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ORIGINAL ARTICLE

Impact of the presence of median arcuate ligament on biliary complications after liver transplantation

Eleftherios Gialamas[1] | Michela Assalino[1,2] | Laure Elkrief[3,4] | Fani Apostolidou-Kiouti[5] | Arthur Piveteau[6] | Graziano Oldani[1] | Philippe Compagnon[1] | Thierry Berney[1]

[1]Division of Transplantation, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland

[2]Unit of Digestive and Hepato-Pancreatic-Biliary Surgery, Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Créteil, France

[3]Hepatogastroenterology Unit, Regional University Hospital Centre Tours, Tours, France

[4]Division of Hepato-Gastroenterology, Geneva University Hospitals, Geneva, Switzerland

[5]Department of Hygiene, Social-Preventive Medicine and Medical Statistics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

[6]Department of Radiology, Geneva University Hospitals, Geneva, Switzerland

Correspondence
Eleftherios Gialamas, Division of Transplantation, Department of Surgery, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205, Geneva, Switzerland.
Email: gialamaslefteris@hotmail.com

Abstract

Introduction: The presence of median arcuate ligament (MAL) during orthotopic liver transplantation (OLT) may cause a significant reduction in the arterial hepatic flow. The aim of the present study is to investigate the impact of MAL on biliary complications in patients who underwent OLT.

Methods: We performed a retrospective case-control study among patients who underwent OLT in Geneva University Hospital between 2007 and 2017, depending on the presence or absence of MAL. The matching was performed according to age, gender, lab-MELD score at the time of OLT and type of donor (living or dead). The presence of MAL was assessed by an expert liver radiologist on the preoperative CT angiographic evaluation.

Results: The incidence of MAL was 6.1% (19 patients). Baseline characteristics were comparable between the two groups. No significant difference in biliary complications was found between patients with and without MAL (37% and 24%, respectively). No patient presented hepatic artery thrombosis. After logistic regression, in patients with MAL, the MAL release and gastroduodenal artery preservation compared to no treatment, showed an odds ratio for post-OLT biliary complications of 1.5 and 1.25, respectively. There was no difference in overall graft survival and in hazard for biliary complications between patients with and without MAL.

Conclusion: In the present study, we did not find any difference in the prevalence of biliary and arterial complications between patients with and without MAL. The choice of MAL treatment did not influence in a significant way the overall outcome and development of complications. However, if, at the end of arterial reconstruction, the arterial flow is not adequately established, MAL needs to be treated with the least invasive technique.

KEYWORDS
biliary complications, liver transplantation, median arcuate ligament, post-transplant cholangiopathy

1 | INTRODUCTION

The median arcuate ligament (MAL) is a fibrous arch joining the crura of the diaphragm. This ligament may be low-lying, causing some degree of extrinsic compression of the celiac trunk.[1] Under normal conditions, this anatomical condition is usually asymptomatic, thanks to collateral circulation provided by the superior and inferior mesenteric arteries.[2] Eventually, a small proportion of patients will experience unspecific abdominal symptoms, due to functional ischemia associated with hemodynamically significant compression of the celiac trunk. In OLT, only scarce clinical evidence is available with regards to the incidence, clinical relevance, diagnosis, and treatment of MAL compression.[3,4] Various reconstructive vascular techniques have been proposed to maintain arterial hepatic flow during OLT in these cases: standard anastomosis using the proper hepatic artery of the recipient with gastroduodenal artery (GDA) preservation, release of MAL when GDA sacrifice is required, or the use of an aorto-hepatic arterial reconstruction.[2] As the vascular supply of the bile ducts originates from the hepatic artery, we can assume that the presence of a MAL can be deleterious for the hepatic arterial flow, thus leading to biliary complications. The aim of the present study is to investigate the impact of MAL on post-transplantation biliary complications in patients undergoing OLT.

2 | METHODS

We performed a retrospective case-control study, looking at adult patients who had undergone OLT from January 2007 to September 2017 at the Geneva University Hospitals. All patients with MAL (the cases) at the time of pretransplant evaluation were included. The presence of a MAL was assessed on preoperative CT angiographic evaluation: focal narrowing of the celiac trunk looking like a hook associated with a post-stenotic dilatation, without calcification or atherosclerotic changes.[5] All CT-scan were assessed by an interventional radiologist with expertise in hepatobiliary imaging to confirm the presence of MAL. We included two controls (i.e., patients without MAL) for each case (2:1) and the matching was performed according to age, gender, lab-MELD score at the time of OLT and type of donor (living or dead donor). Pediatric patients (<16 years old), adult patients with previous OLT and adults without preoperative angiographic CT scan evaluation were excluded from the analysis. The study was approved by the local Ethics committee (BASEC ID 2017–02310).

For each included patient, the following data were extracted from digital or paper medical records: demographics (gender, age, BMI, ASA score, blood type, underlying liver disease, comorbidities, preoperative treatment), transplant data (donor age, type of donor between living or dead donor, combined transplantation or not, CMV status, perioperative need of transfusion units and catecholamines, type of MAL treatment), laboratory (MELD score, liver function tests), radiology (presence of MAL, presence of preoperative atheromatous lesions, appearance of postoperative hepatic artery thrombosis), and post-transplant outcomes (biliary and arterial complications and type of treatment, length of total stay, length of ICU stay, date of death, reoperation, retransplantation, last follow-up).

2.1 | Endpoints

Primary endpoint was the presence of any clinically significant biliary complication (significant stenosis or leak requiring intervention or responsible for blood liver test abnormality, in the absence of other cause of abnormal blood liver test) within one year after transplantation. Secondary endpoints were the rate of hepatic artery thrombosis and stenosis (early <30 days or late >30days), overall patient and graft survival.

2.2 | Statistical analysis

Appropriate descriptive measures were derived for all recorded variables and were expressed by mean (and SD) or median (and IQR) according to normality. Differences in patients' characteristics were assessed with appropriate tests. Logistic regression was used to assess the impact of the predefined predictors on the incidence of biliary complications. Multivariate models were run with clinically significant predictors along with those found to satisfy the criterion of $p < .2$ on univariate models. Results are reported as odds ratios with 95% confidence intervals, along with degrees of freedom and R-squared values. Variance inflation factors were calculated to address multicollinearity. To assess time until biliary complication development, overall mortality and graft failure in the MAL population Kaplan Meier curves were used and compared using the log rank test. To assess the impact of effect modifiers a Cox regression model was used and hazard ratios along with 95% confidence intervals were calculated and reported. Statistical analyses were run in R, v.4.0.2.

3 | RESULTS

3.1 | Baseline and transplant characteristics

The patients' selection flowchart based on the predefined matching criteria is depicted in Figure 1. Nineteen patients were found to have

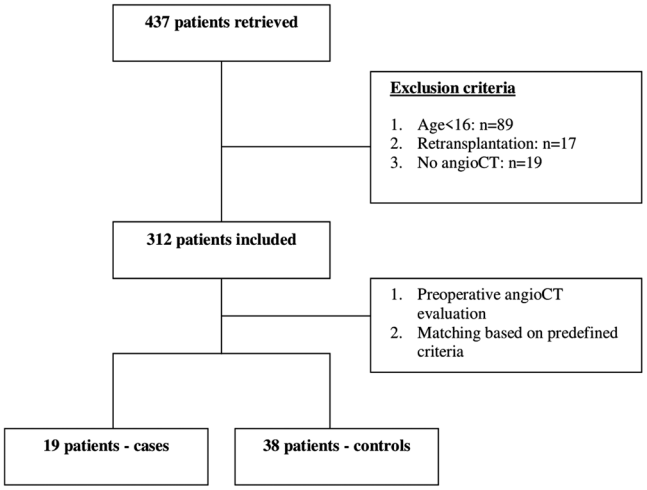

FIGURE 1 Patients' selection flowchart

median arcuate ligament (6.1%). Baseline characteristics did not differ significantly, according to the study design, as shown in Table 1. No patient had transplantation from donors with circulatory death (DCD). Three patients in the group with MAL and six in the group without MAL received a live donor graft. Median age was 58 in both groups (IQR 14 in patients with MAL and 11 in patients without), median BMI in the MAL group was 24 (IQR 3.5) whereas without MAL was 25.0 (IQR 5.5). Median ASA score was 3 in both groups. The most common primary hepatic disease was viral hepatitis (HCV, HBV) in both groups (32% in patients without MAL and 53% in the other group). Median MELD score was 14 in the group without MAL (IQR 15) and 13 in the group with MAL (IQR 15).

The most common type of anastomosis was end-to-end choledochal anastomosis (95% in the MAL absent group and 89% in the MAL present group). A choledocho-jejunostomy was performed in two patients in each group. The different options for MAL treatment were the use of an aortohepatic graft (1 patient, 5.3%), GDA preservation (8 patients, 42%), MAL release (3 patients, 16%), and no treatment (7 patients, 37%).

TABLE 1 Patients' baseline and transplant characteristics

	Without MAL $N = 38$	With MAL $N = 19$	p-value[a]
Baseline characteristics			
Median age, yrs (IQR)	58 (11)	58 (14)	.5
Male/female, *n*	36/2	15/4	.088
Median BMI, kg/m^2 (IQR)	25.0 (5.5)	24.0 (3.5)	.2
Median MELD score, (IQR))	14 (15)	13 (15)	.7
Primary liver disease, *n* (%)			.5
Viral hepatitis	12 (32%)	10 (52.6%)	
Alcohol	7 (18%)	4 (21.1%)	
Hepatocellular carcinoma	6 (16%)	1 (5.3%)	
NASH	4 (11%)	2 (10.5%)	
Other	9 (24%)	2 (10.5%)	
Blood type, *n* (%)			.5
A	21 (55%)	11 (57.8%)	
B	5 (13%)	1 (5.3%)	
AB	0 (0%)	1 (5.3%)	
O	12 (32%)	6 (31.6%)	
Transplant characteristics			
Mean donor age, yrs (SD)	48 (20)	52 (16)	.4
Living donor, *n* (%)			>.9
Yes	6 (16%)	3 (16%)	
No	32 (84%)	16 (84%)	
Type of anastomosis, *n* (%)			.6
Choledochojejunostomy	2 (5.3%)	2 (11%)	
End-to-end	36 (94.7%)	17 (89%)	
Mean transfusion units, *n* (SD)	5.4 (7.9)	3.3 (3.7)	.7
MAL treatment, *n* (%)			>.9
Aortohepatic graft	NA	1 (5.3%)	
Gastroduodenal artery preservation	NA	8 (42.1%)	
MAL release	NA	3 (15.8%)	
No treatment	NA	7 (36.8%)	

Abbreviations: IQR, inter-quartile range; SD, standard deviation; MAL, median arcuate ligament; BMI, body mass index; MELD, model for end-stage liver disease; NASH, non-alcoholic steato-hepatits; NA, not applicable.
[a]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test.

3.2 | Outcomes and biliary complications

Table 2 depicts the postoperative outcomes and biliary complications. Median length of stay was 23 days in patients without MAL (IQR 18) and 20 days in the patients with MAL (IQR 13). Median stay in the ICU was 4 days in the MAL absent group (IQR 3) and 3 days in the MAL present group (IQR 6). All patients had at least 1 year follow-up with a minimum of 70 days (deceased patient) and a maximum of 10 years (median follow-up 865 days, IQR 1119).

Nine patients in the controls and seven in the MAL group developed biliary complications (24% and 37%, respectively). Median time until complication development was 59 days in the control group (IQR 54) and 74 in the MAL group (IQR 663). Only one patient (from the group of controls) was treated with radiologically guided drainage due to the presence of a choledocho-jejunostomy. Endoscopic treatment was selected for seven patients in the group without MAL and for five in the group with MAL (18% and 26%, respectively). Moreover, two patients from the control group required reoperation for biliary complications, whereas two patients of the MAL group developed biliary stricture that needed no treatment at all. One patient in the control group presented ischemic cholangiopathy due to biliary stenosis, which was initially treated by endoscopic dilatation, but needed retransplantation 9 months later. Last but not least, non-anastomotic biliary stricture was

TABLE 2 Post-transplant outcomes

	Without MAL $N = 38$	With MAL $N = 19$	p-value[a]
All biliary complications, *n* (%)			.3
Yes	9 (24%)	7 (37%)	
No	29 (76%)	12 (63%)	
Biliary stricture, *n* (%)			.2
Yes	7 (18%)	7 (37%)	
No	31 (82%)	12 (63%)	
Biliary leak, *n* (%)			>.9
Yes	3 (7.9%)	1 (5.3%)	
No	35 (92.1%)	18 (94.7%)	
Hepatic artery thrombosis in the US, *n* (%)			
No	36 (100%)	18 (100%)	
Reoperation, *n* (%)			.7
Yes	7 (18%)	2 (11%)	
No	31 (82%)	17 (89%)	
Retransplantation, *n* (%)			>.9
Yes	1 (2.6%)	0 (0%)	
No	37 (97.4%)	19 (100%)	
Treatment of biliary complication			
Endoscopic, n (%)			.5
Yes	7 (18%)	5 (26%)	
No	31 (82%)	14(74%)	
Surgical, n (%)			.5
Yes	2 (5.3%)	0 (0%)	
No	36 (94.7%)	19 (100%)	
Radiological drainage, n (%)			>.9
Yes	1 (2.6%)	0 (0%)	
No	37 (97.4%)	19 (100%)	
No treatment, n (%)			.11
Yes	0 (0%)	2 (11%)	
No	38 (100%)	17 (89%)	
Median length of stay, days (IQR)	23 (18)	20 (14)	.4
Median length of stay in the ICU, days (IQR)	4 (3)	3 (6)	.3
Overall mortality, *n* (%)			.4
Yes	6 (16%)	1 (5.3%)	
No	32 (84%)	18 (94.7%)	

Abbreviations: IQR, inter-quartile range; US, ultrason; MAL, median arcuate ligament.

[a]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test.

observed in only one patient, who was part of the case group (presence of MAL). Diminished hepatic arterial flow was incriminated for the peripheral biliary stricture.

No patient presented hepatic artery thrombosis. The only arterial complication observed was a hepatic artery kinking in the group of patients without MAL that required reoperation. Overall, seven patients without MAL (7/38) and two with MAL (2/19) underwent reoperation for various reasons (artery kinking, biliary leak, bleeding, colonic perforation, ileus, incarcerated hernia, peritonitis, and recurrent cholangitis).

Intraoperative parameters did not differ significantly between the groups or among the patients treated for MAL. Laboratory tests on operation day, day 7, day 30, and 1 year after the transplantation did not differ between groups except for alkaline phosphatase on operation day which differed significantly in patients without MAL (Median 108, IQR 664) and those with MAL (Median 68, IQR 35). Ultrasonographic findings were compared between the two groups and statistically significant differences were found for US-defined hepatic arterial Resistive Index (RI) at day 30 and day 365. RI at day 30 was higher in the patients with MAL (.71 vs. .63, p .046), together with RI in the first year after transplantation (.72 vs. .66, p .037).

3.3 | Biliary complications in patients with MAL according to therapeutic strategy

Among the groups for different types of MAL treatment, there were no significant differences regarding intraoperative findings, postoperative laboratory tests, as well as ultrasonographic findings (Table 3). No T-tube was used during biliary anastomosis. The primary outcome (occurrence of biliary complications) was assessed with univariate logistic regression among the different therapeutic strategies applied in patients with MAL (Table 4). Since there was only one patient who had undergone an aorto-hepatic arterial reconstruction, it was excluded from further analysis to allow for model fit. The OR for development of biliary complications when MAL was released was 1.5 (95% CI .09, 42.1, p-value = .779, df = 17) compared to no treatment and 1.25 when the gastroduodenal artery was preserved (95% CI .15, 10.6, p-value = .833, df = 17) compared to no treatment.

Secondary analysis of warm and cold ischemia periods, length of stay in the ICU, type of biliary anastomosis, transfusion, whether the transplant was from a living donor and the donor's age are presented in Table 5. Warm ischemia period had statistical significance in the univariate analysis (OR 1.10 with a 95% CI ranging from 1.04 to 1.19). The significance was retained in the multivariate model. Length of stay in the ICU reached statistical significance in the univariate analysis (OR .94, 95% CI .87, .99) but not in the multivariate model.

TABLE 3 Intraoperative and postoperative characteristics for different types of MAL

Characteristic	No treatment $N = 7$	MAL release $N = 3$	GDA preservation $N = 8$	Aortohepatic bypass $N = 1$	*p*-value[a]
Median cold ischemia, minutes (IQR)	342 (149)	347 (204)	418 (152)	480 (NA)	.7
Median warm ischemia, minutes (IQR)	54 (16)	57 (13)	59 (6)	60 (NA)	.9
Type of anastomosis, *n* (%)					.076
Choledochojejunostomy	1 (14%)	0 (0%)	0 (0%)	1 (100%)	
End-to-end	6 (86%)	3 (100%)	8 (100%)	0 (100%)	
Median transfusion units, *n* (IQR)	0 (4.5)	1 (1)	5 (6.75)	3 (NA)	.6
Living donor, *n* (%)					.4
Yes	2 (29%)	1 (33%)	0 (0%)	0 (0%)	
No	5 (71%)	2 (67%)	8 (100%)	1 (100%)	
Mean donor age, yrs (SD)	52 (20)	43 (12)	57 (12)	33 (NA)	.3
Median length of stay in the ICU, days (IQR)	5 (10)	1 (3)	3 (2)	13 (NA)	.3

Abbreviations: IQR, inter-quartile range; SD, standard deviation; MAL, median arcuate ligament; GDA, gastroduodenal artery; yrs, years; NA, not applicable; ICU, intensive care unit.
[a]Fisher's exact test; Kruskal-Wallis test.

TABLE 4 Logistic regression for biliary complications for different types of MAL treatment

Type of MAL treatment	OR	95% CI	*p*-value
No treatment	—	—	
MAL release	1.50	.09, 25.39	.78
GDA preservation	1.25	.16, 9.92	.83

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; MAL, median arcuate ligament; GDA, gastroduodenal artery.
The one patient with aortohepatic graft had to be excluded to allow for model fit.

3.4 | Survival analysis for biliary complications, patient, and graft survival

In the survival analysis for development of biliary complications, there was no significant difference in the hazard for biliary complications between patients with and without MAL (Figure 2). Using Cox regression to incorporate the time of complication development, a shorter warm ischemia time was related with reduced hazard ratio for biliary complications and longer ICU stay was related with increased hazard for biliary complications. The multivariate model did not show any difference in the results (Table S1).

TABLE 5 Secondary analysis for biliary complications among patients with MAL

	Univariate logistic regression			Multivariate logistic regression		
Characteristic	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Cold ischemia, minutes	1.00	1.00, 1.01	.6			
Warm ischemia, minutes	1.10	1.04, 1.19	.005	1.09	1.03, 1.18	.013
Length of stay in the ICU, days	.94	.87, .99	.046	.95	.88, 1.00	.091
Type of biliary anastomosis						
Choledochojejunostomy	—	—				
End-to-end	1.27	.06, 14.2	.9			
Transufsion, units	.94	.86, 1.02	.2	.96	.88, 1.07	.4
Donor age, years	.99	.96, 1.02	.5			
Living donor						
No	—	—				
Yes	1.48	.31, 10.8	.6			

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; MAL, median arcuate ligament; ICU, intensive care unit.
The one patient with aorthohepatic graft had to be excluded to allow for model fit.

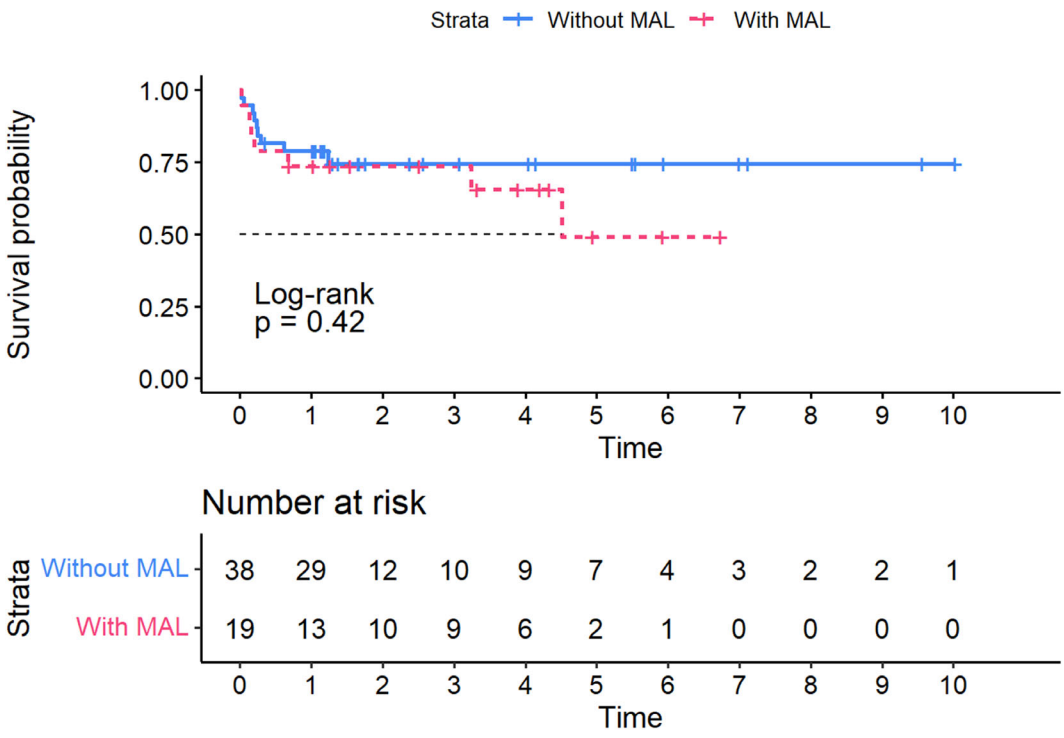

FIGURE 2 Survival analysis for biliary complications (time is counted in years)

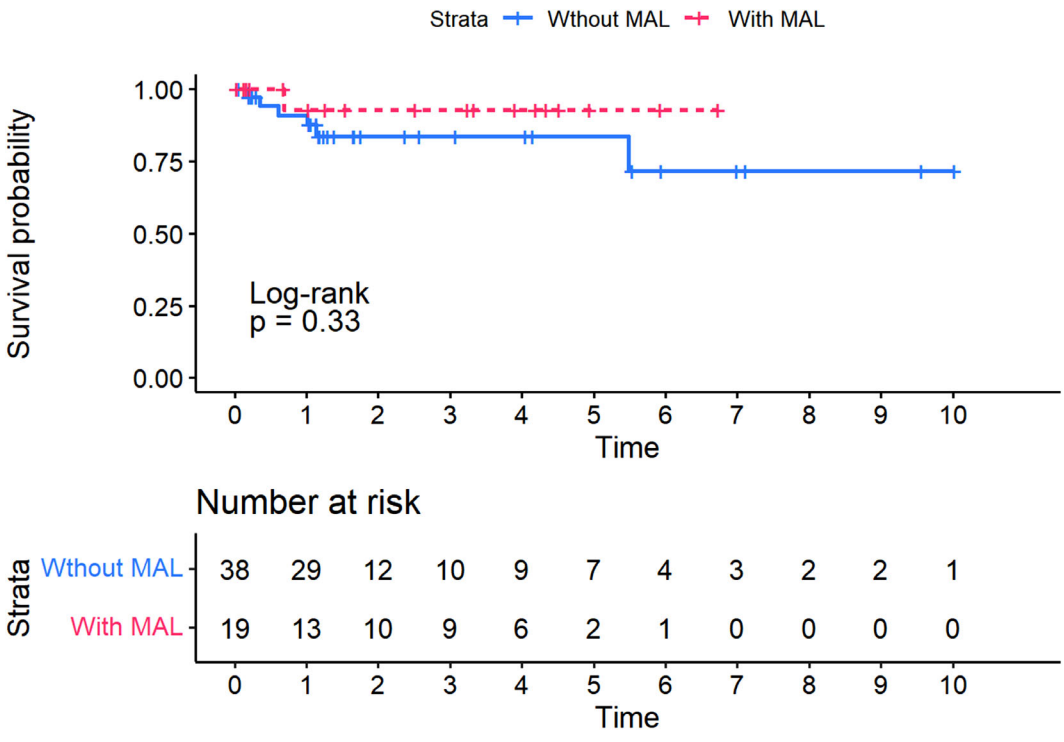

FIGURE 3 Survival analysis for overall patient mortality (time is counted in years)

Overall patient survival did not differ significantly among the two groups (Figure 3). Increased mortality was associated with longer ICU stay (HR 1.10, 95% CI 1.04, 1.16) and need for transfusion of blood units (HR 1.08, 95% CI 1.01, 1.15) both in univariate and multivariate Cox regression models (Table S2). Similarly, overall graft survival did not differ significantly among the two groups (Figure 4). Increased graft loss was associated with longer ICU stay (HR 1.10, 95% CI 1.05, 1.15) and need for transfusion of blood units (HR 1.09, 95% CI 1.04, 1.16) both in univariate and multivariate Cox regression models (Table S3).

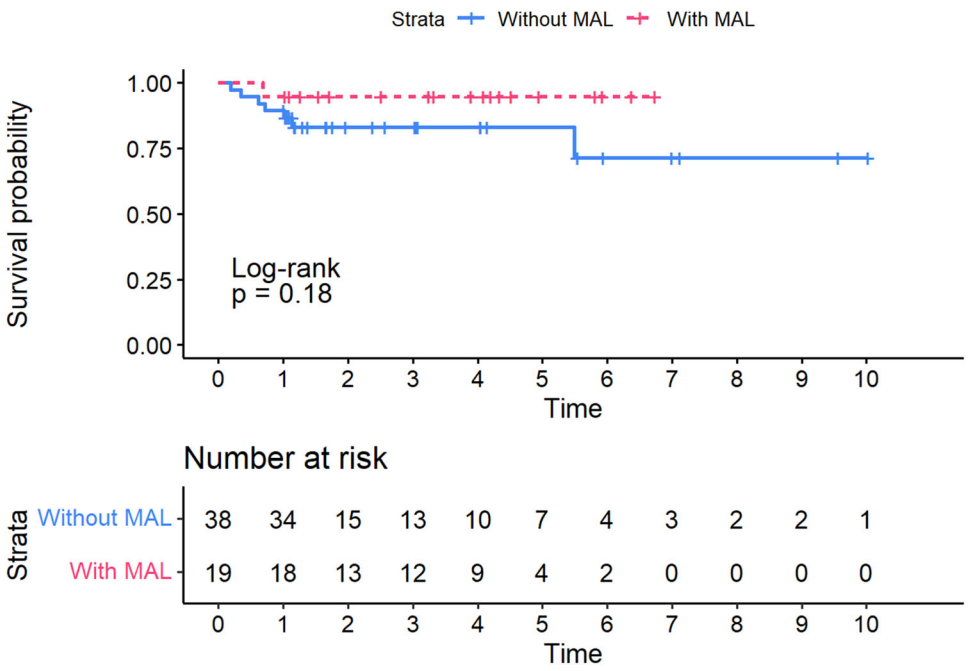

FIGURE 4 Survival analysis for overall graft survival (time is counted in years)

4 | DISCUSSION

The incidence of significant compression due to MAL presence in orthotopic liver transplantation varies with studies reporting a 3.7–10% rate.[6,7] The gold standard for identification of MAL during preoperative OLT evaluation remains the angioCT scan, mainly in the sagittal reconstruction. It can depict the severity of compression due to MAL as well as other vascular modifications.

The diagnosis of MAL preoperatively is not always established, as shown in a recent survey conducted among various European liver transplant centers; indeed, 24% of centers did not search actively for MAL presence before OLT.[4] In our study, 6.1% of all patients screened were found to have a MAL, with or without significant compression. In our center, the majority of MALs are diagnosed during preoperative evaluation by angioCT scan. However, in some cases, diagnosis was not reported and no special treatment was performed.

Management of MAL during OLT is variable among studies and no specific recommendations or consensus exist to date. If not detected or if it does not cause any severe compression, no treatment at all may be needed. Otherwise, many surgical techniques have been proposed to restore blood flow during OLT. There are studies advocating that MAL release is a safe and sometimes necessary procedure to maintain adequate blood supply to liver graft.[4,6,8] On the contrary, some authors suggest that this technique has depicted poor outcomes and important postoperative complications, such as bleeding, pancreatitis, pancreatic fistula, gastroparesis, and pneumothorax.[2,9,10] A more conservative treatment has also been proposed, with preservation of the GDA during dissection, thus maintaining the blood flow from the superior mesenteric artery. Finally, an intraoperative aorto-hepatic bypass by allograft or prosthetic graft can be performed as an alternative. However, it has been demonstrated that an aorto-hepatic bypass, mainly by a prosthetic graft, may be accompanied by increased risk of hepatic artery thrombosis (HAT) compared to conventional arterial reconstruction.[2,11] Pre-transplantation management of MAL stenosis by endovascular placement of stent has not yet demonstrated better results compared to the abovementioned surgical procedures during transplantation.[4]

Even though consensus does not exist regarding the ideal treatment of MAL during OLT, it is of general agreement that adequate arterial flow should be achieved to avoid arterial and biliary complications. In many cases, preoperative diagnosis of MAL is not even described, let alone a specific surgical treatment; in general, if adequate arterial flow is obtained during reconstruction, no further measure, such as MAL release, is taken. In our study, there seems to be no unanimous treatment strategy among the MAL patients. Although in most cases, surgeons were more conservative and preserved the GDA during OLT, the final choice was made during surgery based on perioperative factors and surgeon preference; the only common parameter remains the need of adequate blood flow in the end. Performance of a clamping test of the GDA is mandatory before deciding to divide it. In our institute, arterial flow is systematically assessed at the end of anastomosis with an intra-operative ultrasound.

In our study, we did not have any case of HAT. HAT remains the most frequent arterial complication in patients undergoing OLT, with an occurrence rate of 3–9%.[11,12] It has been also described as an independent risk factor for development of late biliary complications after OLT.[13] Lubrano et al. suggest that HAT rate in the presence of a MAL is significantly lower in cases of GDA preservation than those with more

invasive surgical techniques (MAL release, bypass), thus questioning the usefulness of such procedures.[2]

Unfortunately, no study has addressed the incidence of biliary complications after OLT in the presence of MAL. Biliary complications after OLT can appear on the early or late postoperative period and most commonly include biliary leaks or anastomotic strictures. Various risk factors have been incriminated, but in most cases, etiology of biliary complications lays on ischemic problems or inadequate surgical technique.[14] As vascular supply to the common bile duct relies upon the hepatic artery, it can be suggested that deficient blood flow caused by a MAL significant stenosis may lead to ischemic injury in the biliary tree and result in early or late biliary complications. Incidence is similar in OLT from a live or deceased donor, with the exception of a higher rate of bile leaks when OLT is performed from a live donor.[14,13] Type of biliary anastomosis can be of significance and it is generally accepted that end-to-end biliary anastomosis is preferred, though in many cases the choice of a choledocho-jejunostomy may vary according to situations (discrepancy in donor-recipient diameter, live donor transplantation, primary sclerosing cholangitis).[15,16]

In the present study, the rate of biliary complications did not differ significantly between patients with or without MAL. Unsurprisingly, shorter warm ischemia time was related to lower risk for biliary complications, whereas longer ICU stay was found to be a risk factor, with every additional day of stay in ICU leading to 5% higher risk. This comes in accordance with a recent expert review with retrospective data analysis in the Hungarian Liver Transplant Program, showing that a warm ischemia time superior to 65 min and prolonged ICU stay are independent risk factors for biliary complications after OLT, together with advanced donor age.[15,17,18]

Additionally, the prevalence of post-transplantation biliary complications did not differ between the various groups of MAL treatment. However, we found a greater trend of biliary complications occurrence among patients with MAL treated either by MAL release or GDA preservation than those where no specific treatment was performed. The absence of statistical difference might be because of the small sample size. Finally, it is worth mentioning that, due to the retrospective design of the study, we could collect only few information concerning the dosage of catecholamines used during the OLT and the hemodynamic status of the patients, that could possibly affect the blood supply towards the graft and contribute eventually to further complications.

The most important limitation of this study is, as mentioned, its retrospective design. It is the main reason why we opted for a case-control match to reduce confounding factors. Furthermore, as shown in statistical analysis, the confidence intervals in logistic regression for biliary complications are wide. A bigger sample would be required to reach a safer conclusion regarding the OR for biliary complications.

In conclusion, despite the fact that many authors recommend preoperative systematic research for MAL, we did not find any significant difference in the prevalence of biliary and arterial complications between patients with and without MAL in our study. Till now, there is no gold standard in the treatment strategy of MAL in patients undergoing OLT. It seems that the choice of technique for treatment of MAL does not influence in a significant way the overall outcome and the development of complications. It is, however, obvious that at the end of arterial reconstruction, establishing adequate arterial flow is mandatory in order to avoid devastating complications. MAL should be suspected, if not preoperatively detected, if a systematic GDA clamping test shows a decreased hepatic arterial flow, and needs to be treated with the less invasive technique.

CONFLICT OF INTEREST

The authors disclose no conflict of interest or funding.

AUTHOR CONTRIBUTIONS

E.G.: Concept/design, data collection, data analysis/interpretation, drafting article, statistics and critical revision of article. M.A.: Concept/design, data collection, data analysis/interpretation, drafting article and critical revision of article. L.E.: Concept/design, drafting article and critical revision of article. F.A-K.: Data analysis/interpretation, drafting article, statistics and critical revision of article. A.P.: Data collection, data analysis/interpretation and critical revision of article. G.O.: Data analysis/interpretation and critical revision of article. P.C.: Data analysis/interpretation and critical revision of article. T.B.: Concept/design, data analysis/interpretation and critical revision of article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Eleftherios Gialamas https://orcid.org/0000-0001-7557-7953
Graziano Oldani https://orcid.org/0000-0002-6637-0675

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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