Research of Navarra (IdisNA), Pamplona, Spain, [j]Department of Hepato-Pancreato-Biliary Surgery and Department of Transplantation, Moscow Clinical Scientific Center, Moscow, Russia and [k]Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy

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**Corresponding author. Address: Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit University Hospital of Modena "Policlinico" University of Modena and Reggio Emilia 41124, Modena, Italy. Tel.: +39 059 422 4740. E-mail: fabrizio.dibenedetto@unimore.it (F. Di. Benedetto).*

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Introduction

Involvement of the inferior vena cava (IVC) and hepatic veins (HV) have been considered relative or even absolute contraindications to hepatic resection for liver tumors, due to the difficulty to obtain a negative margin and the high rate of surgical complications[1]. Moreover, the high risk of recurrence even after a radical resection may discourage surgeons from adopting technically demanding procedures in this setting.

On the other hand, patients with tumors involving the IVC or HV have extremely limited options to obtain a curative treatment and may access only chemotherapy or interventional radiology, while survival without surgical treatment is typically less than 1 year[2]. The advantage of resection over other treatments in both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) is well established[3,4]. Therefore, some patients' characteristics such as good performance status and favorable biology of the tumor, indicating a partial or complete response to chemotherapy, may suggest the opportunity to pursue a surgical approach to obtain a radical resection, even in the presence of major vascular involvement.

Advanced surgical strategies like total vascular exclusion[5], veno-venous bypass[6] and ex vivo liver resection[7,8] increase the feasibility of a radical liver resection, with acceptable perioperative morbidity and mortality for both primary and metastatic neoplasms[9–11]. Other technical innovations such as perfusion of the future liver remnant (FLR) with cold solutions may reduce the injury to the FLR improving the safety of the procedure[12,13].

Although a tangential resection of the IVC is often enough to obtain clear margins and can be directly repaired without causing IVC stenosis, larger resections may necessitate reconstruction through IVC replacement. Autologous, cadaveric, and prosthetic vein grafts have been used without evidence of significant differences[14–16].

We decided to collect data from expert HPB centers to evaluate safety, feasibility, technical tips, and possible benefits of major liver resections with IVC replacement in a cohort of patients affected by primary and metastatic liver tumors.

HIGHLIGHTS

- All patients with occurrence of death at 90 days had alanine aminotransferase peak higher than the 75° percentile of those alive and international normalized ratio peak > 3 in the first 10 days after surgery.
- Two-years OS was 63%, with a cumulative incidence of tumor recurrence at 1 year of 29%.
- Disease recurrence was registered in 47% of patients, and 43% of them had liver-only recurrence, while 36% of the recurrences were extrahepatic and the remaining 21% were mixed.

Methods

Study group

We conducted a retrospective analysis of prospectively maintained databases from seven European, one US, one Indian and two Brazilian Institutions, selecting patients who had undergone liver resection with vena cava replacement from January 2000 to December 2020. Patients who had undergone major liver resection for primary or metastatic liver tumors with concomitant vena cava resection and replacement with the interposition of synthetic prosthesis or allografts were considered for inclusion. Patients with tangential vena cava resections were not considered eligible to enter the study. Clinical data and short-term outcomes were analyzed.

Data collection

The study was performed according to the Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) guidelines[17] (Supplemental Digital Content 1, http://links.lww.com/JS9/C389) and after Institutional Review Board approval for data collection (protocol number 215/2013/OSS/AOUMO), all institutions obtained their respective approvals according to their local centers requirements.

Tumor diagnosis is achieved based on international approved radiological criteria with computed tomography or MRI[18–21]. We collected baseline characteristics of the patients including age, sex, BMI, ASA score, presence of underlying liver disease, previous liver resections, initial diagnosis, and tumor size on the imaging, and neoadjuvant chemotherapy. Data were extracted from the latest lab exams before liver resection.

Perioperative outcomes included estimated blood loss, operative time, length of stay in the ICU, and length of postoperative hospital stay. Extension of the hepatectomy and approach to the liver (in-situ, ante-situm, and ex-situ[22]), the adoption of strategies to increase the FLR, and intraoperative need for veno-venous by-pass were collected. Finally, each center was asked to report the type of graft used to replace the vena cava, and the rate of vascular and biliary resections and reconstructions in addition to that of the vena cava.

Postoperative data included trends of aspartate aminotransferase, alanine aminotransferase (ALT), bilirubin, international normalized ratio (INR), albumin, creatinine, and platelets from postoperative day (pod) 1 to 10. Incidence of post hepatectomy liver failure (PHLF) and biliary fistula were evaluated according to the International Study Group for Liver Surgery (ISGLS) definitions[23,24]. Histological findings, anticoagulation management, incidence of recurrence, and incidence of graft complications were collected and reported.

All patients signed an informed consent prior to surgery to authorize anonymized data collection and audio-visual registration of the surgical procedure.

Statistical analysis

Continuous data were reported as median and ranges. Categorical data were reported as counts and percentages.

Wilcoxon's signed-rank test for continuous variables and Fisher's exact test for categorical variables were used to compare the distribution of the evaluated characteristics between patients with and without 90-days mortality.

The overall survival (OS) was defined as the time from surgical treatment until death or last contact and was estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between patients with and without intrahepatic cholangiocarcinoma (iCCA) at diagnosis. The cumulative incidence function (CIF) of disease recurrence was estimated according to

Table 1

Patients' characteristics (*N* = 36).

Variable	Level	Overall (*N* = 36)
Age (years), median (min-max)		57 (28–75)
Sex, *N* (%)	Female	22 (61)
	Male	14 (39)
BMI (kg/m^2), median (min-max)		24.3 (18.0–38.1)
ASA score, *N* (%)	1	6 (17)
	2	22 (61)
	3	7 (19)
	4	1 (3)
Preoperative liver disease, *N* (%)	None	33 (92)
	Steatosis	3 (8)
Initial diagnosis, *N* (%)	HCC	7 (19)
	iCCA	16 (44)
	PCCA	1 (3)
	CRLM	4 (11)
	Sarcoma	4 (11)
	Hepatocholangiocarcinoma	1 (3)
	Other	3 (8)
Tumor max size (mm), median (min-max)		98 (25–250)
Recurrent disease, *N* (%)	No	32 (89)
	Yes	4 (11)
Previous liver resection, *N* (%)	No	35 (97)
	Yes	1 (3)
Neoadjuvant chemotherapy, *N* (%)	No	26 (72)
	Yes	10 (28)

CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma.

method described by Kalbfleisch and Prentice[25], considering the death as first event as a competing event.

All reported *P* values were two sided, with *P*-value less than 0.05 considered as statistically significant.

All analyses were performed with the statistical software SAS 9.4 (SAS Institute).

Results

General characteristics

Forty cases of primary and metastatic liver tumors with vena cava infiltration from 10 international centers were collected (7 European, 1 USA, 2 Brazilian, 1 Indian). Thirty-six patients met the inclusion criteria listed above, four patients were excluded due to missing data on postoperative outcomes and follow-up.

As reported in Table 1, our population shows a slightly higher prevalence of female patients (61%), with a median age of 57 years (range: 28–75), and a median BMI of 24.3 kg/m^2 (range: 18–38.1). Patients were mostly in good general conditions, with 78% of cases staged as ASA 1 or 2, and 92% that did not have any underlying liver disease. Median tumor size was 98 mm (range: 25–250), with most of the cases diagnosed as iCCA (44%). The second tumor was with a prevalence of 19%, followed by colorectal liver metastases (CRLM) and sarcoma. The tumor was newly diagnosed in 89% of the cases, and for 97% of the patients it was the first liver resection. Only 28% of patients underwent neoadjuvant chemotherapy, therapeutic schemes are provided as Supplemental Material (Supplemental Digital Content 2, http://links.lww.com/JS9/C390).

Table 2

Intraoperative data (*N* = 36).

Variable	Level	Overall (*N* = 36)
Surgical procedure, *N* (%)	Right trisectionectomy	22 (61)
	Left trisectionectomy	5 (14)
	Right hepatectomy	7 (19)
	Central hepatectomy	2 (6)
Procedure, *N* (%)	Single stage	32 (89)
	Two-stage, PVE *	2 (6)
	Two-stage, ALPPS †	2 (6)
Hepatic vascular exclusion, *N* (%)	No	5 (14)
	Partial	7 (19)
	Complete	24 (67)
Venous vascular bypass, *N* (%)	No	21 (58)
	Yes	15 (42)
Liver resection, *N* (%)	In-situ	23 (64)
	Ante-situ	11 (31)
	Ex-situ	2 (6)
Vena cava graft, *N* (%)	Cadaveric	13 (36)
	Dacron	5 (14)
	PTFE	14 (39)
	Reinforced goretex	4 (11)
Hepatic veins preservation, *N* (%)	No	11 (31)
	Yes	25 (69)
Portal vein reconstruction, *N* (%)	No	26 (72)
	Yes	10 (28)
Hepatic artery reconstruction, *N* (%)	No	34 (94)
	Yes	2 (6)
Biliary reconstruction, *N* (%)	No	26 (72)
	Yes	10 (28)
Operative time (min), median (min-max)		462 (230–750)
Estimated blood loss (ml), median (min-max)		750 (100–5000)
N of packed red blood cells transfused, median (min-max)		1 (0–27)

*Days between surgery and 2nd stage (PVE) for the two patients: 14, 67.
†Days between surgery and 2nd stage (ALPPS) for the two patients: 9, 69.

Intraoperative data

Most of the patients included in this study underwent a right trisectionectomy (61%), five received a left trisectionectomy, seven underwent a right hepatectomy, and in two cases a central hepatectomy was performed (Table 2). The 'in-situ' approach for liver resection was the most frequently adopted (64%). Four patients required a two-stage approach with radiological preoperative PVE, with a reported interval between the two stages of 9, 14, 67, and 69 days. Complete liver vascular exclusion was adopted in 67% of cases, however, only 42% required a veno-venous vascular bypass (Fig. 1). Several kinds of vascular grafts were used for reconstruction, with cadaveric ones being the most frequently chosen (36%) (Fig. 2). Tumor extension did not require any reconstruction of the HV in 69% of cases, and similarly portal vein and biliary resections were performed only in 28% of cases. Finally, only two cases of arterial reconstruction were reported. In detail, the two patients that received arterial

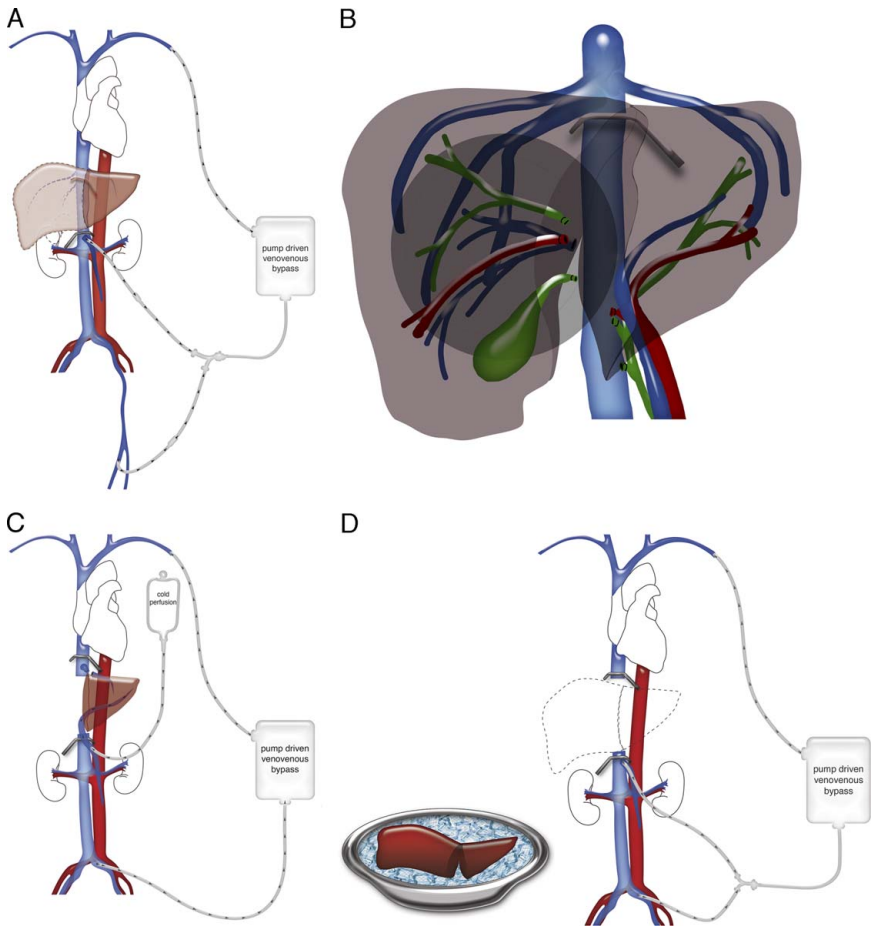

Figure 1. Illustrations with technical details of the different approaches adopted for major hepatectomy with en-bloc vena cava resection: (A) In situ split: The setting of an in-situ right hepatectomy with the use of veno-venous bypass is depicted here. The outflow of the liver is preserved with the upper clamp placed on the inferior vena cava below the hepatic veins cuff. The portal vein flow is diverted in the bypass to avoid congestion of the small bowel in case of a tumor involving the portal confluence. (B) Detail of in situ split: In situ split is a good option for tumor infiltrating the vena cava below the hepatic vein cuff. Here, a detail of the in situ right hepatectomy is provided, with parenchyma split, division of the right hepatic duct, hepatic artery and portal vein, clamp placed below the hepatic vein cuff and preserved outflow from the left hepatic vein, which is not involved by the tumor. (C) Ante situm split: This approach is preferred for tumors involving the hepatic vein cuff and/or the posterior aspect of the vena cava towards the retroperitoneum. The vena cava is divided and the liver is rotated anteriorly and medially. For a better preservation of the FLR and reduction of the ischemia-reperfusion injury the left liver can be perfused with cold organ preservation solution, that is flushed from the left hepatic vein, although have been reported experiences without the use of cold solutions[26]. (D) Ex situ split: Ex situ approach helps reducing the ischemia-reperfusion injury and allows a precise and blood-less dissection at the back-table, however, it always requires a veno-venous bypass. Here, the portal vein can be shunted in the vena cava with a port-cava anastomosis according to the preference of the surgeon.

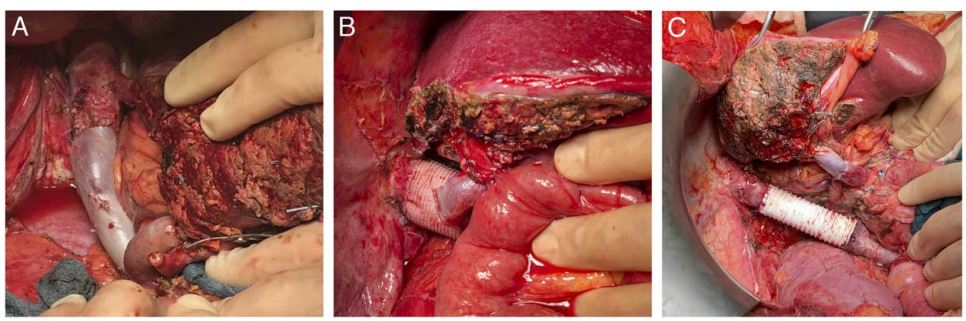

Figure 2. Vena cava replacement with cryopreserved allograft (A), dacron prosthesis (B) or Goretex (PTFE) ringed prosthesis (C).

Table 3

Postoperative data and follow-up (*N* = 36).

Variable	Level	Overall (*N* = 36)
ICU stay (days), median (min-max)		4 (1–30)
In-hospital stay (days), median (min-max)		15 (3–46)
Bilirubin peak (mg/dl), median (min-max)		2.68 (0.80–36.38)
ALT peak (U/l), median (min-max)		500 (34–8567)
INR peak, median (min-max)		2.10 (1.00–5.90)
CCI score, median (min-max)		20.9 (0–100)
Morbidity, *N* (%) *	No	13 (39)
	Yes	20 (61)
Clavien–Dindo > 3a (%)		6 (16)
PHLF, *N* (%)	0	21 (58)
	A	11 (31)
	B	2 (6)
	C	2 (6)
Resection margin (mm), median (min-max) *		8 (0–34)
Macrovascular invasion, *N* (%) *	No	14 (42)
	Yes	19 (58)
Microvascular invasion, *N* (%) *	No	16 (49)
	Yes	17 (52)
N of lymph nodes retrieved, median (min-max) †		8 (0–24)
N of positive nodes, *N* (%) †	0	26 (81)
	1	1 (3)
	2	1 (3)
	3	0 (0)
	4	3 (9)
	5	1 (3)
Satellites, *N* (%)	No	33 (92)
	Yes	3 (8)
Adjuvant chemotherapy, *N* (%) ‡	No	24 (69)
	Yes	11 (31)
Graft thrombosis, *N* (%)	No	34 (94)
	Yes §	2 (6)
Graft stenosis, *N* (%)	No	35 (97)
	Yes ‖	1 (3)
90-days mortality, *N* (%) ‡¶	No	30 (86)
	Yes	5 (14)

*3 missing.
†4 missing.
‡1 missing.
§Graft thrombosis management: 1 LMWH, 1 transplant.
‖Graft stenosis management: 1 radiological stenting.
¶1 Patient alive 15 days after surgery, then lost to FU.

resection both underwent ex-situ resection, therefore the resection and reconstruction represented a technical necessity. Meanwhile, 10 patients needed a portal vein resection and reconstruction: two were ex-situ cases, six were infiltrated by the tumor at the bifurcation, and two were resected and reconstructed for technical reasons. Median operative time was 462 min, ranging between 230 and 750 min. Estimated blood loss was quite high, with a median of 750 ml (range 100–5000 ml), however, the median number of pRBC transfused intraoperatively was 1 unit, ranging between 0 and 27 units.

Postoperative outcomes

Perioperative results are summarized in Table 3, showing that median in-hospital stay was 15 days (range: 3–46), including a median of 4 days of ICU stay (range: 1–30). Figure 3 reports individual and median trends of preoperative and postoperative levels of bilirubin, aspartate aminotransferase, ALT, INR, albumin, platelets count, and creatinine. Postoperative morbidity was present in 61% of patients, with a median CCI score of 20.9, ranging from 0 to 100. Notably, only two cases of PHLF grade C were reported (6%), while 58% of patients did not show any sign of liver decompensation. The resected tumors confirmed their aggressiveness on final pathology showing 58% macrovascular invasion, 52% microvascular invasion, 8% satellitosis, and 19% of positive nodes. Lastly, 31% of cases underwent adjuvant chemotherapy. Ninety-days mortality was 14% (five cases), and the event occurred due to multiorgan failure (MOF) in three cases, sepsis and heart failure in the remaining two cases. No correlations were found between preoperative characteristics of the patients and 90-days mortality, while higher ALT and INR peak in the first 10 postoperative days showed a statistically significant association with the incidence of mortality at 90 days (Table 4). All patients with the outcome of death at 90 days had their ALT peak higher than the 75° percentile of those who survived and INR peak > 3 in the first 10 days after surgery (Fig. 4).

Long-term outcomes

In the follow-up period, two patients developed graft thrombosis and one patient developed a graft stenosis. The two cases of thrombosis required therapy with LMWH, nonetheless, one of the patients was eventually listed for liver transplantation. Conversely, the stenosis was effectively treated by placing a radiological stent in the vena cava with a good long-term outcome (alive at 8 years from surgery).

Five-year OS was 48% (95% CI: 27–66%), with a CIF at 1 year of 29% (95% CI: 15–45%) and 55% at 5 years (95% CI: 33–73%) (Fig. 5A–B). Disease recurrence was registered in 47% of patients, and 43% of them had liver-only recurrence, while 36% of the recurrences were extrahepatic and the remaining 21% were mixed.

Given the high prevalence in our series of patients affected by iCCA, we compared the long-term outcomes of those cases versus non-iCCA tumors, which resulted similar without statistically significant differences (Fig. 5C, D).

In particular, 5-year OS for patients treated for iCCA was 55%, compared to 40% for those with different indications. Interestingly, the CIF for patients with a diagnosis of iCCA was significantly lower compared to those with other indications ($P = 0.026$), with a 14% incidence of recurrence versus 53% of the no-iCCA group after 2 years and 41 versus 69%, respectively, after 5 years.

Discussion

Technical difficulties and risk of adverse outcomes may discourage surgical indications in patients affected by liver tumors with vena cava involvement requiring complete vena cava replacement. Nevertheless, at the beginning of this century some series already demonstrated the feasibility and safety of liver surgery associated with vena cava resection for advanced liver tumors[16,27]. The most relevant benefit of such an advanced procedure comes from the lack of alternative curative approaches[1], however, results published in literature may be confounding due to the mixed series including partial resections of the vena cava. Therefore, we aimed to collect only cases of

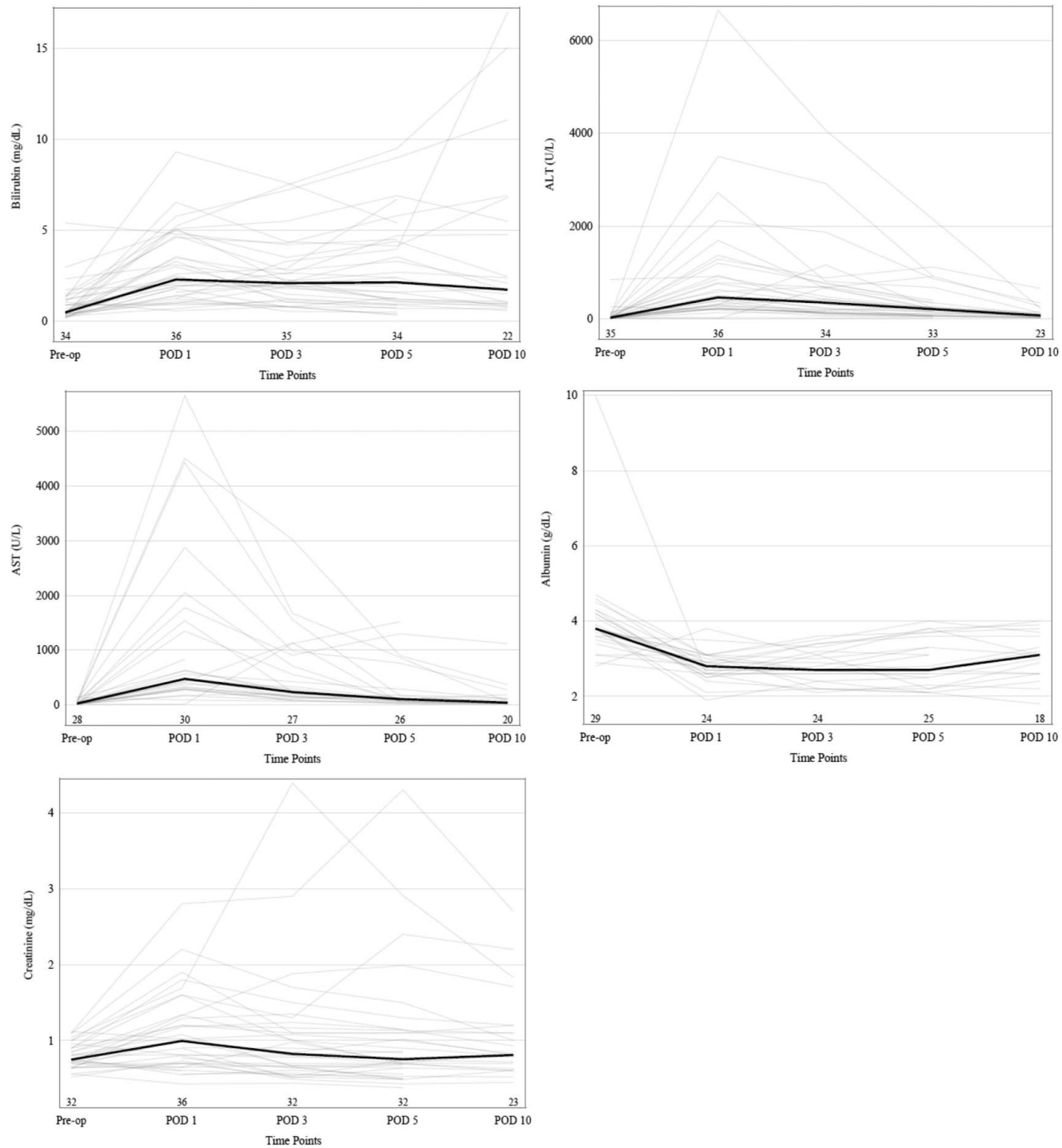

Figure 3. Individual and median trajectories of laboratory tests.

major hepatectomies with concomitant full vena cava replacement from high-volume international Institutions to reduce the risk of bias in the analysis of the results.

Our study shows that, besides a relatively high intraoperative blood loss and overall morbidity, patients can be effectively treated, with a low incidence of complications of the vena cava graft, few cases of severe postoperative liver decompensation and reasonable long-term survival. Patient selection plays a major role in the outcome of the procedure, as demonstrated by the prevalence of ASA 1-2. Only one third of the population received preoperative neoadjuvant chemotherapy, however, this result should be interpreted under the light of the heterogeneity of the study cohort. Despite a 75% of extended liver resections, only 12% of patients needed to be

Table 4

Association between patients' characteristics and 90-days mortality (*N* = 35).

Variable	Level	90-days mortality		*P*
		No (*N* = 30)	Yes (*N* = 5)	
Age (years), median (min-max)		53 (28–75)	67 (29–74)	0.31
Sex, *N* (%)	Female	19 (90)	2 (10)	0.37
	Male	11 (79)	3 (21)	
BMI (kg/m^2), median (min-max)		24.5 (18.0–38.1)	24.6 (21.3–37.3)	0.59
ASA score, *N* (%)	1/2	23 (85)	4 (15)	1.00
	3/4	7 (88)	1 (13)	
Initial diagnosis, *N* (%)	HCC	7 (100)	0 (0)	0.25
	iCCA	12 (75)	4 (25)	
	Other	11 (92)	1 (8)	
Tumor max size (mm), median (min-max)		100 (25–250)	70 (46–100)	0.14
Bilirubin (mg/dl) preoperative, median (min-max) *		0.90 (0.17–5.40)	0.45 (0.23–0.68)	0.12
ALT (U/l) preoperative, median (min-max) †		31 (10–853)	16 (11–121)	0.11
AST (U/l) preoperative, median (min-max) ‡		30 (11–142)	21 (17–52)	0.33
Albumin (g/dl) preoperative, median (min-max) §		3.8 (2.8–10.0)	4.2 (3.2–4.5)	0.63
Platelets count (10^3/mmc) preoperative, median (min-max) †		233 (87–615)	212 (185–354)	0.72
INR preoperative, median (min-max) †		1.10 (0.96–1.80)	1.01 (0.96–1.14)	0.17
Creatinine (mg/dl) preoperative, median (min-max) ‖		0.78 (0.52–1.12)	0.72 (0.65–0.72)	0.26
Vena cava graft, *N* (%)	Cadaveric	13 (100)	0 (0)	0.13
	Artificial	17 (77)	5 (23)	
Hepatic veins preservation, *N* (%)	No	10 (91)	1 (9)	1.00
	Yes	20 (83)	4 (17)	
Portal vein reconstruction, *N* (%)	No	22 (88)	3 (12)	0.61
	Yes	8 (80)	2 (20)	
Hepatic artery reconstruction, *N* (%)	No	28 (85)	5 (15)	1.00
	Yes	2 (100)	0 (0)	
Biliary reconstruction, *N* (%)	No	22 (88)	3 (12)	0.61
	Yes	8 (80)	2 (20)	
N of packed red blood cells transfused, median (min-max)		1 (0–27)	4 (0–9)	0.35
Bilirubin peak (mg/dl), median (min-max)		2.68 (0.80–16.03)	7.17 (1.80–36.38)	0.22
ALT peak (U/l), median (min-max)		440 (34–6645)	1692 (915–8567)	0.007
INR peak, median (min-max)		1.70 (1.00–3.30)	3.30 (3.10–5.90)	0.001

*2 missing without 90-days mortality.
†1 missing without 90-days mortality.
‡8 missing without 90-days mortality.
§5 missing without 90-days mortality, 2 missing with 90-days mortality.
‖2 missing without 90-days mortality, 2 missing with 90-days mortality.

scheduled for two-stage procedures such as PVE or ALPPS. Interestingly, while the frequency of complications may be quite high at a glance, the median CCI score was 20.9, meaning one complication grade 2 according to the classical Clavien–Dindo[28,29]. The trends of lab exams during the first ten days after surgery are associated with the incidence of mortality at 90-days, in particular, INR peak > 3 and ALT peak over 1000 UI/l. Patients affected by iCCA showed a significant reduction in the incidence of tumor recurrence after surgery compared to those who underwent surgery for other indications.

Most importantly, only three patients in the series developed complications related to the vascular graft, two thrombosis, and one stenosis. The choice between different materials for IVC reconstruction is another key aspect in this kind of surgery. The use of homograft (cryopreserved or autologous) has been reported to reduce the risk of infection and thrombosis, but this option is not always easily available. Although the risk of infection represents a theoretical disadvantage with the use prosthetic material, there is evidence supporting that this event is very unlikely[9,16]. Moreover, cryopreserved allografts need a complex storage system (tissue banks), are generally expensive, and usually must be ordered in advance, while prosthetic materials are an easy off-the-shelf alternative. Dacron was the material of choice in the past, but high rates of thrombosis and stenosis have been reported[16,30]. Ringed reinforced PTFE (polytetrafluoroethylene) grafts for replacing the IVC is nowadays preferred as they seem to resist compression by the abdominal viscera and the regenerating liver[31–33]. In our series all kind of grafts were used, with a slight prevalence of cadaveric grafts (36%). Notably, the two cases of grafts thrombosis occurred with the use of an unreinforced Gore-Tex prosthesis (PTFE), while the stenosis occurred with a cadaveric cryopreserved allograft. No cases of graft infection were reported. Our data demonstrated that artificial and cryopreserved grafts are equally efficient in the long-term, therefore they can be liberally selected according to the preference and the experience of the surgeon without any impact on the patient.

Surgical techniques adopted for liver resection and vena cava replacement reported in literature show different

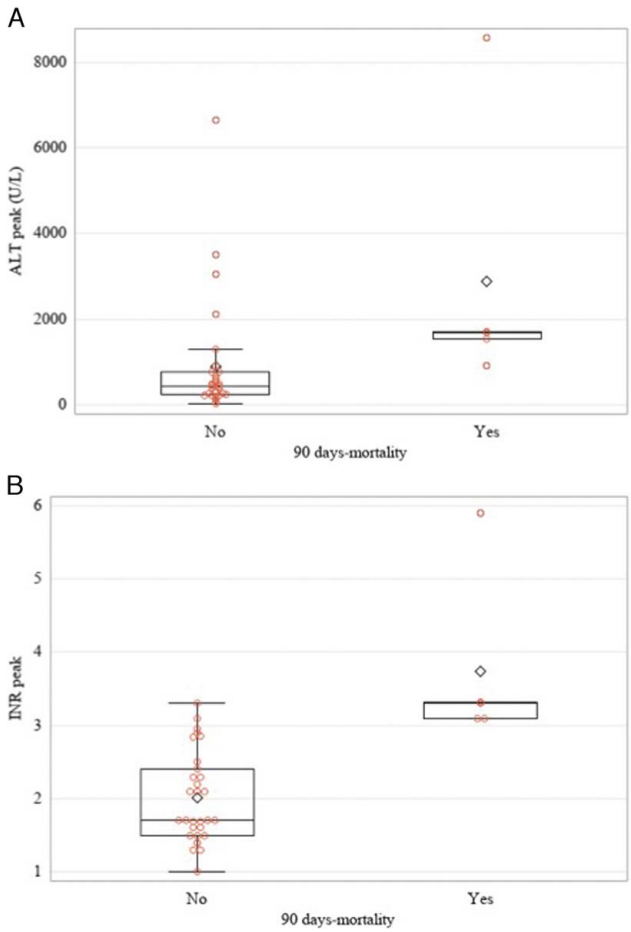

Figure 4. Distribution of ALT peak (U/L) (A) and INR peak (B) among 90-days mortality status.

peculiarities among each series. All the procedures were performed through laparotomy or thoraco-phreno-laparotomy without any reported minimally invasive approach, as in our series. Most of the time the extension of resection required a total hepatic vascular exclusion (THVE). Moreover, the hanging maneuver can be challenging when centrally located lesions infiltrate the IVC[34]. Tolerance test is usually performed and the decision to use a veno-venous bypass may be based on its result, with decrease in blood pressure of more than 30% or a decrease of the cardiac index of more than 50% being considered as sign of THVE intolerance[35]. Abdominal aorta clamping has been reported to be a safe technique to keep hemodynamics stable, while on THVE without the need of installing a veno-venous bypass[36]. The use of active or passive veno-venous bypass, with or without oxygenation (ECMO), may be a useful tool to increase safety throughout the procedure. In our experience its use allows optimal hemodynamic stability of the patient during IVC clamping. It is recommended to perform a clamping test and evaluate the hemodynamic impact. If blood pressure and cardiac index do not drop and the time of clamping is expected to be less than 60–90 min, it could be safe to proceed without a shunt. Our opinion is that while planning these cases in a multidisciplinary meeting, it could be useful to consider an easy and ready switch to a bypass when THVE is not tolerated, without using it systematically in every case. Another key aspect in this kind of surgery is the anatomy of the confluence of middle and left HV and its potential infiltration. In fact, it is often necessary to perform a THVE which may require a veno-venous bypass when resecting huge right-sided tumor, clamping the IVC above the hepatic vein cuff, with or without perfusion of the FLR with cold preservation solution to reduce the impact of ischemia-reperfusion injury[12]. On the other hand, in some cases it is possible to place the caval clamp below the insertion of hepatic vein on the IVC allowing normal inflow and outflow to the FLR. In our series a veno-venous by-pass was adopted in 42% of cases, and two patients required a 'ex-vivo' approach. The hepatic vein of the FLR was preserved without the need of reconstruction in 70% of the cases. Notably, portal and biliary resections have been associated with liver resection and vena cava replacement in nearly one third of the cases, as a result of a direct infiltration or technical choice. Arterial reconstruction was required only in the ex-situ cases.

While it is crucial to select patients with high tolerance of the surgical procedure, multidisciplinary discussion is key to select those cases in which there is a high probability of obtaining a radical resection and tumor biology appears favorable. We believe that it is fundamental to not deny surgical evaluation to patients presenting with liver tumors and IVC involvement, especially due to the risk of worsening of quality of life related to vena cava compression. Some features should represent a counterindication to surgery such as distant metastasis. On the other hand, a careful evaluation of the response to neoadjuvant therapies, accurate preoperative imaging study including 3D modeling and expertise in extreme hepatic surgery technique and vascular management are key element to be evaluated to predict the benefit of surgery for these patients. In fact, survival rates in this cohort are encouraging, with half of the population alive at 36 months after surgery and 48% at 5 years. An analysis of data published in literature revealed that 1 year, 3-year, and 5-year OS rates in patients that underwent liver resection with vena cava graft replacement were of 72, 49, and 39%, respectively[37].

This study has some limitations that should be highlighted. Namely, the retrospective nature of the study, the lack of randomization and the lack of a control group are the principal characteristics that may bias the results. Nonetheless, the inclusion of only major liver resections with full vena cava resection and replacement, and the participation of high-volume centers with experience in this advanced liver surgery and liver transplantation make our results generalizable and usable by other surgeons who aim to approach these difficult cases. Moreover, we provide data for the early interpretation and prediction of the outcomes.

Conclusions

Major hepatectomies with IVC replacement are feasible with reasonable outcomes in expert centers with extensive multidisciplinary expertise in advanced hepatic surgery. Besides the risk of perioperative morbidity, they can be a valuable option for patients with locally advanced liver tumors With the limits of a small cohort, iCCA shows better oncological outcomes compared

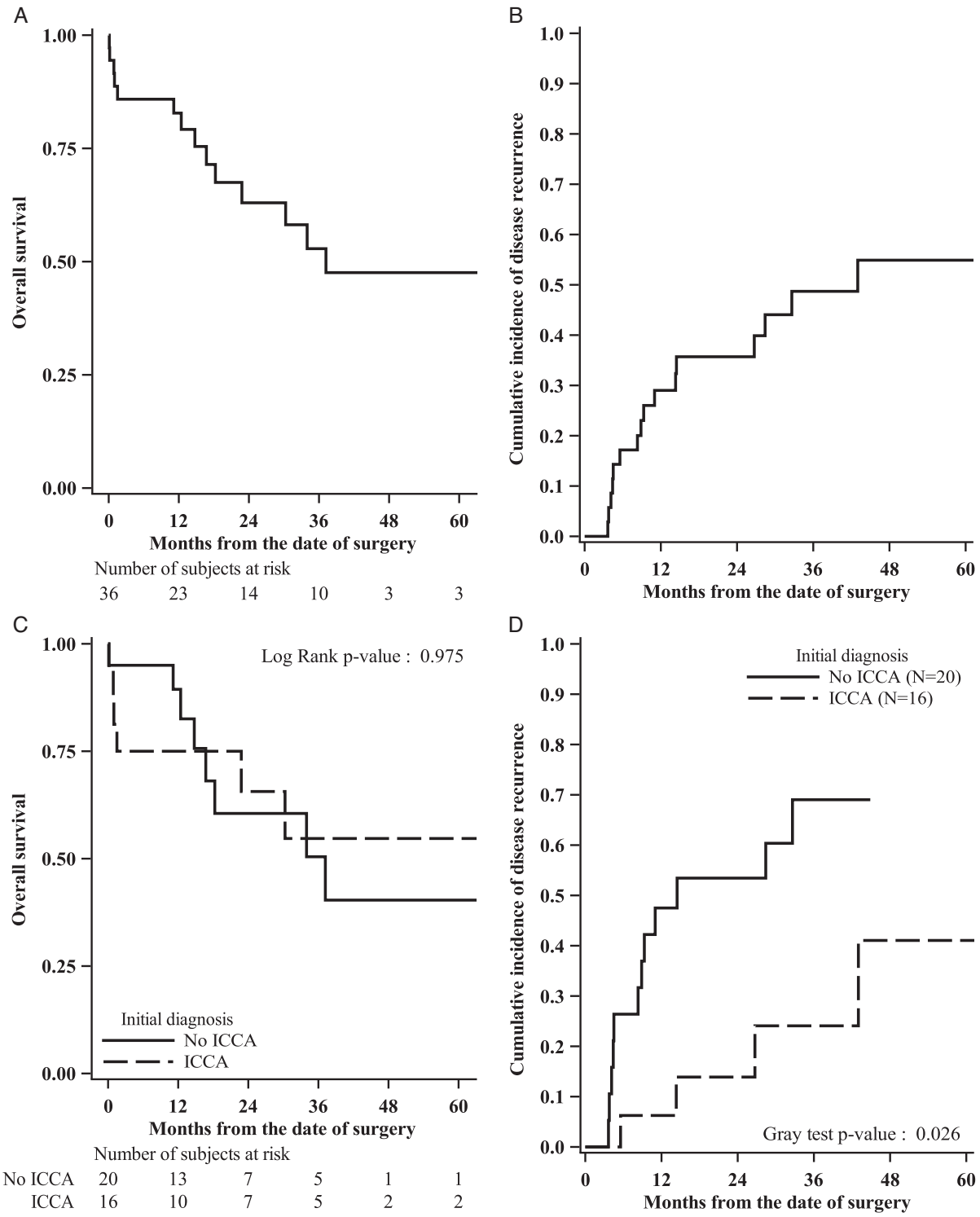

Figure 5. (A) Overall survival (*N* = 36, Median FU (Q1–Q3) in months: 17 (11–37)); (B) Cumulative incidence of disease recurrence (*N* = 36); (C) Overall survival by initial diagnosis (ICCA vs. No ICCA, N = 36); (D) Cumulative incidence of disease recurrence by initial diagnosis (ICCA vs. No ICCA, *N* = 36).

to other indications. The accurate selection of patients, evaluation of tumor biology and integrated anesthesiologic and surgical management are crucial to obtain good short-term outcomes and long-term survival.

Ethical approval

Institutional Review Board approval for data collection: Area Vasta Emilia Nord (AVEN) Ethical Committee, protocol number 215/2013/

OSS/AOUMO. The study was performed according to Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) guidelines.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

F.D.B. and H.P.M.: conceptualization; P.M., F.D.B., S.F., and V. B.: writing – original draft. All authors contributed in data curation, writing – review and editing, and validation.

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Collaborators

Gian Piero Guerrini, Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy; Cristiano Guidetti, Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy; Ronaldo Andrade, Department of Surgery and Abdominal Organ Transplantation – Hospital Adventista Silvestre, Rio de Janeiro, Brazil; Hepato-Pancreato-Biliary Unit and Transplant – DHR Health, McAllen, Texas, USA; Leandro Pimentel, Department of Surgery and Abdominal Organ Transplantation – Hospital Adventista Silvestre, Rio de Janeiro, Brazil; Hepato-Pancreato-Biliary Unit and Transplant – DHR Health, McAllen, Texas, USA.

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