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A study of rate of volumetric regeneration of liver after liver resection and its correlation with platelets and synthetic liver function tests: a single tertiary care centre experience

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ABSTRACT

Background: Aim of our study was to evaluate the impact of pre and postoperative platelet counts and synthetic liver function tests on liver regeneration and its correlation with CT volumetry in patients undergoing liver resections with curative intent.
Methods: All major and minor liver resections (maximum 30) between July 2016 and May 2019 at our hospital were included in the study according to the inclusion criteria and patients who had data available on preoperative, 2 weeks and 2 months postoperative platelet counts, synthetic liver function tests as well as triple phase CECT images, were identified retrospectively and these tests will be done for patients who are included prospectively.
Results: The rate of regeneration expressed as % RFLR is proportional to the extent of resection. It was less than 20% in WLE and less than 100% in left lobe resections and 100 to 300% in patients undergoing right hepatectomies and extended right hepatectomies**.** There was no statistically significant effect of sex, age, BMI, serum albumin, platelet count, INR, preoperative chemotherapy and presence of cirrhosis on percentage of regeneration as well as rate of regeneration. However, perioperative low serum albumin and platelet count had statistically significant effect on mortality ($p<0.001$).
Conclusions: We conclude that; greater the extent of liver resection, faster is the rate of regeneration. Perioperative low serum albumin and platelet counts have significant effect on mortality.

Keywords: Volumetric regeneration, Liver resection, Liver function test, Hepatectomies, Platelet count

INTRODUCTION

Indications for hepatectomyinclude malignancies, benign tumors, metastasis from GI tumors, parasitic cysts and hemangiomas.[1] Partial hepatectomy (PHx) is also done on a live healthy donor to obtain a part of the liver for liver transplantation.[2] PHx removes two thirds of the liver mass.[3] The flow of portal blood per hepatocyte or unit liver mass theoretically increases threefold after PHx. Several signaling changes appear in liver tissue and hepatocyte nuclei within 15 minutes after PHx.[4] Regeneration of the liver after hepatectomy has been reported to be regulated by many factors, including the percentage of resected liver volume, insulin or insulin-like growth factor, humoral factors in the portal blood flow, the vagus nerve and many of the growth factors in the serum.[5,6] Platelets contain proteins required for hemostasis, as well as many growth factors required for organ development, tissue regeneration and repair.[7] The regenerative effect of platelets in the liver involves a direct effect on hepatocytes, a cooperative effect with liver sinusoidal endothelial cells, and a collaborative effect with Kupffer cells.[8-10] Recent studies show that platelets have a vital role in liver regeneration after a partial liver resection. It has been shown to be a strong and independent predictor of postoperative liver dysfunction and postoperative mortality.[11,12]

The future liver remnant volume (FLRV) is an important potential risk-factor for the development of post-hepatectomy liver failure (PHLF), which is associated with an increase of postoperative complications and with a longer hospitalization. PHLF is characterized by an increase of the international normalized ratio values and of serum bilirubin levels from the fifth post-operative day and is a main contributor to mortality post-surgery.[13] In living donor liver transplantation (LDLT), preoperative computerized topography (CT) volumetry is essential to assess the volume of the future liver remnant (FLR) in donors and the volume of the future resected liver in recipients so that possible regeneration can be estimated for the best chance of surgical success in both. FLR in this method is usually expressed as a ratio of remnant volume to the total functional liver volume (total liver volume-tumor volume).[14,15] There is evidence from radionuclide studies that the increase in the functional capacity of the liver after preoperative (PVE) portal vein embolization may be more than the increase in volumes that are measured using CT volumetry.[16]CT volumetry also is routinely performed when major liver resection is planned for tumors, and it is used for guidance of portal vein embolization based on the calculated volumes.[17,18]In the present era of advanced hepatobiliary surgery, FLRV represents an important potential risk factor for the development of PHLF. Therefore, a preoperative CT/MRI evaluation of accurate liver volumes with precision, is of paramount importance to reduce surgical complications, especially for extensive resections.[19-21]

Aim and objectives

Current study aims at evaluating the accuracy of preoperative CT volumetry and the impact of perioperative synthetic liver function tests and platelet counts on regeneration.

METHODS

All 30 major and minor liver resections between July 2016 and May 2019 in Army hospital research and referral, Delhi were included in the study.

Inclusion and exclusion criteria

An inclusion criterion was all patients undergoing elective liver resection (major or minor liver resections) including living donor liver transplantation (LDLT). Exclusion criteria were all patients with prior history of cholangitis and patients with preoperative diagnosis of hepatolithiasis. Primary outcome was to measure the impact of preoperative and postoperative platelet counts and synthetic liver function tests on liver regeneration and short-term outcomes among patients undergoing liver resections with curative intent. Secondary outcomes evaluated were length of hospital stay, postoperative liver failure and postoperative morbidity/ mortality.

Patients' data available on preoperative, 2 weeks and 2 months postoperative platelet counts, synthetic liver function tests like serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin (Se ALB) and International normalized ratio (INR) as well as triple phase CECT images, were collected. Performa was used for demographic, perioperative, laboratory and clinicopathological data collection, including age, sex, co-morbidities, and tumor type, number, size and laterality. Preoperative laboratory variables of interest were recorded, including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), INR, albumin, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum albumin levels. All the above variables were repeated at 2 weeks and at 2months postoperatively. All patients underwent multi-slice contrast-enhanced triple phase CT after written informed consent before surgery and 2 weeks, 2 months post-surgery. The total liver volume (TLV)/left lobe/right lobe volumes were measured by tracing the liver outline on the axial portal venous phase images using Myrian software system. In this method, major vessels, including the inferior vena cava and extrahepatic portal vein, in addition to major fissures such as that for the ligamentum teres, were excluded and the right lobe volumes were calculated including the MHV (middle hepatic vein). At surgery, the exact weight of the resected liver was measured in grams using a digital weighing machine.

Treatment and operative details collected included type of liver resection (WLE or sectionectomies, right hepatectomy, left hepatectomy, extended right hepatectomy, extended left hepatectomy,right hepatectomy+additional procedure, left hepatectomy+ additional procedure), duration of surgery, biliary reconstruction, additional procedure done, concomitant use of ablation, external biliary drainage, preoperative(if available) and postoperative histopathological reports and length of hospital stay. Following liver surgery, the resected liver volume was subtracted from TLV to define postoperative remnant liver volume (RLVp). The absolute resected liver weight was considered the actual resected liver volume because liver has nearly the same density as water. To determine the regeneration index, liver volume was measured at 2 weeks and at 2 months after surgery. Rate of regeneration (in other words) % regenerated future liver remnant (RFLR) was calculated by dividing the regeneration index by the time (in weeks) that elapsed between surgery and the subsequent volumetric scan. Perioperative data included whether the patient had undergone preoperative portal vein embolization or received perioperative chemotherapy/ radiotherapy. We defined short term outcomes as the complications like perioperative major/minor bleed, postoperative biliary leak, postoperative intra-abdominal collections, surgical site infection, PHLF and mortality within 30days of postoperative period. PHLF (Post Hepatectomy Liver Failure) was defined as "A post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying function, characterized by increase in the INR and hyperbilirubinemia on or after postoperative day 5." We defined low albumin as less than 3.5g/dl and low platelet count as less than 1.5 lakh/ml of blood.

Type of study, study population and sample size

Current study was an original research article, cohort study (both retrospective and prospective). The study population was derived from the serving and retired army personnel and their dependent families who reported to our hospital. A total of 30 consecutive patients undergoing liver resections who met the inclusion and exclusion criteria were enrolled. The sample size was decided based on the patient load at our hospital in previous one year.

Statistical methods

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD. Normality of data was tested by Kolmogorov-Smirnov test. Statistical tests were applied as follows; student's paired t-test was used to see the change in variables with respect to time. ANOVA test followed by post-hoc test was applied for testing mean values between more than 2 groups. Linear regression was applied to see the effect of set of variables on a dependent variable, p value less than 0.05 was considered as significant at 95% confidence level. SPSS version 18.0 was used for analysis.

RESULTS

In current study average age of the group was 51.7 years (range of 2 years to 75 years). The male:female ratio was 7:3. In our study, out of 30 patients, hepatocellular carcinoma was the most common indication for surgery followed by cholangiocarcinoma. Cirrhosis was seen in 4 (13.33%) patients, out of which 2 (6.66%) were Hepatitis B antigen positive. Overall, 7 patients were Hepatitis B antigen positive and 01 was HCV positive. Average serum albumin of the patients was 3.51 (1.8 to 4.3). Average body mass index (BMI) of the group was 23.27 kg/m^2 (17.2 to 28.7kg/m^2). There was no statistically significant effect of sex, age, serum albumin, platelet count, INR, BMI, preoperative chemotherapy and presence of cirrhosis on percentage of regeneration as well as rate of regeneration (Table 1). However, perioperative low serum albumin and platelet count had statistically significant effect on mortality (p<0.001). (Figure 1-2).

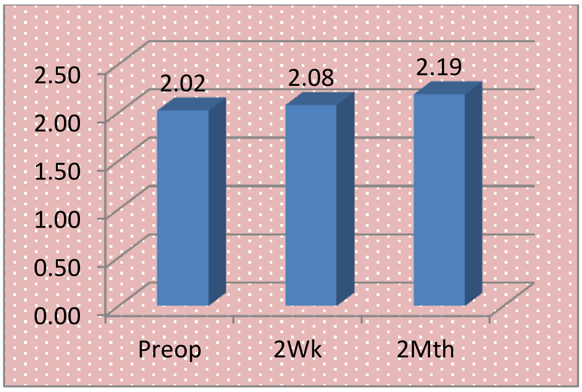

Figure 1: Platelets (lakhs).

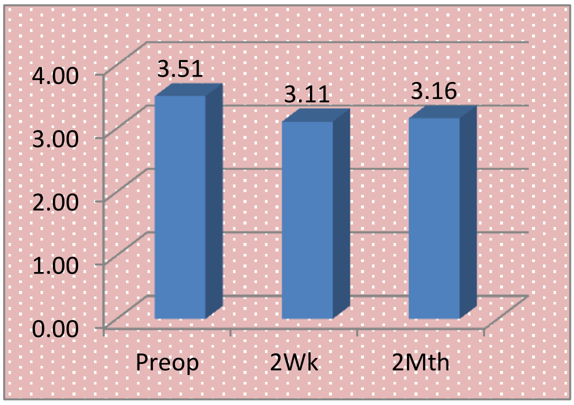

Figure 2: Albumin levels.

In our study, we had 2 (6.67%) mortality within 30 days of postoperative period and 4 (13.33%) after the 30 days postoperative period (Figure 3).

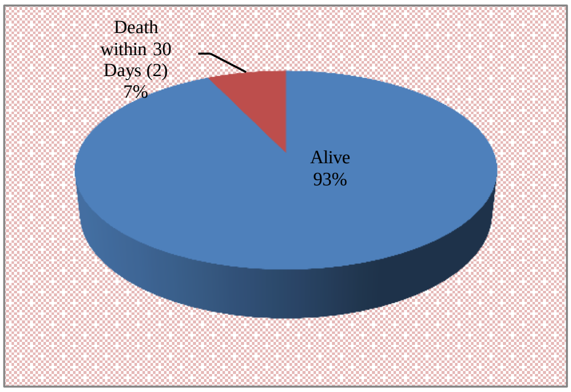

Figure 3: Death rates.

Out of these 4 patients one patient died of post-hepatectomy liver failure and the other three died subsequently due to disease recurrence in a one year follow up. Two (6.67%) patients had post-hepatectomy liver failure out of whom one patient subsequently didn't survive and the same patient also developed a pleuro-biliary fistula. In our study, most common complications seen were bile leak and SSI (surgical site infection), with an incidence of 20% each. One patient had a major GI bleed for which he underwent re-exploration. The average hospital stay was 17.79 days (08 to 57 days). Duration of hospital stay was statistically significant in patients with postoperative bile leak. Our study group involved six types of surgeries from S0 to S6. (Table 2) (S0=wide local excision, S1= right hepatectomy, S2= right extended hepatectomy, S3= left hepatectomy, S4= left extended hepatectomy, S5= S1+additional surgical procedure like hepaticojejuno-stomy etc. S6=S3+additional surgical procedure like hepaticojejunostomy etc). The percentage of regeneration was least in the S6 group and highest in the S2 group both at 2 weeks and at 2 months (Figure 4). For the ease of calculation, the surgical groups were grouped into GS1 and GS2 which include S1, S2, S5 and S0, S3 and S6 respectively. S4 surgery was not performed. The percentage of regeneration is highest in the GS1 group both at 2 weeks and at 2 months, but it is not statistically significant when compared to the percentage of regeneration in GS2 group. The rate of regeneration expressed as % RFLR is proportional to the extent of resection. It was less than 20% in WLE and less than 100% in left lobe resections and 100 to 300% in patients undergoing right hepatectomies and extended right hepatectomies (Figure 4). RH group: there was no statistically significant difference between mean of (ELrW) estimated resected liver weight and actual resected liver weight (ALrW) in RH (815.89±134 vs. 887.2±126 gm; p=0.06). The correlation between ELrW and ALrW for RH was very strong and statistically significant (r=0.82, p<0.001). LH: although ELrW and ALrW correlated strongly (r =0.81, p<0.001), mean of ELrW was significantly high as compared to mean of ALrW (460±118 *vs.* 433±102 gm; p=0.003). (Figure 5-7).

DISCUSSION

In our study preoperative low serum albumin and platelet count had statistically significant effect on mortality (p<0.001). Margonis et al published a study of 99 patients undergoing liver resections.[22] Overall, 25 patients (25%) had a low platelet count (less than 150 × 10(9)/l), whereas 74 had a normal-high platelet count (at least 150 × 10(9)/l). Despite having comparable clinicopathological characteristics and RLVp/TLV at surgery (p=0·903), the relative increase in liver volume within 2 months was considerably lower in the low-platelet group (3·9 vs. 16·5 per cent; p=0.043).

Patients with a low platelet count had an increased risk of postoperative complications (72 vs. 38%; p=0·003), longer hospital stay (8 versus 6 days; p=0·004) and worse median overall survival (24·5 vs. 67·3 months; p=0·005) than those with a normal or high platelet count. Though the perioperative platelet count did not show any statistically significant effect on liver regeneration, regarding the mortality and morbidity, our results are similar to that of this study. Immediate postoperative platelet count may be an early indicator to identify patients at increased risk of worse outcomes. Mitzner et al, in his study, compared the various forms of albumin administration in patients with liver disease and liver resections and concluded that albumin has a role in liver regeneration.[23] In our study though there was no statistically significant effect of albumin on liver regeneration, low perioperative albumin levels had statistically significant effect on mortality and morbidity. Ibis et al in their study showed that postoperative liver enlargement rates were significantly higher in the right hemi-hepatectomy (RHH) group than in the left lateral sectionectomy (LLS) group.[24]

The size of the liver remnant or graft has a major effect on regeneration rate. Their results are similar to those of our study. The rate of regeneration expressed as percentage RFLR is proportional to the extent of resection. It is less than 20% in WLE and 20 to 100% in left lobe resections and 100 to 300% in patients undergoing right hepatectomies and right extended hepatectomies. The rate of regeneration was highest in the GS1 group both at 2 weeks and at 2 months and it is statistically significant when compared to the rate of regeneration in GS2 group (p<0.001).

Table 1: Coefficients of dependent variable; % of regeneration.

Model	Unstandardized coefficients		Standardized coefficients	t value	Significance
	B	Std. Error	Beta		
Constant	96.819	7.183		13.478	0
Age (years)	-0.06	0.071	-0.231	-0.85	0.406
Sex	0.089	2.1	0.01	0.042	0.967
BMI	-0.088	0.403	-0.068	-0.218	0.829
Diagnosis	0.448	0.619	0.283	0.725	0.477
Post-op chemotherapy	-4.137	3.706	-0.374	-1.116	0.277
Cirrhosis	-2.346	2.966	-0.194	-0.791	0.438

Table 2: Distribution according to %RFLR.

Surgery	%RFLR at 2 weeks	%RFLR AT 2 months
S0	3.50	7.78
S1	144.34	161.80
S2	198.88	216.42
S3	39.75	51.19
S4	0.00	0.00
S5	178.76	195.21
S6	29.63	36.88
Total	75.14	80.54

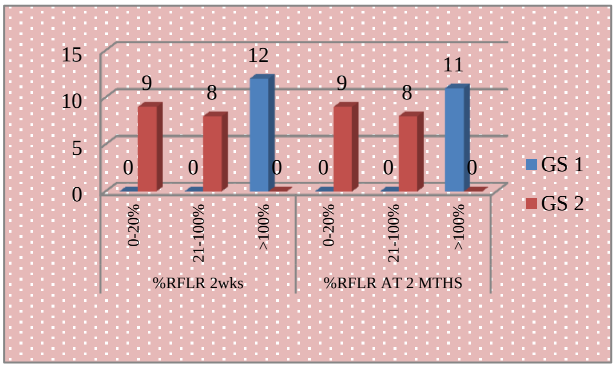

Figure 4: % RFLR.

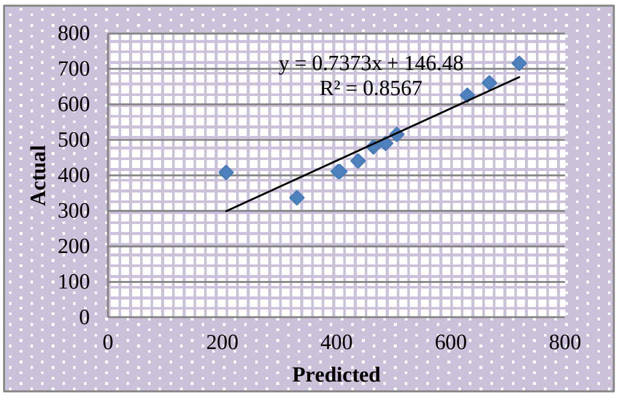

Figure 5: RH: Predicted vs. actual liver weight.

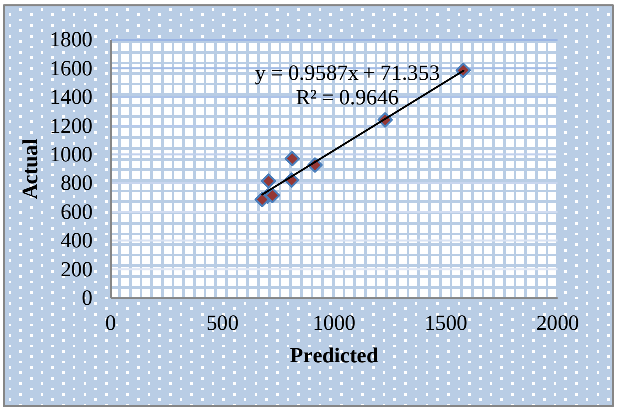

Figure 6: LH: Predicted vs. actual liver weight.

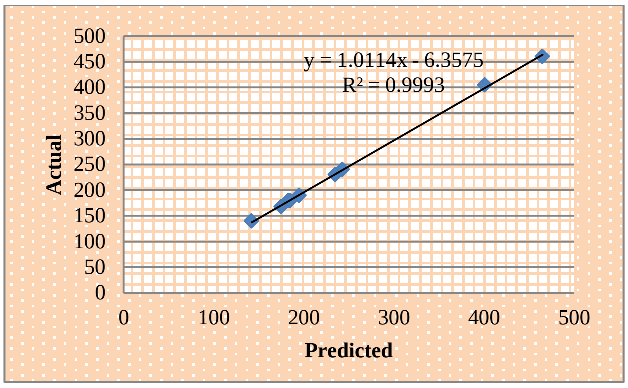

Figure 7: WLE: Predicted vs. actual liver weight.

So, we can conclude that the greater the extent of resection, the faster is the rate of regeneration. Our study involved three types of resection, (RH) right and extended right hepatectomies, (LH) left and extended left hepatectomies, and (WLE) wide local excision. RH group: there was no statistically significant difference between mean of EGW (estimated graft weight) and (actual graft weight) ALrW in RL (815.89±134 vs. 887.2±126 gm; p=0.06). The correlation between ELrW and ALrWfor RL was very strong and statistically significant (r=0.82, p<0.001). LH: although ELrW and ALrW correlated strongly (r=0.81, p<0.001), mean of ELrW was significantly high as compared to mean of ALrW (460±118 vs. 433±102 gm; p=0.003). Itoh et al stated that the meticulous preoperative evaluation based on volumetric analysis of 3D CT images, together with improved surgical techniques, were fundamental to achieve "zero mortality" and minimized intraoperative blood loss in his series of 300 hepatic resections.[25] Lee et al reported the usefulness of semi-automated liver MR volumetry using hepatobiliary phase gadoxetic acid-enhanced images with the quadratic MR image division to measure liver volume in potential living liver donors; the average volume measurement error of the semi-automated MR volumetry was 2.35% ± 1.22%.[26] Zappa et al applied CT volumetry to the evaluation of total and segmental liver regeneration after hepatectomy: CT was able to identify even segmental regeneration, reporting a 64% increase in liver volume from the future remnant 7 days after hepatectomy.[27] CT imaging can be useful also to evaluate volumetric modifications after the induction of liver hypertrophy prior to surgery. Ulla et al reported that CT volumetry, being able to calculate the mean absolute future-liver-remnant (FLR) and FLR/total liver volume (TLV) ratio before and after surgery, plays a key role in decision-making, monitoring and predicting liver hypertrophy pre- and post-operatively; in particular, if the enlargement of the FLR is as expected 6 days after surgery on CT examination, a second-step surgery can be safely performed.[28]

Limitations

As with the majority of studies, the current study is subject to limitations. First, ours is a single centre study, which limits the number of patients enrolled as compared to a multi-centre trial. It also can make the study result biased however, four trained GI surgeons operated the various cases taken in the study under strict protocol guidelines, which makes our study results more generalised. Single center study carried out in a relatively short period (4 years), however, has the advantage of reducing the possible differences in indication for surgery, surgical technique, and transection devices. Additional external validation is required to confirm that our findings would be applicable to other surgical teams. Second, only one GI surgery resident was involved in CT liver volumetry. However, because the inter-observer variation of CT volumetry is considered to be small, we believe that this was unlikely to be a substantial limitation.

CONCLUSION

Our study included 30 patients undergoing liver resections over 3 years. We evaluated the impact of pre and postoperative platelet counts, synthetic liver function tests, on liver regeneration and short-term outcomes, amongst these patients. We conclude that perioperative low serum albumin and platelet counts have significant effect on mortality. The size of the liver remnant or graft has a major effect on regeneration rate. We conclude that greater the extent of resection, faster is the rate of regeneration. These results of our study provide an impetus for understanding liver regeneration rates and extent, in major liver resections which can aid to optimize patient recovery and ensure better surgical outcomes.

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REFERENCES

1. Lopes-Junior AG, Belebecha V, Jacob CE. Hepatectomy: a critical analysis on expansion of the indications. Arq Bras Cir Dig. 2014;27(1):47-52.
2. Vibha V, Naimish M, Vinay K, Nundy S. Indications and contraindications for liver transplantation. Int J Hepatol. 2011;9:121-4.
3. Lesurtel M, Nagorney DM, Mazzaferro V, Jensen RT, Poston GJ. When should a liver resection be performed in patients with liver metastases from neuroendocrine tumours? A systematic review with practice recommendations. HPB (Oxford). 2014;17(1):17-22.
4. Zhang W, Huang ZY, Ke CS. Surgical treatment of giant liver hemangioma larger than 10 cm: a single center's experience with 86 patients. Medicine (Baltimore). 2015;94(34):e1420.
5. Ouyang G, Liu J, Wang P, Ren Y, Yi P, Zhou Q. Multiple factors affect the regeneration of liver. Rev Assoc Med Bras. 2018;64(9):791-8.
6. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. Am J Pathol. 2010;176(1):2-13.
7. Lisman T, Porte RJ. Mechanisms of platelet-mediated liver regeneration. Blood. 2012;128(5);625-9.
8. Kurokawa T, Ohkohchi N. Platelets in liver disease, cancer and regeneration. World J Gastroenterol. 2017; 23(18):3228-39.
9. Michalopoulos GK. Liver regeneration. J Cell Physiol. 2007;213(2):286-300.
10. Payam S, Pahlavan REF, Christos Z, Jannis KP. Challenge: molecular, cellular and systemic aspects of liver regeneration. J Surg Res. 2006;134(2):238-51.
11. Porte RJ, Lisman T. Mechanisms of platelet-mediated liver regeneration. Blood. 2016;128(5):625-9.
12. Ren Y. Liver regeneration. J Cell Physiol. 2010; 213(2):159-165.
13. Aragon RJ, Solomon NL. Techniques of hepatic resection. J Gastrointest Oncol. 2012;3(1):28-40.
14. Goja S, Yadav SK, Yadav A. Accuracy of preoperative CT liver volumetry in living donor hepatectomy and its clinical implications. Hepatobiliary Surg Nutr. 2018;7(3):167-74.
15. Jeong WK. Clinical implication of hepatic volumetry for living donor liver transplantation. Clin Mol Hepatol. 2018;24(1):51-3.
16. Kenji S, Mark L, Epstein K. Quantitative radiology: automated ct liver volumetry compared with interactive volumetry and manual volumetry. Am J of Roentol. 2011;197(4):W706-12.
17. Strasberg SM, Phillips C et al. Use and dissemination of the Brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg. 2013;257:377.
18. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C, et al. How much remnant is enough in liver resection? Dig Surg. 2012;29(1):6-17.
19. Goja S, Yadav SK, Yadav A. Accuracy of preoperative CT liver volumetry in living donor hepatectomy and its clinical implications. Hepatobiliary Surg Nutr. 2018;7(3):167-74.
20. Jeong WK. Clinical implication of hepatic volumetry for living donor liver transplantation. Clin Mol Hepatol. 2018;24(1):51-3.
21. Karlo C, Reiner CS, Stolzmann P, Breitenstein S, Marincek B, Weishaupt D, et al. CT- and MRI-based volumetry of resected liver specimen: comparison to intraoperative volume and weight measurements and calculation of conversion factors. Eur J Radiol. 2010; 75(1): e107-11.

22. Margonis GA, Amini N, Buettner S, Besharati S, Kim Y, Sobhani F, et al. Impact of early postoperative platelet count on volumetric liver gain and perioperative outcomes after major liver resection. Br J Surg. 2016;103:899-907.
23. MitznerS, Klammt S, Stange J, Schmidt R. Albumin regeneration in liver support-comparison of different methods.TherApher Dial. 2006;10(2):108-17.
24. Ibis C, Asenov Y, Akin M, Azamat IF, Sivrikoz N, Gurtekin B et al. Factors Affecting Liver Regeneration in Living Donors After Hepatectomy. Med Sci Monit. 2017;23:5986-93.
25. Itoh S, Shirabe K, Taketomi A. Zero mortality in more than 300 hepatic resections: validity of preoperative volumetric analysis. Surg Today. 2012;42(5):435-40.
26. Lee J, Kim KW, Kim SY. Feasibility of semiautomated MR volumetry using gadoxetic acid-enhanced MRI at hepatobiliary phase for living liver donors. Magn Reson Med. 2014;72(3):640-5.
27. Zappa M, Dondero F, Sibert A, Vullierme MP, Belghiti J, Vilgrain V, et al. Liver regeneration at day 7 after right hepatectomy: global and segmental volumetric analysis by using CT. Radiology. 2009; 252:426-32.
28. Ulla M, Ardiles V, Levy-Yeyati E, Alvarez FA, Spina JC, Garcia-Mónaco RD, De Santibañes Eetal. New surgical strategy to induce liver hypertrophy: role of MDCT-volumetry to monitor and predict liver growth. Hepatogastroenterology. 2013;60:337-42.

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