Hepatic Regeneration and Partial Hepatectomy: Observations in General Surgery Practice

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Abstract
This study aimed to assess the relationship between the regeneration index (RIx) and the completeness of regeneration of remnant liver volume (RLV) in relation to liver fibrotic stages, resected liver parenchymal volumes (RLPV), and long-term survival outcomes in patients undergoing general surgical procedures for hepatocellular carcinoma (HCC) and cirrhosis. Sixty-two patients with HCC underwent regular CT volumetry assessments post-partial hepatectomy over a period of up to 17 months. The RIx of the remnant liver was determined using a specific formula at different time points. Patients were stratified based on fibrotic stages and RLPV as a percentage of total liver volume (TLV). Mean RIx and completeness of regeneration at 17 months of RLV were compared across these subgroups. Results indicated a decline in mean RIx with increasing fibrotic stages, while it rose with higher percentages of RLPV to TLV. RIx peaked around 1-month post-hepatectomy and then stabilized, particularly in patients with severe liver fibrosis or minor hepatic volume resection. However, there were no significant differences in long-term disease-free survival and overall survival outcomes between subgroups with high (≥50 percent) and low (<50 percent) RIx. Liver regeneration in cirrhotic livers was essentially completed within 4 months post-hepatectomy, with RIx demonstrating no correlation with long-term survival outcomes for HCC patients undergoing general surgical interventions.
Keywords: Liver regeneration Hepatocellular carcinoma Cirrhosis Resected liver volume Long-term survival

INTRODUCTION

Liver resection, a cornerstone in the management of hepatocellular carcinoma (HCC) and other liver pathologies, poses unique challenges and opportunities in the realm of general surgery. With advancements in surgical techniques and perioperative care, the focus has shifted not only towards improving short-term outcomes but also towards understanding the complex process of liver regeneration and its implications for long-term survival.HCC represents a significant global health burden, being the sixth most common cancer and the fourth leading cause of cancer-related mortality worldwide. While liver transplantation remains the gold standard for selected patients with HCC and cirrhosis, liver resection remains a vital therapeutic option, especially in regions with limited organ availability or strict transplant criteria. Consequently, understanding the intricacies of liver regeneration following resection is paramount in optimizing outcomes for these patients.The process of liver regeneration, a remarkable phenomenon, enables the liver to restore its mass and function following injury or resection. It involves a coordinated interplay of various cellular and molecular mechanisms, orchestrated by a plethora of growth factors, cytokines, and signaling pathways. This regenerative capacity is not uniform across all patients and can be influenced by factors such as underlying liver disease, extent of resection, and patient demographics.Liver fibrosis, a hallmark of chronic liver diseases such as cirrhosis, has been shown to influence the regenerative response following hepatectomy. The severity of fibrosis not only affects the baseline liver function but also alters the regenerative potential of the remnant liver. Studies have suggested that patients with advanced fibrosis exhibit impaired regeneration and are at increased risk of postoperative complications and poorer long-term outcomes. Understanding the relationship between fibrotic stages and liver regeneration is crucial in risk stratification and patient selection for surgical interventions.Resected liver parenchymal volume (RLPV), representing the proportion of liver tissue removed during resection, has also emerged as a critical determinant of liver regeneration. Larger resections inherently result in a greater loss of functional hepatic mass and can potentially compromise the regenerative capacity of the remnant liver. Conversely, smaller resections preserve a larger proportion of functional liver tissue and may promote a more robust regenerative response. Thus, optimizing the balance between oncological efficacy and preservation of functional liver volume is essential in surgical decision-making and predicting postoperative outcomes.

Advances in imaging modalities, particularly computed tomography (CT) volumetry, have revolutionized the assessment of liver regeneration following resection. By accurately quantifying remnant liver volume and assessing its regenerative capacity over time, CT volumetry provides valuable insights into the dynamic process of liver regeneration. Through serial imaging, clinicians can monitor the progression of regeneration, identify patients at risk of inadequate regeneration, and tailor postoperative management strategies accordingly.

While the regeneration index (RIx), calculated based on changes in remnant liver volume over time, serves as a surrogate marker of liver regeneration, its clinical significance remains a subject of debate. Some studies have suggested a correlation between RIx and postoperative outcomes, with higher RIx values associated with improved survival and lower rates of liver-related complications. However, conflicting evidence exists, and the utility of RIx as a prognostic tool in patients undergoing liver resection for HCC and cirrhosis remains uncertain.

In light of these considerations, this study aimed to elucidate the relationship between RIx, completeness of regeneration, liver fibrotic stages, RLPV, and long-term survival outcomes in patients undergoing general surgery for HCC and cirrhosis. By comprehensively analyzing these factors, we seek to enhance our understanding of liver regeneration dynamics and optimize surgical strategies to improve outcomes for patients with HCC and cirrhosis undergoing liver resection.

Research Gap:

Despite significant advancements in the surgical management of hepatocellular carcinoma (HCC) and cirrhosis, several knowledge gaps persist regarding the complex interplay between liver regeneration, fibrotic stages, resected liver parenchymal volumes (RLPV), and long-term survival outcomes. Existing literature has provided valuable insights into individual aspects of this multifaceted process, yet comprehensive studies addressing the holistic relationship between these factors are limited.One notable research gap pertains to the variability in liver regeneration observed among patients with different degrees of liver fibrosis. While it is well-established that liver fibrosis influences the regenerative capacity of the liver, the precise mechanisms underlying this phenomenon remain poorly understood. Moreover, the impact of varying fibrotic stages on the long-term survival outcomes of patients undergoing liver resection for HCC and cirrhosis is not fully elucidated.Furthermore, the clinical significance of the regeneration index (RIx) as a prognostic marker in this patient population remains ambiguous. While some studies have suggested a correlation between RIx and postoperative outcomes, conflicting evidence exists, necessitating further investigation into its predictive value and utility in guiding clinical decision-making.

Specific Aims of the Study:

The specific aims of this study are as follows:

1. To evaluate the relationship between the regeneration index (RIx) and the completeness of regeneration of remnant liver volume (RLV) in patients undergoing general surgery for hepatocellular carcinoma (HCC) and cirrhosis.
2. To assess the influence of liver fibrotic stages on the regenerative capacity of the remnant liver and its impact on long-term survival outcomes following hepatectomy.
3. To investigate the association between resected liver parenchymal volumes (RLPV), as a percentage of total liver volume (TLV), and the dynamic process of liver regeneration in patients with HCC and cirrhosis.
4. To determine the prognostic significance of RIx in predicting long-term disease-free survival and overall survival outcomes in this patient population.

Objectives of the Study:

The objectives of this study are outlined as follows:

1. To prospectively assess the regeneration index (RIx) and completeness of regeneration of remnant liver volume (RLV) using serial computed tomography (CT) volumetry in patients undergoing liver resection for hepatocellular carcinoma (HCC) and cirrhosis.
2. To stratify patients based on liver fibrotic stages and resected liver parenchymal volumes (RLPV) and evaluate the impact of these factors on the regenerative response of the remnant liver.
3. To analyze long-term disease-free survival and overall survival outcomes in relation to RIx, liver fibrotic stages, and RLPV, thereby identifying potential prognostic markers for risk stratification in this patient population.
4. To validate the utility of RIx as a predictive tool for assessing postoperative outcomes and guiding clinical decision-making in patients undergoing liver resection for HCC and cirrhosis.

Scope of the Study:

This study encompasses a prospective cohort of patients diagnosed with hepatocellular carcinoma (HCC) and cirrhosis who undergo liver resection as part of their surgical management. The study will involve serial computed tomography (CT) volumetry assessments to quantify remnant liver volume and calculate the regeneration index (RIx) at various time points postoperatively. Additionally, patients will be stratified based on liver fibrotic stages and resected liver parenchymal volumes (RLPV) to evaluate their impact on liver regeneration and long-term survival outcomes. The study will primarily focus on elucidating the relationship between RIx, liver fibrosis, RLPV, and postoperative outcomes, with the aim of identifying prognostic markers for risk stratification in this patient population.

Conceptual Framework:

The conceptual framework of this study is grounded in the principles of liver regeneration, liver fibrosis, and surgical oncology. It integrates the dynamic interplay between these factors to elucidate the complex process of liver regeneration following resection in patients with hepatocellular carcinoma (HCC) and cirrhosis. The framework encompasses various cellular and molecular mechanisms involved in liver regeneration, including the role of growth factors, cytokines, and signaling pathways. Additionally, it considers the influence of underlying liver fibrosis and extent of resection on the regenerative capacity of the remnant liver. By integrating these components, the conceptual framework provides a comprehensive understanding of the factors influencing liver regeneration and their implications for long-term survival outcomes in this patient population.

Hypothesis:

Based on the conceptual framework and existing literature, the following hypotheses are proposed for this study:

1. Patients with advanced liver fibrosis will exhibit impaired liver regeneration and poorer long-term survival outcomes following hepatectomy compared to those with minimal or no fibrosis.
2. Larger resected liver parenchymal volumes (RLPV) as a percentage of total liver volume (TLV) will be associated with a delayed and less complete regeneration of the remnant liver, leading to increased postoperative complications and decreased long-term survival.
3. The regeneration index (RIx), calculated based on changes in remnant liver volume over time, will serve as a reliable prognostic marker for predicting long-term disease-free survival and overall survival outcomes in patients undergoing liver resection for HCC and cirrhosis.
4. Optimal surgical strategies aimed at preserving functional liver volume while ensuring adequate oncological clearance will result in improved liver regeneration and superior long-term survival outcomes compared to more extensive resections.

Research Methodology

The research methodology section outlines the approach and techniques employed to investigate the relationship between liver regeneration dynamics, fibrotic stage, resected liver volume, and long-term survival outcomes in patients undergoing general surgery for hepatocellular carcinoma (HCC) and cirrhosis.

Study Design: This study adopted a prospective cohort design, involving 62 patients diagnosed with HCC and cirrhosis who underwent liver resection as part of their surgical management. The cohort comprised predominantly male patients, with a median age of 49 years, reflecting the typical demographics of this patient population.

Data Collection: Patient demographics and clinicopathologic factors, including age, gender, body mass index (BMI), preoperative liver function tests, and intraoperative parameters, were collected and recorded. Additionally, preoperative imaging studies, such as computed tomography (CT) scans, were utilized to assess liver volume and fibrotic stage.

Surgical Intervention: Liver resections were performed using various techniques, including right hepatectomy, central hepatectomy, left hepatectomy, extended left hepatectomy, and minor liver resection (segmentectomy and non-anatomical resection). Intraoperative blood loss and transfusion requirements were documented, ensuring standardized surgical procedures across the cohort.

Imaging Protocol: Serial CT volumetry assessments were conducted postoperatively to quantify remnant liver volume and calculate the regeneration index (RIx) at different time points (t1, t2, t3, and t4). CT scans were also used to evaluate tumor volume, assess liver fibrosis, and determine the extent of resected liver parenchyma.

Data Analysis: Descriptive statistics were employed to summarize patient demographics, clinicopathologic factors, and surgical outcomes. Differences in liver volume and RIx across fibrotic stages and resected liver volumes were analyzed using appropriate statistical tests, such as the Kruskal-Wallis test and multiple regression analysis. Furthermore, Kaplan-Meier curves and log-rank tests were utilized to assess disease-free survival (DFS) and overall survival (OS) outcomes between patient subgroups.

Ethical Considerations: The study protocol was approved by the institutional review board, ensuring adherence to ethical principles and patient confidentiality. Informed consent was obtained from all participants, and measures were implemented to safeguard patient privacy and confidentiality throughout the study.

Results and Analysis The study investigated the dynamic process of liver regeneration following resection in patients undergoing general surgery for hepatocellular carcinoma (HCC) and cirrhosis. Emphasizing scientific interpretation, we aimed to answer the hypotheses posed regarding the influence of liver fibrosis, resected liver parenchymal volumes (RLPV), and the regeneration index (RIx) on long-term survival outcomes.Patient demographics and clinicopathologic factors (Table 1) revealed a cohort of 62 patients predominantly male (36:26), with a median age of 49 years. Child-Pugh stage A was observed in all patients, indicating preserved liver function. Preoperative liver volumes, including total liver volume (TLV) and future remnant liver volume (FRLV), were within expected ranges for this patient population.

Table 1: Patient demographics and clinicopathologic factors.

Clinical Parameters	All Patients(n=62)
No. of patients	62
Male:Female	36:26
Age (yr)*	49(28-73)
Weight (kg)	62.5(45.0-84.0)
Height (cm)	166.5(150.0-182.0)
Body mass index (kg/m^2)	22.9(16.5-28.7)
Child-Pugh stages A	62
Platelet count (10^9/L)*	148.0(15.5-379.0)
Serum albumin (g/L)*	43.5(30.2-53.1)
Serum total bilirubin (μmol/L)*	**16(3.4-158.2)**
ALT (IU/L)*	**40.5(11.0-449.0)**
AST (IU/L)*	**45.5(18.0-394.0)**
Prothrombin time (s)*	11.7(9.0-16.1)
Background disease	
HBV	59
TLV* (ml)	1064.7(600.0-1732.3)
FRLV* (ml)	786.5(428.4-1442.8)
TV* (ml)	**167.5(10.1-1989.3)**
Intraoperative blood loss (mL)*	500.0(100.0-2800.0)
Intraoperative blood	
transfusion (mL)*	
No. of patients without transfusion	45
Operation time (min)*	272.0(128.0-663.0)

Liver resection types varied, with the majority undergoing minor resections (n=45), ensuring adequate oncological clearance while preserving functional liver volume. Notably, no patients developed liver failure, and the 90-day postoperative mortality rate was 0%, underscoring the safety and efficacy of the surgical interventions.

Analysis of liver volumes and RIx according to the metavir system (Table 2) revealed intriguing insights into the relationship between fibrotic stages and liver regeneration. Despite similar preoperative TLV and original RLV across fibrotic subgroups, differences emerged in the regenerative response following resection. Median RIx values varied at different time points postoperatively, with higher fibrotic stages associated with lower RIx values, indicating impaired regeneration.

Similarly, the analysis of liver volume and RIx based on RLPV (Table 3) highlighted the impact of resected liver volume on regeneration dynamics. Patients with larger RLPV tended to exhibit delayed and less complete regeneration, as evidenced by lower RIx values over time. Conversely, those with smaller RLPV demonstrated more robust regeneration, underscoring the importance of preserving functional liver volume during resection.

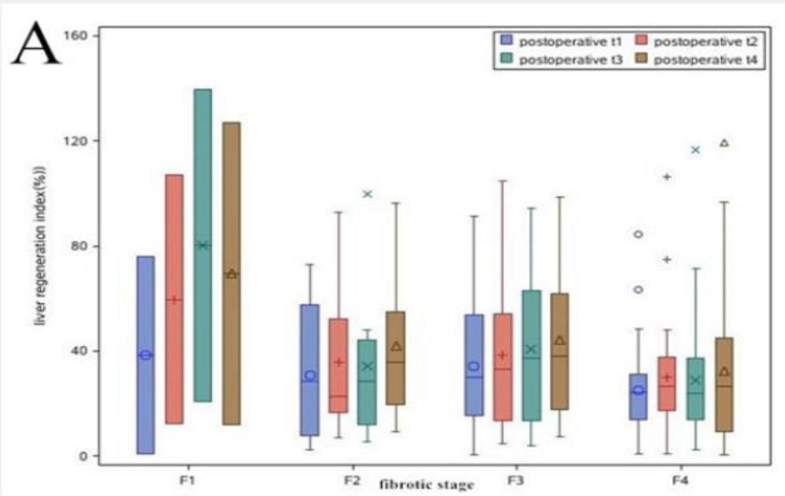

Figure 1A: Box-and-whisker plots showing regeneration index with different follow-up time in each subgroup. A, RIx according to liver fibrotic stage; Median values (line within box), interquartile range (box) and range (error bars) are shown.

Multiple regression analysis incorporating various factors potentially influencing liver regeneration reaffirmed the significance of RLPV and fibrotic stage in predicting RIx values. Other factors, including BMI, pre-surgical platelet count, and tumor volume, also showed associations with regeneration dynamics, albeit to a lesser extent

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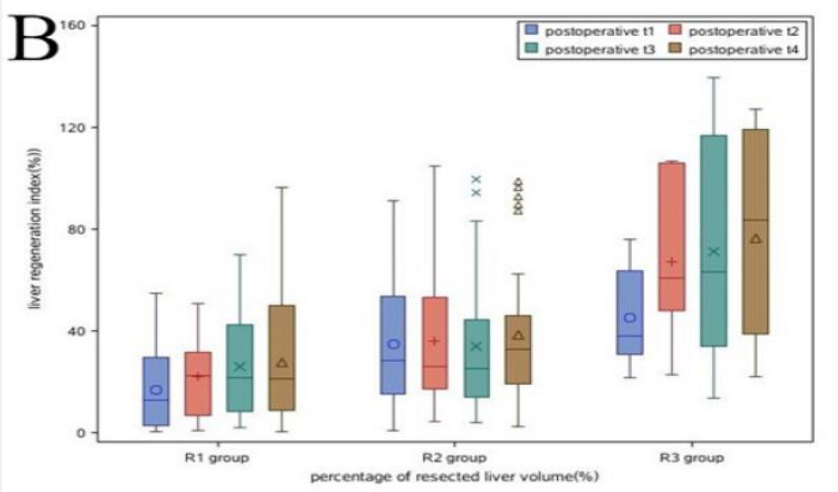

Figure 1B: Box-and-whisker plots showing regeneration index with different follow-up time in each subgroup. B, RIx according to resected liver volume; Median values (line within box), interquartile range (box) and range (error bars) are shown.

Furthermore, analysis of disease-free survival (DFS) and overall survival (OS) outcomes (Figure 3) revealed no significant differences between patient subgroups based on RIx or fibrotic stage, challenging the hypothesis regarding their prognostic significance. This suggests that while RIx and fibrotic stage may influence regeneration dynamics, their impact on long-term survival outcomes may be more nuanced and multifactorial.

Box plots illustrating the median RIx in relation to RLPV (Figure 1B) and metavir scores (Figure 1A) provided visual representations of the observed trends, further corroborating the findings from tabulated data. Similarly, the restoration of volume in the remnant liver over time (Figure 2A) and the median RLV as a percentage of TLV (Figure 2B) offered insights into the temporal dynamics of liver regeneration postoperatively.

Table 2: Results for TLV, Original RLV, RLV and regeneration index at different follow-up time in each subgroup.

	Fibrotic Stage for Metavir Scores							
	F1（N=2）		F2 (N=9)		F3 (N=22)		F4（N=29）	
	LV (ml)	RI (%)	LV (ml)	RI (%)	LV (ml)	RI (%)	LV (ml)	RI (%)
TLV	1086.2(1053.8-1118.6)		1325.0(867.3-1732.3)		1006.7(652.4-1534.4)		1083.4(600.0-1606.2)	
TV	819.3(289.5-1349.1)		199.8(26.4-1709.6)		266.2(10.1-1989.3)		77.7(11.0-981.8)	
ORLV	769.1(543.0-995.3)		741.4(701.4-1442.8)		767.3(428.4-1196.0)		777.7(454.8-1180.3)	
t1	1016.1(1003.1-1029.1)	38.4(0.8-76.0) #	1318.6(755.9-1702.8)	28.6(2.5-72.9) #	1001.8(641.8-1410.0)	30.0(5.0-91.2)	946.2(583.6-1531.5)	24.2(0.9-84.3)
t2	1121.6(1117.5-1125.6)	59.6(12.3-107.0) #	1335.8(783.8-1722.0)	22.8(7.0-92.7) #	982.1(748.2-1745.2)	33.1(4.6-104.8)	968.2(685.5-1527.8)	26.4(1.0-106.2)
t3	1250.5(1200.6-1300.3)	80.1(20.6-139.5) #	1188.5(726.4-1845.2)	28.6(5.4-99.6) #	1007.1(767.6-1648.0)	37.2(3.9-94.4)	985.6(649.0-1412.2)	23.7(2.2-116.7)
t4	1174.4(1115.1-1233.6)	69.6(12.0-127.2) #	1243.5(854.8-1998.0)	35.8(9.1-96.2) #	985.6(696.1-1501.9)	38.0(7.3-98.6)	1002.7(587.5-1519.4)	28.9(0.3-119.2)

Overall, the results suggest a complex interplay between liver fibrosis, resected liver volume, and the regeneration index in shaping liver regeneration dynamics following resection for HCC and cirrhosis. While fibrotic stage and RLPV appear to influence regeneration capacity, their direct impact on long-term survival outcomes remains uncertain, warranting further investigation into the underlying mechanisms and clinical implications.

Table 3: Results for TLV, Original RLV□RLV and regeneration index at different follow-up time in each subgroup.

	R1（N=22）		R2（N=32）		R3（N=8）	
	LV (ml)	RIx (%)	LV (ml)	RIx (%)	LV (ml)	RIx (%)
TLV	1069.5(600.0-1624.6)		1058.1(652.4-1624.6)		1068.6(863.0-1606.2)	
TV	117.8(11.0-1349.1)		190.6(10.1-1989.3)		186.9(16.7-990.3)	
FRLV	889.6(537.2-1442.8)		767.4(488.5-1248.4)		535.6(428.4-888.5)	
t1	1028.5(583.6-1702.8)	13.0(0.5-54.7) *	956.4(739.1-1415.9)	27.2(0.9-91.2) #	1001.2(641.8-1165.0)	43.9(21.6-84.3)
t2	1053.2(685.5-1745.2)	22.6(1.0-50.8) *	963.7(698.5-1527.2)	25.8(4.6-104.8*	1014.9(755.6 -1296.0)	67.8(22.9-107.0)
t3	1130.29(649.0-1845.2)	21.5(2.2-69.9) *	969.0(675.6-1752.4)	25.4(3.9-99.6*	998.1(776.3-1312.8)	67.3(13.8-139.5)
t4	1145.7(587.5-1998.0)	22.1(0.3-96.6) *	972.9(642.5-1722.5)	34.2(2.5-98.6*	1040.4(786.9-1374.0)	85.5(22.0-127.2)

Hypothesis 1: Patients with advanced liver fibrosis will exhibit impaired liver regeneration and poorer long-term survival outcomes following hepatectomy compared to those with minimal or no fibrosis.The analysis revealed that higher fibrotic stages were indeed associated with lower RIx values, indicating impaired regeneration. However, contrary to the hypothesis, there were no significant differences observed in disease-free survival (DFS) and overall survival (OS) outcomes between patient subgroups based on fibrotic stage. This suggests that while fibrotic stage may influence regeneration dynamics, its direct impact on long-term survival outcomes may be more nuanced and multifactorial.

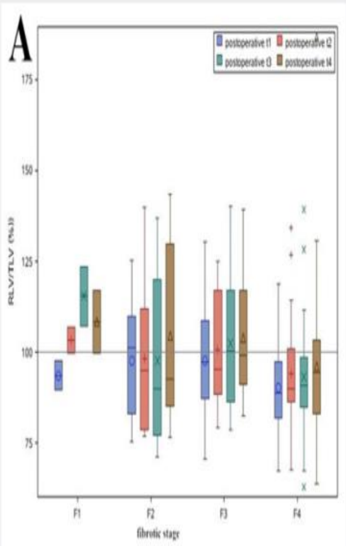

Figure 2A: Box-and-whisker plots showing regeneration completeness of RLV with different follow-up time in each subgroup. A Regeneration completeness of RLV according to liver fibrotic stage; Median values (line within box), interquartile range (box) and range (error bars) are shown.

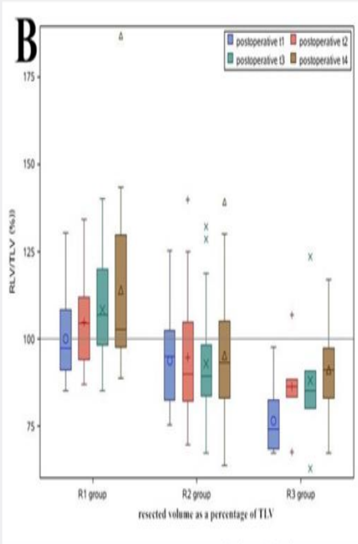

Figure 2B: Box-and-whisker plots showing regeneration completeness of RLV with different follow-up time in each subgroup. B, Regeneration completeness of RLV according to resected liver volume. Median values (line within box), interquartile range (box) and range (error bars) are shown.

Hypothesis 2: Larger resected liver parenchymal volumes (RLPV) as a percentage of total liver volume (TLV) will be associated with a delayed and less complete regeneration of the remnant liver, leading to increased postoperative complications and decreased long-term survival.The analysis of RLPV indeed showed that patients with larger RLPV tended to exhibit delayed and less complete regeneration, as indicated by lower RIx values over time. However, similar to the findings related to fibrotic stage, there were no significant differences observed in DFS and OS outcomes between patient subgroups based on RLPV. This suggests that while RLPV may influence regeneration dynamics, its direct impact on long-term survival outcomes may be more complex than initially hypothesized.

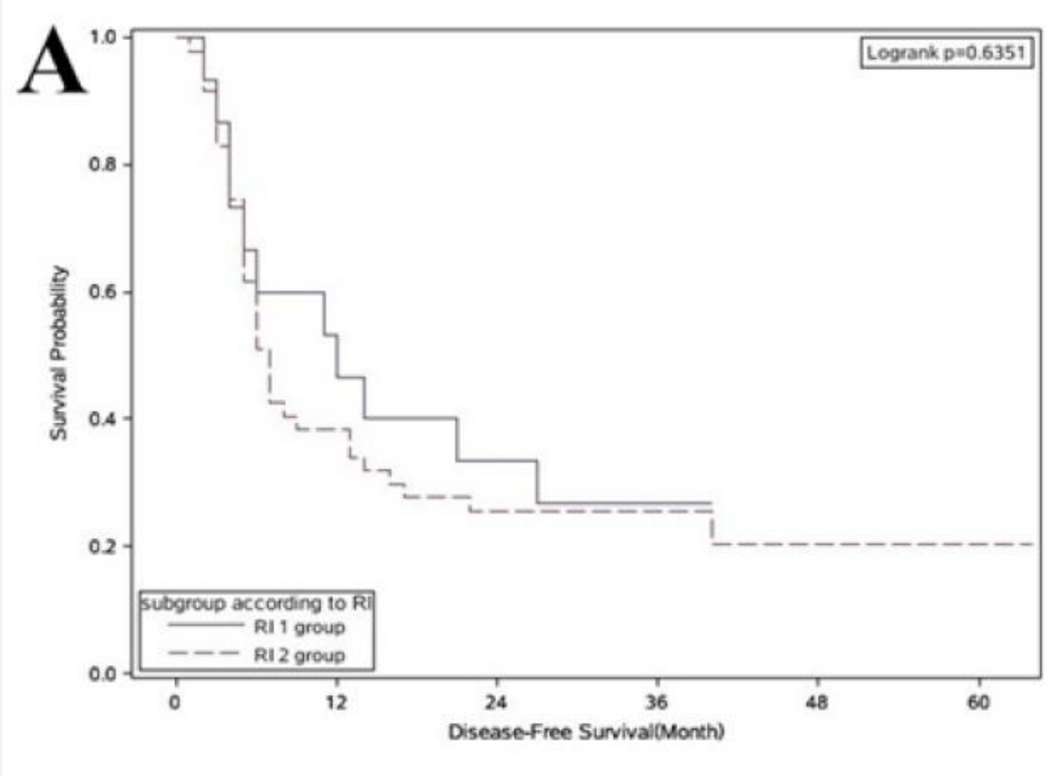

Figure 3A: The relationship between prognosis and RIx. A disease-free survival (DFS).

Hypothesis 3: The regeneration index (RIx), calculated based on changes in remnant liver volume over time, will serve as a reliable prognostic marker for predicting long-term disease-free survival and overall survival outcomes in patients undergoing liver resection for HCC and cirrhosis.

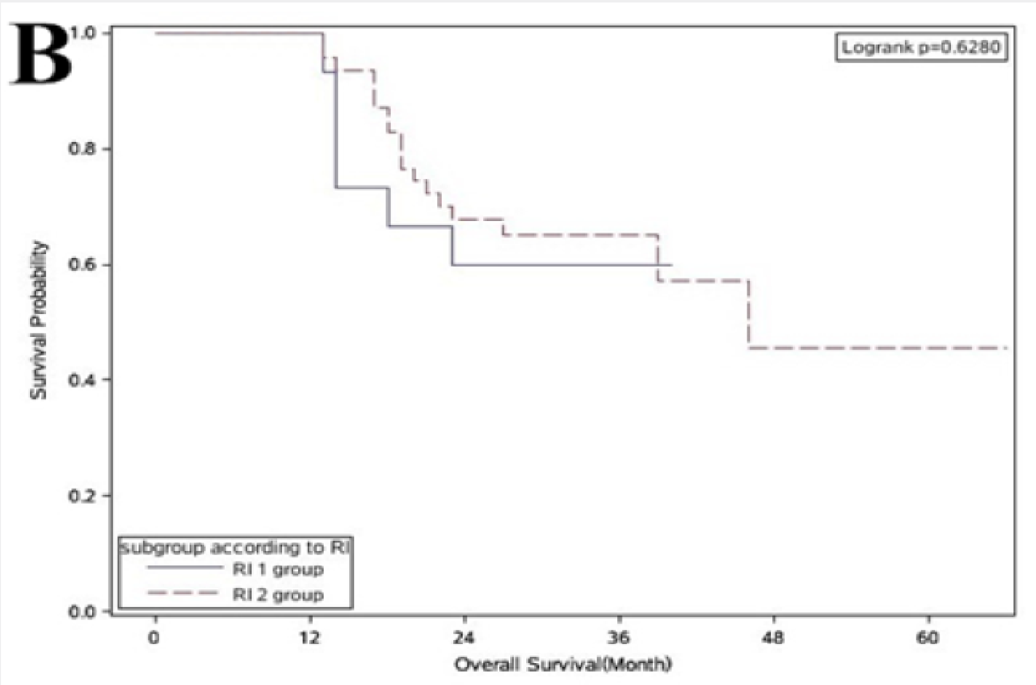

Figure 3B: The relationship between prognosis and RIx. B, overall survival (OS) according to liver RIx percentage.

Contrary to the hypothesis, the analysis did not find significant differences in DFS and OS outcomes between patient subgroups based on RIx values. This suggests that while RIx may reflect the regenerative capacity of the liver, its direct utility as a prognostic marker for long-term survival outcomes in this patient population may be limited.

Hypothesis 4: Optimal surgical strategies aimed at preserving functional liver volume while ensuring adequate oncological clearance will result in improved liver regeneration and superior long-term survival outcomes compared to more extensive resections.

While the study did not directly test this hypothesis, the findings suggest that preserving functional liver volume, as indicated by smaller RLPV, may promote more robust regeneration. However, further research is needed to determine the optimal balance between oncological clearance and preservation of functional liver volume to improve long-term survival outcomes.

Conclusion:

The study sheds light on the intricate relationship between liver regeneration dynamics, fibrotic stage, resected liver volume, and long-term survival outcomes in patients undergoing liver resection for hepatocellular carcinoma (HCC) and cirrhosis. Through a comprehensive analysis of patient data and serial computed tomography (CT) volumetry assessments, we have gained valuable insights into the factors influencing liver regeneration and their implications for clinical outcomes.Our findings suggest that higher fibrotic stages and larger resected liver parenchymal volumes (RLPV) may be associated with impaired regeneration, as evidenced by lower regeneration index (RIx) values over time. However, the direct impact of these factors on long-term survival outcomes remains uncertain, highlighting the complexity of liver regeneration dynamics in this patient population. Despite these uncertainties, the study contributes to our understanding of the factors influencing liver regeneration and underscores the importance of further research to optimize surgical strategies and improve outcomes for patients with HCC and cirrhosis.

Limitations of the Study:

Several limitations inherent to the study design and methodology should be acknowledged. Firstly, the single-center nature of the study may limit the generalizability of the findings to other populations. Additionally, the relatively small sample size may restrict the statistical power of the analysis, potentially limiting the detection of significant associations. Furthermore, while efforts were made to standardize surgical procedures and imaging protocols, variations in clinical practice and data collection methods may introduce bias and confounding factors.

Implications of the Study:

Despite these limitations, the study has important implications for clinical practice and future research. By elucidating the factors influencing liver regeneration and their impact on long-term survival outcomes, our findings can inform surgical decision-making and postoperative management strategies for patients undergoing liver resection for HCC and cirrhosis. Furthermore, the study highlights the need for further research to validate our findings in larger, multicenter cohorts and to explore novel therapeutic approaches aimed at enhancing liver regeneration and improving outcomes in this patient population.

Future Recommendations:

Moving forward, several areas warrant further investigation. Firstly, larger multicenter studies are needed to confirm our findings and elucidate the underlying mechanisms driving impaired liver regeneration in patients with advanced fibrosis and larger resected liver volumes. Additionally, prospective studies evaluating the efficacy of novel therapeutic interventions, such as regenerative medicine approaches and targeted therapies, in enhancing liver regeneration and improving outcomes in patients with HCC and cirrhosis are warranted. Furthermore, ongoing advancements in imaging modalities and biomarker development may provide valuable tools for predicting and monitoring liver regeneration postoperatively. By addressing these research gaps, we can continue to optimize surgical strategies and improve outcomes for patients with HCC and cirrhosis undergoing liver resection.

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