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ORIGINAL ARTICLE

Liver growth prediction in ALPPS – A multicenter analysis from the international ALPPS registry

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Abbreviations: AKI, acute kidney injury; ALPPS, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy; BMI, body mass index; CI, confidence interval; CT, computed-tomography; FLR, future liver remnant; FLV, functional liver volume; IQR, interquartile range; ISGLS, International Study Group of Liver Surgery; OR, odds ratio; PHLF, post hepatectomy liver failure; PVE, portal vein embolization; SD, standard deviation; sFLR, standardized future liver remant; TNM, tumour nodule metastases.

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Abstract

Background: While ALPPS triggers a fast liver hypertrophy, it is still unclear which factors matter most to achieve accelerated hypertrophy within a short period of time. The aim of the study was to identify patient-intrinsic factors related to the growth of the future liver remnant (FLR).

Methods: This cohort study is composed of data derived from the International ALPPS Registry from November 2011 and October 2018. We analyse the influence of demographic, tumour type and perioperative data on the growth of the FLR. The volume of the FLR was calculated in millilitre and percentage using computed-tomography (CT) scans before and after stage 1, both according to Vauthey formula.

Results: A total of 734 patients were included from 99 centres. The median sFLR at stage 1 and stage 2 was 0.23 (IQR, 0.18–0.28) and 0.39 (IQR: 0.31–0.46), respectively. The variables associated with a lower increase from sFLR1 to sFLR2 were age>68 years ($p = .02$), height >1.76 m ($p < .01$), weight >83 kg ($p < .01$), BMI>28 ($p < .01$), male gender ($p < .01$), antihypertensive therapy ($p < .01$), operation time >370 minutes ($p < .01$) and hospital stay>14 days ($p < .01$). The time required to reach sufficient volume for stage 2, male gender accounts 40.3% in group <7 days, compared with 50% of female, and female present 15.3% in group >14 days compared with 20.6% of male.

Conclusions: Height, weight, FLR size and gender could be the variables that most constantly influence both daily growths, the interstage increase and the standardized FLR before the second stage.

KEYWORDS
ALPPS, anthropometrics, liver cancer, liver regeneration, rapid hypertrophy

1 | INTRODUCTION

Surgery is the only curative treatment allowing long-term survival for a large number of primary and metastatic liver tumours.[1,2] A high percentage of these tumours are initially unresectable due to the absence of a sufficient future liver remnant (FLR).[3,4] Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a recent two-stage hepatectomy variant that allows resection of advanced bilobar liver tumours in two stages by adding parenchymal transection to portal vein ligation/embolization.[5–9] The performance of ALPPS has significantly improved over the years due to careful patient selection and technical refinements of the procedure.[10,11] Both components decreased interstage complication rates and consequently morbidity and mortality of the whole procedure.

ALPPS obtains a much faster liver hypertrophy (more than 60% in only 7 days) than classic two-stage hepatectomy techniques only utilizing portal vein occlusion (approximately 50% in an interstage interval of at least 3 weeks).[12–14] The extent of liver hypertrophy after ALPPS depends on various clinical factors.

Lay summary/Keypoints

This is the first registry-based multi-institutional analysis modelling liver growth patterns in ALPPS. This analysis first identifies anthropometrical data including age, weight, height and gender as the key factors for rapid liver hypertrophy.

Several studies have identified predictors of liver hypertrophy, including age, body mass index (BMI), tumour type, liver function, platelet count, the use of Pringle manoeuvre in pathological livers, prior chemotherapy or liver steatosis.[15] However, it is still unclear which factors matter most to achieve accelerated hypertrophy within a short period of time. Despite using the same surgical technique, liver growth patterns are widely spread. There is a percentage of patients who do not achieve expected liver hypertrophy or take more than 10–14 days while others achieve it very quickly. In the literature, most authors have focused on the impact of complications, but liver growth prediction has been less studied. The objective of this study was to identify

patient-intrinsic factors related to the growth of the FLR in patients undergoing ALPPS to model a prediction of hypertrophy after the first stage.

2 | METHODS

2.1 | Study design

The present ALPPS cohort study is composed of data derived from the International ALPPS Registry. The Registry prospectively collects data on ALPPS cases since 2011 and is coordinated by the Department of Surgery, University of Zurich, Switzerland. Approval to enter patients into the international ALPPS Registry was obtained by the Cantonal Ethics Committee of Zurich (KEK 2013–0326; ClinicalTrials.gov (NCT01924741). Data extraction for analysis was permitted by the Scientific Committee of the registry and current data set was exported in October 2018. The study was performed in accordance with the recommendations of the Declaration of Helsinki.

2.2 | Outcome measures

The primary endpoint was to analyse the influence of demographic, tumour type and intraoperative results in the growth of the FLR. Data on patient characteristics (age, gender, BMI and comorbidities), tumour aetiology, tumour stage (TNM), neoadjuvant chemotherapy, liver disease in histology (steatohepatitis, fibrosis, macrosteatosis, sinusoid obstruction, cirrhosis and CASH), operative time, Pringle manoeuvre, blood transfusions, surgical technique, complications after stage 1 surgery and length of hospital stay after stage 1 were extracted. The Clavien-Dindo classification was used to assess 90-day morbidity.[16] Post hepatectomy liver failure (PHLF) was analysed according to the International Study Group of Liver Surgery (ISGLS) definition.[17] Depending on the time required to reach sufficient volume for the second stage, we divided our cohort of patients into three groups (less than 7 days, between 7 and 14 days and more than 14 days).

2.3 | Volumetric data

The volume of the FLR was calculated in millilitre and percentage using computed-tomography (CT) scans before both stages. The inter-stage interval was defined as the time period between the first and second stage. For both, prior stage 1 and stage 2 the following liver volumes were measured: total liver volume, tumour volume (in the deportalized liver and in the FLR), functional liver volume (FLV = total liver volume − total tumour volume) of deportalized liver and FLR. Standardized future liver remnant (sFLR) was calculated according to Vauthey formula.[18] The percent (%) growth of the FLR between the first and second stage was also analysed. A FLR was considered insufficient when it was less than 25% in patients with a healthy liver and less than 35% in those who had received chemotherapy or steatosis. A ratio of 0.5 for volume / bodyweight was considered insufficient in patients without neoadjuvant chemotherapy and a ratio of 0.7 in patients with prior chemotherapy or steatosis was insufficient.

2.4 | Statistical analysis

All the data included in the database have been analysed with a professional statistic package (R project, ver. 3.6.1, GLP). For categorical variables, frequencies and their percentages were used. For continuous variables median (range) or interquartile range (IQR) and the mean ± standard deviation (SD) was used, depending on the normal distribution. Patients were grouped (less than 7 days, between 7 and14 days and more than 14 days) according to inter-stage interval. Intergroup differences in continuous variables were assessed for significance using Kruskal–Wallis H-test and in categorical data using the Pearson's Chi-Squared test. A mixed model, with random intercept, was used to examine change over time in FLR between the first and second surgical operations, and whether the changes were different within the groups of patient characteristics. For the study of the relationship between the variables, the chi-square test was applied between two qualitative variables and the Pearson correlation if the variable was quantitative. To test the association of the studied factors, a multivariable logistic regression analysis was performed with the factors that turned out significant in the univariable analysis. From this multivariable analysis, we obtained the odds ratio (OR) with its 95% confidence interval (CI). Statistical significance was defined by a p value ≤.05.

3 | RESULTS

3.1 | Definition of the study population

A total of 734 patients were included between November 2011 and October 2018 from 99 centres. The median number of cases per centre was 3 (IQR: 3–10). The median age was 60 with 60.1% of men included. The mean height, weight and BMI were 1.70 m, 73 kg and 25, respectively. The most frequent indication was colorectal cancer liver metastases (CRLM) (65.1%) followed by hepatocellular carcinoma (13.4%) and intrahepatic cholangiocarcinoma (7.2%).

3.2 | Growth patterns from stage 1 to stage 2

The median sFLR at stage 1 was 0.23 (IQR, 0.18–0.28), the median sFLR at stage 2 was 0.39 (IQR: 0.31–0.46) and median sFLR increase was 0.15 (IQR: 0.1–0.2). Relationships between demographics, tumour characteristics and perioperative stage 1 outcomes with FLR measurements in stages 1 and 2 and percentage of volume increase are given in Table 1. The variables associated with a lower increase from sFLR1 to sFLR2 were age>68 years ($p = .02$), height >1.76 m ($p < .01$), weight >83 kg ($p < .01$), BMI>28 ($p < .01$), male gender ($p < .01$), antihypertensive therapy ($p < .01$), operation time >370 minutes ($p < .01$) and hospital stay>14 days ($p < .01$). The variables related with a lower rate of volume increase were age >68 years ($p < .01$), weight >83 kg ($p < .01$), male gender ($p = .03$), no chemotherapy ($p < .01$), antihypertensive therapy ($p < .01$), liver disease ($p = .01$), operation time>370 minutes ($p = .01$,) and hospital stay >14 days ($p < .01$).

Regarding anthropometric parameters, difficulties in achieving a higher sFLR2 were observed in elderly, obese and male patients (Figure 1A–C). In detail, median sFLR increase was 0.17 (IQR: 0.12–0.22) for less than 53 years and 0.14 (IQR: 0.09–0.18) for more than 68 years, 0.16 (IQR:0.12–0.23) for less than 63 kg and 0.14 (IQR: 0.09–0.18) for more than 83 kg; and 0.15 (IQR: 0.10–0.19) for male and 0.16 (IQR: 0.11–0.21) for female. The only factor that presents a significant difference was inter-stage interval with a median of 8.5 days (IQR: 7–13) for male and 7.5 days (IQR: 5–11) for female.

3.3 | Influential factors in the interstage interval

The time required to reach sufficient volume for stage 2 was divided into three groups: less than 7 days, between 7 and 14 days and more than 14 days (Table 2). No significant differences in the groups were observed except gender ($p = .03$), operative time ($p < .01$) and hospital stay ($p < .01$). In this case, male gender accounts for 40.3% in group <7 days, compared with 50% of female, and female present 15.3% in group >14 days compared with 20.6% of male. Interestingly, female patients present in a marked higher proportion in the shorter time groups to achieve the second stage than male counterparts (Figure 2). We have included details on patients completing stage 2 surgery and those who did not in Table S1. Patients who did not reach stage 2 presented a higher rate of complications (29.1% vs 63.4%, $p < .001$) and mortality (0.7% vs 43.3%, $p < .001$).

3.4 | Factors affecting modelled daily growth of the FLR

The slope of the mixed lineal model for patient characteristics is presented in Table 3. This model characterizes the growth of the FLR with respect to time and as expected a different initial situation for each patient, we propose a random intercept. Overall, the FLR increases by 0.0142 (CI: 0.0134–0.0150) per day after the first stage. Table 3 presents this slope for the reference group of each factor and the differences with the other groups. The factors associated with a significant lower difference in the increase per day were age >68 years [−0.0026 (CI: −0.0048 to 0.0003)], weight >83 kg [−0.0033 (CI: −0.0056 to 0.0009)], male gender [−0.0017 (CI: −0.0034 to 0.0001)], antihypertensive therapies [−0.0026 (CI: −0.0043 to 0.0008)], renal disease [−0.0145 (CI: −0.0026 to 0.0215)] and hospital stay >14 days [−0.0045 (CI: −0.0067 to 0.0023)]. Figure 3A-F displays the increase in FLR respect to the age, weight and gender.

3.5 | Colorectal liver metastases cohort

In this cohort, the dominant tumour entity was CRLM with total of 472 patients (64%). In this group, variables associated with a lower increase from sFLR1 to sFLR2 and rate of volume increases were age>68 years ($p = .09$ and $p = .02$), height >1.76 m ($p < .01$ and $p = .03$), weight >83 kg ($p < .01$ and $p < .01$), BMI>28 ($p = .03$ and $p = .04$), male gender ($p < .01$ and $p = .03$), antihypertensive therapy ($p < .01$ and $p < .01$) and hospital stay>14 days ($p < .01$ and $p = .01$), respectively (Table S2). In Table S3 we have analysed factors related with the time needed to reach sufficient volume for stage 2 surgery and created three groups (less than 7 days, between 7 and 14 days and more than 14 days). No differences between patients who had received chemotherapy or not have been observed. Comparing the cohort of liver primary malignancies with CRLM patients, these patients present a higher increase of %FLR [0.16 (0.11–0.21 vs 0.14 (0.09–0.18), $p < .001$] with less blood transfusions (18.2 vs 34.1%, $p < .001$), a shorter hospital stay [9 (7–13) vs 12 (8–16), $p < .001$] and less interstage complications (27.1 vs 38.2%, $p = .01$) (Table S4). Interestingly, the CRLM cohort presents with more histological liver alterations (steatohepatitis, fibrosis, macrosteatosis, sinusoid obstruction, cirrhosis and CASH) in CRLM vs. liver primary malignancies, which was classified as 'liver disease' in this study.

4 | DISCUSSION

This is the first registry based multi-institutional analysis modelling liver growth patterns in ALPPS. This analysis first identifies anthropometrical data including age, weight, height and gender as key factors for liver regeneration following ALPPS. Antihypertensive medication was also associated with an impaired liver regeneration. Interestingly, the negative effect of chemotherapy, classically related to liver damage was not related to a decreased liver regeneration.[19]

PHLF is the most feared complication after extended liver resections, as it is associated with high mortality rates.[20] In cases of insufficient FLR, classical regeneration techniques can increase the FLR by up to 50%, requiring, however, a higher regeneration time. Clinical studies show that a significant percentage of patients do not reach completion hepatectomy, varying between 10 and 40%.[21,22] Tumour progression and the absence of regeneration (or insufficient regeneration) are the two fundamental causes of failure of these

TABLE 1 Relationships between demographics, tumour characteristics and perioperative stage 1 outcomes with sFLR measurements in stages 1 and 2 and percentage of volume increase

	N		sFLR Stg1	*p*	sFLR Stg2	*p*	Increasement	*p*
	734		**0.23 (0.18–0.28)**		**0.39 (0.31–0.46)**		**0.15 (0.1–0.2)**	
Age (years)	729							
<53	186	25.5%	0.23 (0.18–28)	.476	0.40 (0.33–0.47)	.022	0.17 (0.12–0.22)	.001
53–68	364	49.9%	0.22 (0.18–0.28)		0.39 (0.31–0.46)		0.15 (0.11–0.20)	
>68	179	24.6%	0.23 (0.18–0.27)		0.37 (0.31–0.44)		0.14 (0.09–0.18)	
Height (m)	734							
<1.63	176	24.0%	0.24 (0.19–0.3)	<.001	0.4 (0.34–0.49)	<.001	0.16 (0.1–0.21)	.153
1.63–1.76	388	52.9%	0.23 (0.18–0.28)		0.39 (0.32–0.45)		0.15 (0.1–0.2)	
>1.76	170	23.2%	0.21 (0.16–0.26)		0.35 (0.29–0.45)		0.14 (0.1–0.19)	
Weight (kg)	734							
<63	174	23.7%	0.25 (0,2–0.3)	<.001	0.42 (0.35–0.51)	<.001	0.16 (0.12–0.23)	.002
(63,83)	377	51.4%	0.22 (0.18–0.28)		0.39 (0.31–0.45)		0.15 (0.1–0.2)	
>83	183	24.9%	0.21 (0.17–0.26)		0.35 (0.3–0.44)		0.14 (0.09–0.18)	
Body mass index	734							
<22.7	183	24.9%	0.24 (0.19–0.3)	.004	0.41 (0.35–0.49)	.007	0.16 (0.11–0.22)	.076
(22.7–28)	368	50.1%	0.22 (0.17–0.28)		0.38 (0.31–0.45)		0.15 (0.11–0.2)	
>28	183	24.9%	0.22 (0.08–0.27)		0.39 (0.31–0.45)		0.14 (0.1–0.19)	
Gender	730		023 (0.18–0.28)	.048	0.39 (0.31–0.46)	.007	0.15 (0.1–0.2)	.033
Male	439	60.1%	0.22 (0.18–0.28)		0.37 (0.3–0.45)		0.15 (0.1–0.19)	
Female	291	39.9%	0.24 (0.19–0.28)		0.4 (0.32–0.47)		0.16 (0.11–0.21)	
Diagnosis	725		0.23 (0.18–0.28)	.001	0.39 (0.31–0.46)	.153	0.15 (0.1–0.2)	<.001
CRLM	472	65.1%	0.22 (0.18–0.28		0.39 (0.32–0.47)		0.16 (0.11–0.21)	
HCC	97	13.4%	0.27 (0.21–0.31)		0.4 (0.31–0.46)		0.12 (0.09–0.16)	
Other	57	7.9%	0.23 (0.18–0.25)		0.4 (0.34–0.49)		0.17 (0.12–0.23)	
IHCC	52	7.2%	0.22 (0.19–0.26)		0.39 (0.31–0.43)		0.16 (0.1–0.19)	
PerihiliarCC	30	4.1%	0.22 (0.17–0.27)		0.33 (0.29–0.42)		0.14 (0.10–0.17)	
Neuroendocrine	17	2.3%	0.21 (0.19–0.26)		0.36 (0.29–0.4)		0.13 (0.1–0.18)	
Tumour nodules	421		0.23 (0.18–0.29	.457	0.39 (0.32–0.47)	.702	0.15 (0.1–0.2)	.419
1	116	27.6%	0.24 (0.18–0.3)		0.41 (0.32–0.49)		0.15 (0.10–0.18)	
2–6	191	45.4%	0.23 (0.18–0.29)		0.39 (0.32–0.46)		0.15 (0.11–0.20)	
>6	114	27.1%	0.22 (0.19–0.28)		0.4 (0.32–0.48)		0.16 (0.11–0.23)	

(Continues)

TABLE 1 (Continued)

	N		sFLR Stg1	p	sFLR Stg2	p	Increasement	p
	734		**0.23 (0.18–0.28)**		**0.39 (0.31–0.46)**		**0.15 (0.1–0.2)**	
Tumour size (mm)	440		0.23 (0.18–0.28)	.053	0.39 (0.31–0.46)	.537	0.15 (0.1–0.21)	.608
<35	110	25.0%	0.24 (0.18–0.28)		0.38 (0.31–0.47)		0.15 (0.12–0.20)	
35–85	221	50.2%	0.22 (0.18–0.27)		0.39 (0.31–0.45)		0.16 (0.11–0.21)	
>85	109	24.8%	0.24 (0.19–0.29)		0.4 (0.32–0.47)		0.14 (0.10–0.21)	
Chemotherapy	534							
Yes	460	62.7%	0.22 (0.18–0.28)	.156	0.39 (0.32–0.47)	.493	0.16 (0.11–0.21)	.002
No	274	37.3%	0.23 (0.18–0.28)		0.39 (0.31–0.45)		0.14 (0.10–018)	
Cycles chemotherapy	460		0.22 (0.18–0.28)	.016	0.39 (0.32–0.47)	.516	0.16 (0.11–0.21)	.140
<4	111	24.1%	0.24 (0.19–0.3)		0.40 (0.33–0.48)		0.15 (0.10–0.20)	
4–12	255	55.4%	0.22 (0.17–0.27)		0.39 (0.32–0.47)		0.17 (0.12–0.21)	
>12	94	20.4%	0.22 (0.18–0.27)		0.37 (0.30–0.46)		0.16 (0.10–0.22)	
Antihypertensive	685		0.23 (0.18–0.28)	.274	0.39 (0.31–0.46)	.003	0.15 (0.1–0.2)	<.001
Yes	237	34.6%	0.22 (0.17–0.28)		0.37 (0.3–0.44)		0.14 (0.1–0.19	
No	448	65.4%	0.23 (0.18–0.28		0.4 (0.32–0.47		0.16 (0.11–0.21)	
COPD	705		0.23 (0.18–0.28)	.589	0.39 (0.31–0.46)	.946	0.15 (0.1–0.2)	.515
Yes	24	3.4%	0.21 (0.19–0.25)		0.37 (0.33–0.46)		0.16 (0.11–0.18)	
No	681	96.6%	0.23 (0.18–0.28)		0.39 (0.31–0.46)		0.15 (0.10–0.20)	
Liver disease	684		0.23 (0.18–0.28)	.064	0.39 (0.31–0.46)	.633	0.15 (0.10–0.20)	.012
No	598	87.4%	0.23 (0.18–0.28)		0.39 (0.31–0.46)		0.15 (0.10–0.21)	
Yes	86	12.6%	0.25 (0.19–0.3)		0.39 (0.30–0.45)		0.14 (0.09–0.17)	
Renal disease	710		0.23 (0.18–0.28)	.758	0.39 (0.31–0.46)	.173	0.15 (0.1–0.2)	.837
Yes	12	1.7%	0.22 (0.19–0.31)		0.45 (0.36–0.54)		0.15 (0.10–0.25)	
No	698	98.3%	0.23 (0.18–0.28)		0.39 (0.31–0.46)		0.15 (0.10–0.20)	
Diabetes mellitus	716		0.23 (0.18–0.28)	.142	0.39 (0.31–0.46)	.695	0.15 (0.10–0.20)	.312
Yes	75	10.5%	0.25 (0.18–0.31)		0.40 (0.31–0.49)		0.14 (0.10–0.19)	
No	641	641	0.23 (0.18–0.28)		0.39 (0.32–0.46)		0.15 (0.10–0.20)	
Operative time (minutes)	677		0.22 (0.18–0.27)	.016	0.38 (0.31–0.45)	.005	0.15 (0.10–0.20)	.017
<232	169	25.0%	0.24 (0.19–0.28)		0.39 (0.32–0.48)		0.15 (0.11–0.21)	
232–370	340	50.2%	0.22 (0.18–0.27)		0.39 (0.32–0.46)		0.15 (0.11–0.21)	
>370	168	24.8%	0.22 (0.17–0.26)		0.35 (0.29–0.43		0.14 (0.10–0.19)	
Pringle manoeuvre	734		0.23 (0.18–0.28)		0.4 (0.32–0.47)		0.16 (0.11–0.21)	

TABLE 1 (Continued)

	N		sFLR Stg1	*p*	sFLR Stg2	*p*	Increasement	*p*
	734		**0.23 (0.18–0.28)**		**0.39 (0.31–0.46)**		**0.15 (0.1–0.2)**	
No	546	74.4%	0.23 (0.18–0.28)	.283	0.39 (0.31–0.46)	.899	0.15 (0.10–0.20)	.221
Yes	188	25.6%	0.22 (0.17–0.27)		0.4 (0.31–0.46)		0.15 (0.10–0.21)	
<16 mins	48	25.5%	0.23 (0.19–0.27)	.231	0.41 (0.33–0.47)	.073	0.17 (0.14–0.21)	.385
15–44 min	93	49.5%	0.24 (0.18–0.28)		0.40 (0.32–0.47)		0.15 (0.10–0.21)	
>44 min	47	25.0%	0.20 (0.16–0.27)		0.35 (0.28–0.44)		0.14 (0.10–0.20)	
RBC transfusion	734							
Yes	165	22.5%	0.22 (0.18–0.27)	.344	0.36 (0.31–0.47	.174	0.14 (0.1–0.18)	.123
No	569	77.5%	0.23 (0.18–0.28)		0.39 (0.32–0.46)		0.15 (0.1–0.21)	
Hospital stay stg1	650		0.23 (0.18–0.28)	.252	0.38 (0.31–0.46)	.002	0.15 (0.10–0.20)	<.001
<8	192	29.5%	0.23 (.19–0.28)		0.41 (0.34–0.48)		0.17 (0.13–0.22)	
8–14	306	47.1%	0.22 (0.18–0.27)		0.37 (0.31–0.46)		0.14 (0.10–0.20)	
>14	152	23.4%	0.22 (0.17–0.28)		0.37 (0.30–0.44)		0.14 (0.10–0.18)	
Complications stg1	683		0.23 (0.18–0.28)	.825	0.39 (0.31–0.46)	.586	0.15 (0.10–0.20)	.469
Yes	214	90.3%	0.22 (0.18–0.28)		0.39 (0.32–0.47)		0.15 (0.11–0.21)	
No	469	197.9%	0.23 (0.18–0.28)		0.38 (0.31–0.45)		0.15 (0.10–0.20)	
Clavien-Dindo	205		0.22 (0.18–0.28)	.429	0.39 (0.32–0.47)	.038	0.15 (0.11–0.21)	.085
I	31	15.1%	0.21 (0.17–0.25)		0.37 (0.31–0.44)		0.15 (0.10–0.22)	
II	89	43.4%	0.22 (0.18–0.28)		0.39 (0.31–0.45)		0.15 (0.11–0.20)	
III	56	27.3%	0.24 (0.19–0.30)		0.40 (0.33–0.54)		0.18 (0.13–0.25)	
IV	24	11.7%	0.25 (0.18–0.29)		0.42 (0.32–0.47)		0.16 (0.10–0.22)	
V	5	2.4%	0.22 (0.17–0.22)		0.29 (0.28–0.31)		0.11 (0.07–0.14)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; periCC, perihiliar cholangiocarcinoma; RBC, red blood cells; sFLR, standarized future liver remmant; Stg, stage.

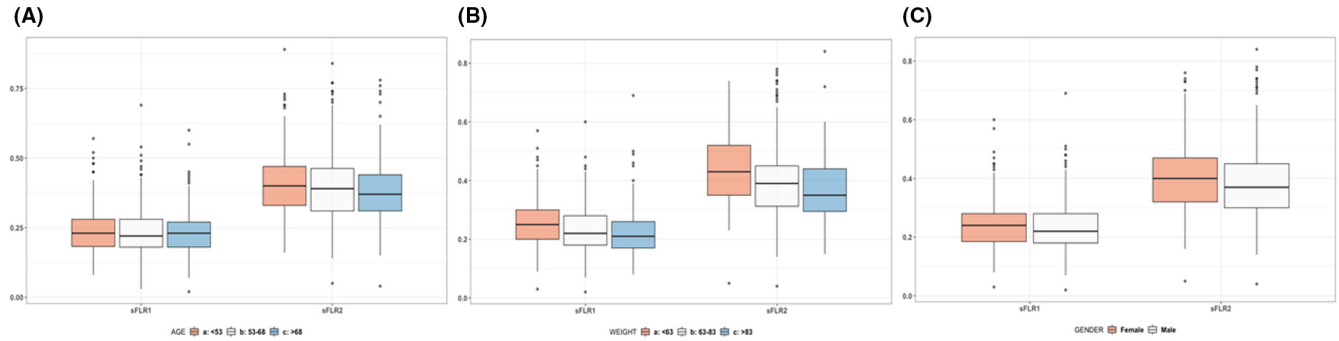

FIGURE 1 Growth patterns between sFLR1 and sFLR2 as a function of age (A), weight (B) and gender (C)

hypertrophy techniques. Denys et al. reported that prolonged and sometimes insufficient hypertrophy was related to blood circulation between both lobes, a finding confirmed in an experimental animal study by angiography.[23] The greater and faster regeneration of ALPPS seems to be related to the occlusion of the intrahepatic circulation, which directs portal flow to the FLR.

When we compare the different liver regeneration techniques, it clear that ALPPS allows a higher resection rate and lower drop-out than portal embolization (PVE) or two-stage liver resection.[12,24–26] Radiological simultaneous portal vein embolization and hepatic vein embolization (LVD) present better results than PVE alone and it has been proposed as an alternative to ALPPS, but Chebaro et al. compare both techniques with a higher successful resection rate for ALPPS with similar 90-day major complications and mortality.[27] Concerning comparative long-term outcomes, the LIGRO RCT comparing ALPPS vs TSH provides highest evidence showing a significantly longer median overall survival (46 vs 26 months) for ALPPS on intent to treat analysis.[28] These analyses highlight that oncological outcomes in ALPPS seem to be favourable.

Clinical and experimental studies effectively reported that there is an early liver regeneration at 24–48 h after hepatectomy and a peak at 48–72 h after portal ligation. It is important to assess whether this early regeneration of the liver (3rd- 4th day) is a simple venous congestion or an efficient regeneration. Schlegel et al., in an experimental study on regeneration in an animal model of ALPPS in mice, showed that the hypertrophy of the FLR in ALPPS was twice that with the portal ligation.[29] According to Alvarez et al., liver biopsies of the FLR in 8 patients, demonstrated true proliferation of hepatocytes with an increase in the mitotic rate after stage 1 and stage 2 surgery.[30]

Clinically, there are factors that can influence liver regeneration. In the first study of the international ALPPS Registry, a decrease regeneration was found due to the following factors: age over 60 years, histological proven liver damage, Pringle manoeuvre and use of chemotherapeutic agents.[31] Performance of the Pringle manoeuvre and liver disease was independently associated with a decreased growth of the FLR. Therefore, to achieve better liver regeneration it is important to avoid the aforementioned factors. In the case of patients with CRLM some authors find inferior regeneration in patients who have received more than six cycles of chemotherapy, while others do not find decreased regeneration. Finally, several factors are considered to impair the growth of FLR. The most commonly cited reasons include the use of pre-procedural chemotherapy, high serum bilirubin levels, concomitant cholangitis and diabetes mellitus.

The human liver is able to regenerate due to a hyperplastic reaction in the residual liver.[32] Some studies suggest that pre-surgical factors such as age, gender, BMI, native liver disease, chemotherapy, platelet count and steatosis have a significant influence on human liver regeneration.[15] Results from different studies are however conflicting and the evidence grade is poor. For example, in this study patients with previous chemotherapy had a higher volume increase than those who did not receive chemotherapy. This finding is counterintuitive, as one would assume that patients with previous chemotherapy could have a higher risk of complications after regeneration because the liver is damaged and there is a greater risk of PHLF. An explanation of this finding is that patients with CRLM are by far the largest number of patients and in general have an advantage in the postoperative course, which seems particularly favourable for improved liver regeneration. Other tumour entities (cholangiocarcinoma, hepatocellular carcinoma, etc), which are not exposed to chemotherapy may not regenerate so well due to cholestasis or other factors, which may impair ~~poor~~ liver function.[33] This difference in liver regeneration of different tumour entities seems to be multifactorial and statistical analysis does not allow to draw clear conclusions on single causes. A novel factor found impairing liver regeneration was antihypertensive medication. However, the present study does not provide sufficient evidence for this conclusion as the percentage of NASH was much too low compared with a high number of patients on antihypertensive treatment (Table 1). It is well known that the use of antihypertensive treatment is related to NASH. In human, there is no evidence of the relationship of these drugs with liver regeneration, but in animals Ramalho et al. describe that the losartan treatment diminished the activated stellate cell population, which is also known to participate in the liver fibrosis process.[34] On the other hand, Ambreen et al. concluded that ACE inhibitor, lisinopril, did not produce major histo-morphological alterations in regenerating fibrotic livers 48 h following partial hepatectomy in a rat model with the exception of non-significant mitosis inhibition and increased hepatocyte binucleation.[35] However, it may improve the hepatic functional capability of fibrotic rats after surgery.

TABLE 2 Influential factors related with interstage interval

	Time			*p*
	0–7 (*n* = 310)	8–14 (*n* = 261)	>14 (*n* = 129)	
Age (years)	60 (53–69)	61 (54–68)	59 (51–69)	.682
Height (m)	1.70 (1.62–1.76)	1.69 (1.64–1.75)	1.71 (1.62–1.78)	.373
Weight (kg)	72 (63–83)	74 (65–83)	73 (61–85)	.432
Body mass index	25.9 (22.4–28)	25.5 (23.3–28.1)	25 (22.2–27.5)	.159
Gender				
Male	170 (0.403)	165 (0.391)	87 (0.206)	.031
Female	137 (0.500)	95 (0.347)	42 (0.153)	
Diagnosis				
CRLM	194 (0.431)	169 (0.376)	87 (0.193)	.074
HCC	37 (0.389)	39 (0.411)	19 (0.200)	
Other	35 (0.648)	13 (0.241)	6 (0.111)	
IHCC	24 (0.471)	22 (0.431)	5 (0.098)	
PeriCC	13 (0.448)	12 (0.414)	4 (0.138)	
Neuroendocrines	6 (0.353)	5 (0.241)	6 (0.353)	
Tumour nodules				
1	56 (0.483)	39 (0.336)	21 (0.181)	.568
2–6	82 (0.436)	72 (0.383)	34 (0.181)	
>6	51 (0.455)	47 (0.420)	14 (0.125)	
Tumour size (mm)				
<35	48 (0.444)	39 (0.361)	21 (0.194)	.634
35–85	85 (0.388)	87 (0.397)	47 (0.215)	
>85	51 (0.477)	36 (0.336)	20 (0.187)	
Chemotherapy				
Yes	198 (0.452)	154 (0.352)	86 (0.196)	.277
No	112 (0.427)	107 (0.408)	43 (0.164)	
Cycles chemotherapy				
<4	45 (0.489)	26 (0.283)	21 (0.228)	.369
4–12	108 (0.429)	93 (0.369)	51 (0.202)	
>12	45 (0.479)	35 (0.372)	14 (0.149)	
Antihyperntesive				
Yes	101 (0.426)	98 (0.414)	38 (0.160)	.260
No	194 (0.453)	151 (0.353)	83 (0.194)	
COPD				
Yes	8 (0.364)	10 (0.455)	4 (0.182)	.676
No	297 (0.451)	243 (0.369)	119 (0.181)	
Liver disease				
No	274 (0.463)	214 (0.361)	104 (0.176)	.157
Yes	30 (0.353)	38 (0.447)	17 (0.200)	
Renal disease				
Yes	4 (0.400)	4 (0.400)	2 (0.200)	.950
No	300 (0.450)	249 (0.373)	118 (0.177)	
Diabetes mellitus				
Yes	31 (0.431)	28 (0.389)	13 (0.181)	.938
No	276 (0.452)	226 (0.370)	109 (0.178)	

(Continues)

TABLE 2 (Continued)

	Time			p
	0–7 (*n* = 310)	8–14 (*n* = 261)	>14 (*n* = 129)	
Operative time (minutes)				
<232	50 (0.309)	73 (0.451)	39 (0.241)	<.001
232–370	156 (0.479)	121 (0.371)	49 (0.150)	
>370	85 (0.509)	50 (0.299)	32 (0.192)	
Pringle				
No	229 (0.445)	186 (0.361)	100 (0.194)	.414
Yes	81 (0.438)	75 (0.405)	29 (0.157)	
RBC transfusion				
Yes	72 (0.453)	56 (0.352)	31 (0.195)	.815
No	238 (0.440)	205 (0.379)	98 (0.181)	
Hospital stay stg1	8 (7–11)	12 (9–14)	11 (7–19)	<.001
Complications stg1				
Yes	85 (0.419)	70 (0.345)	48 (0.236)	.095
No	209 (0.449)	179 (0.385)	77 (0.166)	
Clavien–Dindo				
I	16 (0.516)	13 (0.419)	2 (0.065)	.278
II	38 (0.432)	28 (0.318)	22 (0.250)	
III	18 (0.321)	20 (0.357)	18 (0.321)	
IV	11 (0.478)	8 (0.348)	4 (0.174)	
V	2 (0.400)	1 (0.200)	2 (0.400)	
Sgt1 sFLR	0.23 (0.19–0.28)	0.23 (0.17–0.28)	0.21 (0.17–0.27)	.068
Stg2 sFLR	0.40 (0.33–0.46)	0.39 (0.31–0.46)	0.36 (0.28–0.45)	.015

Note: The time required to reach sufficient volume for stage 2 was divided into three groups: less than 7 days, between 7 and 14 days and more than 14 days.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; periCC, perihiliar cholangiocarcinoma; RBC, red blood cells; sFLR, standarized future liver remmant; Stg, stage.

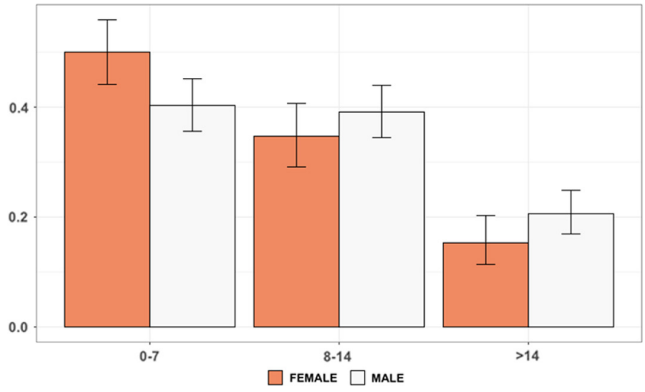

FIGURE 2 Gender influence on the time required to reach sufficient volume for the second intervention in less than 7 days, between 7 and 14 days and more than 14 days

A single centre series has shown that the presence of liver haemodynamic stress intended as a portal vein pressure ≥ 20 mmHg and a pressure gradient <15 mmHg between the portal vein and the hepatic veins at the end of ALPPS stage 1 can negatively influence volume and function of the FLR.[36] However, this is the only experience of the ALPPS Registry on haemodynamic changes of ALPPS needing further validation. To directly assess liver function, some authors have used liver function tests, like mebrofenin hepatobiliary scintigraphy. Truant et al. suggests that this test provides a valuable contribution to determine most appropriate timing of stage 2 surgery[37] and Tomassini et al. observed that patients presenting a KGRFLR ≤4.1%/day and a HBSFLR ≤2.7%/min/m2 are at high risk of PHLF.[38]

In a survey among 133 hepatobiliary centres, the minimal remnant liver volume for resection was 25% (15–40%) in cases of normal liver parenchyma and 50% (25–90%) in the presence of underlying cirrhosis.[39] A recently published large cohort study of 486 patients undergoing ALPPS for CRLM revealed a median pre-stage 1 sFLR of 22%. Earlier reports have shown a discrepancy between FLR function and volume, especially after liver growth induction.[40] Functional analysis has shown to be superior to volumetry in the identification of patients with increased surgical risk.

Anthropometric measurements have been useful to determine the relationship between various body measurements (height, weight, percentage body fat, gender, etc.) and medical outcomes.[41] Anthropometric measurements are frequently used to diagnose

TABLE 3 This model characterizes the growth of the FLR with respect to time and as expected a different initial situation for each patient

	Univariant			Multivariant		
	Estimates	**CI**	***p***	**Estimates**	**CI**	***p***
	0.0142	**0.0134 to 0.0150**	**<0.001**			
Age (years)	0.0149	0.0134 to 0.0165	<.001			
<53						
53–68	−0.0000	−0.0020 to 0.0019	.978			
>68	−0.0026	−0.0048 to −0.0003	.026	−0.0019	−0.0055 to 0.0017	.326
Height (m)	0.0147	0.0130 to 0.0164	<.001			
<1.63						
(1.63–1.76)	−0.0003	−0.0023 to 0.0017	.757			
>1.76	−0.0014	−0.0038 to 0.0009	.235			
Weight (kg)	0.0157	0.0140 to 0.0174	<.001			
<63						
(63, 83)	−0.0013	−0.0033 to 0.0007	.209			
>83	−0.0033	−0.0056 to −0.0009	.007	−0.0006	−0.0047 to 0.0036	.795
Body mass index	0.0156	0.0140 to 0.0173	<.001			
<22.7						
(22.7–28)	−0.0017	−0.0037 to 0.0003	.099			
>28	−0.0023	−0.0047 to −0.0000	.050			
Gender	0.0153	0.0140 to 0.0166	<.001			
Male	−0.0017	−0.0034 to −0.0001	.041	−0.0015	−0.0051 to 0.0021	.436
Diagnosis	0.0141	0.0131 to 0.0151	<.001			
CRLM						
HCC	−0.0003	−0.0029 to 0.0022	.793			
Other	0.0036	0.0001 to 0.0070	.044	0.0001	−0.0094 to 0.0096	.979
IHCC	0.0016	−0.0018 to 0.0050	.348			
PeriCC	−0.0018	−0.0055 to 0.0020	.364			
Neuroencorine	−0.0023	−0.0077 to 0.0032	.415			
Tumour nodules	0.0150	0.0129 to 0.0171	<.001			
1						
2–6	−0.0005	−0.0031 to 0.0021	.702			
>6	0.0005	−0.0025 to 0.0034	.765			
Tumour size (cm)	0.0133	0.0111 to 0.0154	<.001			
<35						
35–85	0.0008	−0.0018 to 0.0033	.556			
>85	0.0022	−0.0009 to 0.0054	.167			
Chemotherapy	0.0139	0.0126 to 0.0153	<.001			
Yes	0.0004	−0.0012 to 0.0021	.608			
No						
Cycles chemo	0.0156	0.0131 to 0.0181	<.001			
<4						
4–12	−0.0018	−0.0046 to 0.0011	.233			
>12	−0.0009	−0.0044 to 0.0026	.604			
Antihypertensive	0.0153	0.0143 to 0.0163	<.001			
Yes	−0.0026	−0.0043 to −0.0008	.004	0.0035	−0.0001 to 0.0071	.066
No						

(Continues)

TABLE 3 (Continued)

	Univariant			Multivariant		
	Estimates	CI	p	Estimates	CI	p
	0.0142	**0.0134 to 0.0150**	**<0.001**			
COPD	0.0143	0.0135 to 0.0151	<.001			
Yes	0.0002	−0.0044 to 0.0047	.947			
No						
Liver disease	0.0144	0.0135 to 0.0153	<.001			
No						
Yes	−0.0002	−0.0028 to 0.0024	.883			
Renal disease	0.0143	0.0135 to 0.0151	<.001			
Yes	0.0120	0.0026 to 0.0215	.012	0.0347	0.0027 to 0.0667	.05
No						
Diabetes mellitus	0.0146	0.0138 to 0.0155	<.001			
Yes	−0.0023	−0.0049 to 0.0002	.076			
No						
Operative time (minutes)	0.0132	0.0117 to 0.0148	<.001			
<232						
232–370	0.0019	−0.0000 to 0.0038	.053			
>370	0.0004	−0.0019 to 0.0027	.715			
Pringle	0.0139	0.0129 to 0.0148	<.001			
No						
Yes	0.0014	−0.0004 to 0.0033	.126			
RBC transfusion	0.0143	0.0134 to 0.0153	<.001			
Yes	−0.0004	−0.0023 to 0.0015	.654			
No						
Hospital stay stg 1	0.0156	0.0141 to 0.0171	<.001			
<8						
8–14	−0.0006	−0.0025 to 0.0014	.553			
>14	−0.0045	−0.0067 to −0.0023	<.001	−0.0036	−0.0074 to 0.0001	.071
Complications stg 1	0.0138	0.0129 to 0.0148	<.001			
Yes	0.0014	−0.0004 to 0.0033	.124			
No						
Clavien–Dindo	0.0165	0.0124 to 0.0207	<.001			
I						
II	−0.0015	−0.0062 to 0.0032	.532			
III	−0.0018	−0.0067 to 0.0030	.469			
IV	0.0007	−0.0054 to 0.0067	.833			
V	−0.0073	−0.0173 to 0.0027	.159			
sFLR sgt1	0.0120	0.0107 to 0.0134	<.001			
<0.19						
0.19–0.24	0.0026	0.0004 to 0.0047	.023	0.0017	−0.0016 to 0.0050	.339
0.24–0.28	0.0016	−0.0005 to 0.0037	.146			
>0.28	0.0017	−0.0004 to 0.0039	.111			

Notes: Linear mixed model with random intercepts and slope (TIME) with marginal effects. The partial effect is presented with respect to the reference value (empty) in each variable.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; periCC, perihiliar cholangiocarcinoma; RBC, red blood cells; sFLR, standarized future liver remmant; Stg, stage.

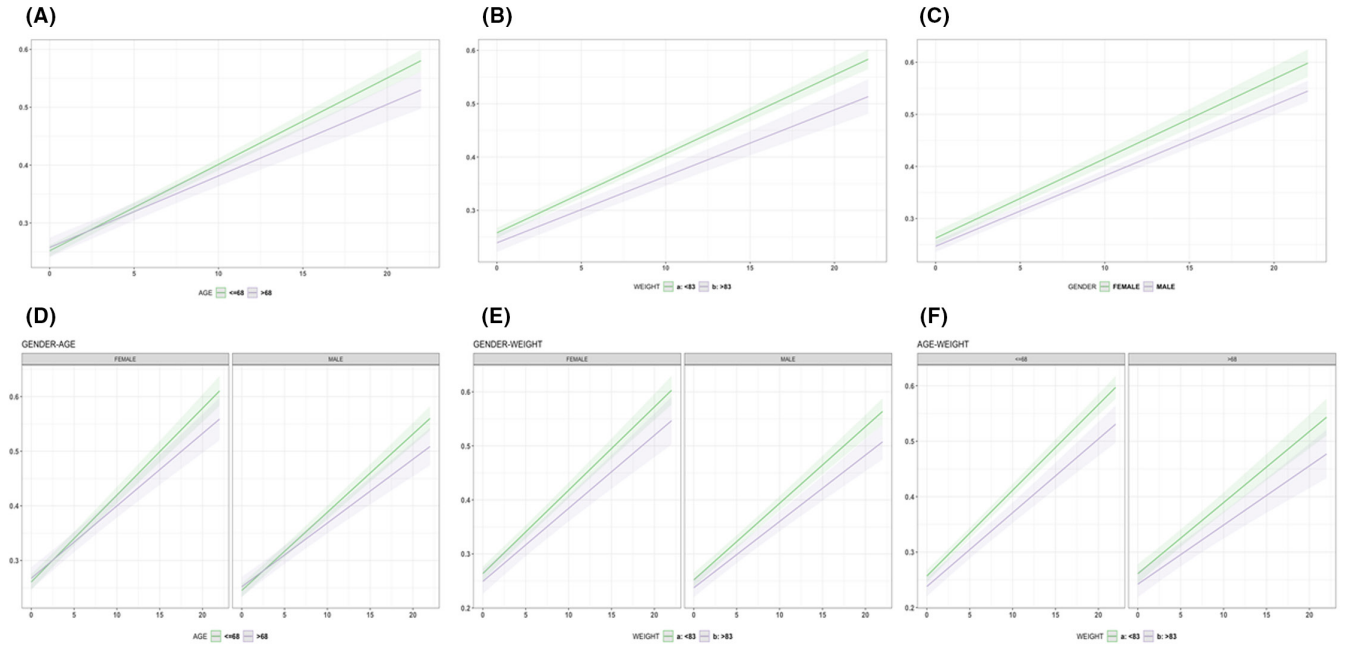

FIGURE 3 Visualizations about the relationship of age (A), weight (B) and gender (C) in the daily growth of the FLR according to the mixed linear model. Correlations between variables gender-age (D), gender-weight (E) and age-weight (F)

malnutrition in resource-poor clinical settings, but their relationship with hepatic regeneration has not been widely studied.[42] The relationship between liver and body mass is exemplified by the precision with which the liver-body mass ratio is restored after partial liver resection. However, the compartments, against which the liver mass is so exquisitely regulated, currently remain undefined. Classically, weight has been associated with a higher risk of liver failure,[43] but recently, Amini et al. reported that BMI did not impact liver regeneration during the first 2 months.[44] In contrast, kinetic growth per week between 2 and 7 months postoperatively was less among overweight and obese patients. The loss of regenerative capacity is the most dramatic age-associated alteration in the liver. Cieslak et al. shows that liver function deteriorates with age.[45] Since the regenerative capacity of the liver correlates with liver function, this finding should be taken into account when assessing surgical risk in patients considered for major liver resection. In the clinical setting, the decline of hepatic regenerative capacity is an important concern because most of the elderly in addition use different medications which could enhance liver injury. In the present study, the presence of a previous kidney disease was related to a growth rate below the average of patients without kidney disease. Following extended liver resection, acute kidney injury (AKI) is associated with an increased morbidity and mortality. ALPPS is a major independent risk factor for the development of AKI and a sufficient future liver remnant could avoid postoperative AKI. Reese et al. included 146 patients undergoing extended liver resection and the incidence of chronic kidney disease was significantly higher in patients with AKI.[46] In the AKI group, the proportion of extended right hepatectomies was the highest (53%), followed by ALPPS (43%). Besides age and chronic kidney disease, ALPPS was an independent risk factor for postoperative AKI.

The two main diagnostic issues in ALPPS are the volumetric assessment of the FLR and the timing of stage 2 (sufficient volume gain or better sufficient gain of functional volume). Correlations of CT volumetry with liver function and postoperative outcomes are, however, not consistent. The size of the FLR may not reflect function, which might be impaired by an underlying parenchymal damage. Of note, liver failure after ALPPS occurred in 14 and 30% after stage 1 and 2, respectively, and 75% of the deaths after ALPPS are related to liver failure.[47]

The main limitation of the present study was related with the missing data. This is an inherent characteristic of all large registries but can be minimized by direct contact to centres to fill data gaps. In favour of our study, we would like to highlight that the main variables analysed related to anthropometric factors (age, sex, height and weight) and liver regeneration present a very low percentage of missing data (Table 1).

5 | CONCLUSION

Height, weight, size and gender are the variables that most constantly influence both daily growths, the interstage percentage increase and the standardized FLR before the second stage. Other variables such as the negative effect of antihypertensive drugs on rapid regeneration represent a novelty that had not been described in humans. This observation requires more studies to know the real extent of their impact on liver regeneration. Similarly, the concept

that chemotherapy increased the risk of liver failure, according to the findings of this study, could be related to drug-induced liver damage, but not to a decreased capacity for regeneration. Even so, more studies in this direction are necessary to corroborate the findings of this study.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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