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ORIGINAL ARTICLE

Demystifying post-hepatectomy enzyme kinetics for the surgical learner: an analysis of 989 major hepatectomies

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Abstract

Purpose Few resources exist for surgical learners in interpreting trends in biochemical markers following major hepatic resections.

Methods Adult patients who underwent major hepatectomy between 2010 and 2020 were included from twelve international centers. Patients were classified as healthy donor, benign disease, non-alcoholic fatty liver disease, prior chemotherapy, or cirrhosis. Median values of total bilirubin and INR were plotted against time and compared across groups using the Kruskal–Wallis test.

Results Across groups ($n=989$), median total bilirubin and INR were observed to peak on postoperative day (POD) 1. While the healthy donor group ($n=156$) had the highest median total bilirubin on POD1 (2.4, IQR: 1.7–3.3), they had the fastest rate of recovery such that by POD5, values were lower than those of the NAFLD ($n=26$), chemotherapy ($n=92$), and cirrhosis ($n=668$) groups. Donor patients also had the highest POD1 INR (median 1.5, IQR: 1.4–1.7), while patients with NAFLD had the highest POD5 INR levels (1.2, IQR: 1.1, 1.4). The lowest POD1 total bilirubin and INR levels were observed in the cirrhosis group (1.5, 1.3, respectively). Statistically significant differences in total bilirubin and INR were observed across groups at all timepoints ($p<0.05$).

Conclusions We observed the healthy donor patients to have the highest postoperative enzyme peaks, but most rapid rate of return to normal. This illustration of the postoperative kinetics of biochemical liver function tests may serve as a useful reference for clinical learners monitoring patients in the first week following major hepatectomy.

Keywords Surgical education · Hepatectomy · Enzyme kinetics · Living donor · Cirrhosis · NAFLD

Introduction

Hepatic resection is considered the first-line treatment for a variety of benign and malignant liver tumors. Following resection, biochemical blood tests are frequently trended to

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assess hepatic function. In the context of a major resection, it is expected that these lab parameters will fall outside the normal range in the immediate postoperative period. However, it is important for clinicians and learners to develop an understanding of the kinetics and expected trends of biochemical markers in the first week following major hepatic resection.

Total bilirubin and international normalized ratio (INR) are widely used as markers of hepatic function. The liver is responsible for conjugating bilirubin (the breakdown product of heme from hemoglobin) and excreting it in bile. Elevations in total bilirubin may signal obstruction of the biliary system or a failure of the liver to execute this excretory function. INR is a standardized measure of the extrinsic pathway of the coagulation cascade. The liver is responsible for synthesizing numerous clotting factors. Elevations in INR may indicate insufficient clotting factors and thus serve as a marker for the synthetic function of the liver.

Prior studies have investigated patterns of biochemical markers following hepatic resection, but many of these analyses were conducted before the twenty-first century [2, 4, 5] or had small sample sizes (largest series, $n = 288$; [1, 6–8]). Although some existing studies have focused on specific patient populations or indications for surgery [3, 7, 9], we are aware of no contemporary studies that directly compare enzyme kinetics based on pre-existing liver impairment. Therefore, the current study may serve as an educational resource for trainees learning to care for patients after major hepatic resection.

Our aims were to trend the kinetics of INR and total bilirubin in the first week following major hepatectomy in a large, diverse international cohort, and to stratify the results by pre-existing liver pathology. This timeframe was selected as previous studies have demonstrated that liver enzymes generally return to normal by postoperative day (POD) 5 (Reissfelder et al. 2011).

Methods

This study was approved by the Institutional Review Board of the University of California, San Francisco (IRB No: 20-31911).

Study population

Patients were derived from a multicenter international cohort that included four centers in Europe, six centers in Japan, one center in the UK, and one center in the United States. Inclusion criteria were age 18 or over as well as major resection (≥ 3 segments, or ≥ 2 segments in the context of cirrhosis) at a participating center from 2010 to 2020. Benign and malignant indications for surgery were included and surgical approaches included pure laparoscopic, robotic, hand-assisted, hybrid, or open liver resection. Both anatomical and non-anatomical hepatectomies were included. Patients were excluded if they underwent preoperative portal vein embolization or underwent two-stage hepatectomies. A complete case analysis was conducted, with the exception that patients with one missing lab value at one timepoint were retained in the sample.

Pre-existing liver pathology

Individuals were classified by pre-existing liver pathology. Patients were categorized as (1) healthy living donors if they were identified as donors and had no evidence of clinical cirrhosis or pre-existing liver impairment; (2) having benign disease if they had a benign indication for surgery with no evidence of clinical cirrhosis or pre-existing liver impairment; (3) having non-alcoholic fatty liver disease (NAFLD) if they had pre-existing metabolic liver impairment or BMI in the obese range (> 30), with no history of cirrhosis or chemotherapy; (4) having undergone chemotherapy with no evidence of clinical cirrhosis; (5) having clinical cirrhosis (Child A–C).

Biochemical markers

Serum total bilirubin and INR were measured preoperatively and on POD1, 3, and 5. All data were converted to mg/dL units for total bilirubin. No unit conversion was necessary for INR as it is a unit free measure.

Statistical analysis

Continuous variables were reported as medians and interquartile ranges. Categorical variables were expressed as counts and percentages. Median serum bilirubin and INR for each patient category were computed at each timepoint and compared across groups using the Kruskal–Wallis test. Post-hoc pairwise comparison using Dunn's test with Bonferroni adjustment was performed to further investigate differences between groups. Data were then stratified by extent of hepatic resection (3–4 segments vs. 5 or more segments) and analysis was repeated. All analyses were conducted using STATA/IC 16.1 and statistical significance was set at $p < 0.05$.

Results

Clinical characteristics by pre-existing liver pathology

Of the 2192 patients in the study, 1517 patients met inclusion criteria, of which 528 (35%) were excluded due to missing data, leaving 989 remaining for analysis (Table 1). Healthy donor and benign patients had lower median ages, Charlson Comorbidity Indices, and ASA classifications compared to those with NAFLD, chemotherapy, and cirrhosis (all $p < 0.001$). In addition, patients with benign disease and cirrhosis had a median of 3 segments resected (vs. 4 segments in other groups). Across all groups, the majority of operations were performed open (85.5%). Finally, the cirrhosis group had the highest percentage of intraoperative transfusion (20.3%, $p < 0.001$), while the NAFLD group had the highest percentage of postoperative complications (61.7%, $p < 0.001$) and 90-day mortality (7.5%, $p = 0.008$).

Trends in postoperative bilirubin and INR

Across all groups, the highest median total bilirubin was observed on POD1 (Fig. 1, Table 2). While the healthy donor group had the highest median total bilirubin on POD1 (2.4, IQR 1.7–3.3), it also demonstrated the most rapid rate of recovery (decreased by 1.3 from POD1 to POD5). In contrast, the cirrhosis group had the lowest total

Table 1 Clinical characteristics of the cohort by pre-existing liver pathology ($n = 989$)

	Overall $n = 989$	Healthy donor $n = 156$	Benign disease $n = 47$	NAFLD $n = 26$	Chemotherapy $n = 92$	Cirrhosis $n = 668$	p value
Age (years) (median, IQR)	64 (52, 72)	42 (29, 56)	46 (29, 62)	66 (56, 73)	64 (55, 70)	67 (60, 74)	< 0.001
Sex ratio (M:F %)	67.6:32.4	54.5:46.5	61.7:38.3	50:50	55.4:44.6	73.5:27.5	< 0.001
ASA (%)							
I	26.1	59.6	87.2	15.4	19.6	15.3	< 0.001
II	64.5	40.4	12.8	46.1	66.3	74.2	
III	9.3	0.0	0.0	38.5	14.1	10.3	
IV	0.1	0.0	0.0	0.0	0.0	0.2	
Charlson Comorbidity Index (median, IQR)	3 (2,5)	0 (0, 0)	0 (0, 1)	3 (2, 6)	8 (8, 8.5)	3 (2, 5)	< 0.001
Segments Resected (median, IQR)	4 (3, 4)	4 (4, 5)	3 (3, 4)	4 (3, 5)	4 (4, 5)	3 (2, 4)	< 0.001
Approach (%)							
Open	85.5	100.0	78.7	76.9	79.4	83.8	< 0.001
Laparoscopic	13.6	0.0	19.2	23.1	20.7	15.0	
Hand-assist	0.9	0.0	2.1	0.0	0.0	1.2	
Intraoperative transfusion (%)	17.0	1.8	4.9	19.8	19.1	20.3	< 0.001
Postoperative complication (%)	41.8	7.6	27.1	61.7	47.7	43.5	< 0.001
90-day mortality (%)	2.64	0.0	2.4	7.5	3.6	2.5	0.008

IQR interquartile range, *NAFLD* non-alcoholic fatty liver disease

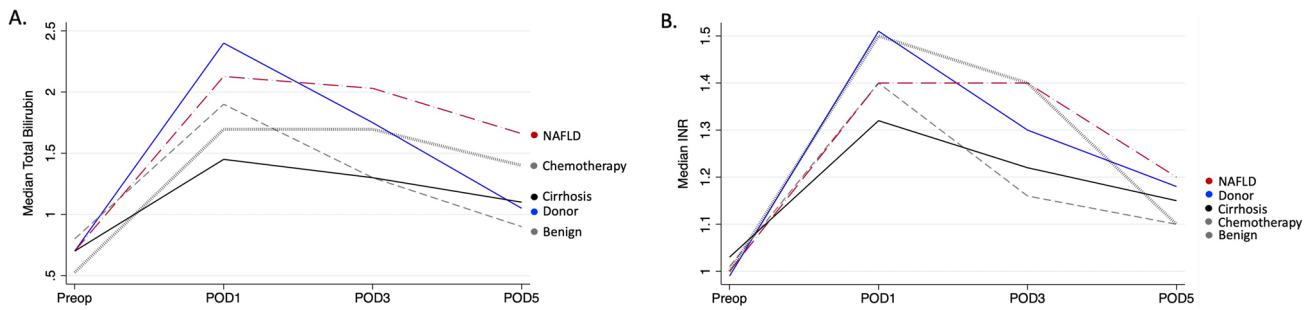

Fig. 1 **A** Postoperative total bilirubin by pre-existing liver pathology ($n = 989$). **B** Postoperative INR by pre-existing liver pathology ($n = 989$). "This figure displays total bilirubin and INR preoperatively and then on postoperative days 1, 3, and 5, stratified by pre-existing liver pathology (donor, benign, NAFLD, chemotherapy, cirrhosis). *NAFLD* non-alcoholic fatty liver disease, *INR* international normalized ratio"

Table 2 Trends in total bilirubin and INR by pre-existing liver pathology ($n=989$)

		Preop T-bili Median (IQR)	POD1 T-bili Median (IQR)	POD3 T-bili Median (IQR)	POD5 T-bili Median (IQR)
Overall	$n=989$	0.7 (0.5, 0.9)	1.6 (1.2, 2.4)	1.4 (1.0, 2.1)	1.1 (0.8, 1.6)
Healthy Donor	$n=156$	0.7 (0.6, 0.9)[d]	2.4 (1.7, 3.3)	1.8 (1.2, 2.5)	1.1 (0.8, 1.4)[c,d]
Benign disease	$n=47$	0.8 (0.5, 1.0)[d]	1.9 (1.3, 2.4)[a]	1.3 (1.0, 1.8)[a,c]	0.9 (0.7, 1.3)[c,d]
NAFLD	$n=26$	0.7 (0.5, 0.8)	2.1 (1.5, 3.4)	2.0 (1.2, 2.9)	1.7 (1.1, 3.1)
Chemotherapy	$n=92$	0.5 (0.4, 0.7)	1.7 (1.0, 2.5)[a]	1.7 (1.0, 2.7)	1.4 (0.8, 2.5)
Cirrhosis	$n=668$	0.7 (0.5, 0.9)[d]	1.5 (1.1, 2.1)[a,c]	1.3 (0.9, 1.9)[a,c,d]	1.1 (0.8, 1.6)[c,d]
		Preop INR	POD1 INR	POD3 INR	POD5 INR
Overall	$n=989$	1.0 (1.0, 1.1)	1.4 (1.2, 1.5)	1.2 (1.1, 1.4)	1.2 (1.1, 1.2)
Healthy Donor	$n=156$	1.0 (0.9, 1.0)	1.5 (1.4, 1.7)	1.3 (1.2, 1.4)[e]	1.2 (1.1, 1.2)
Benign disease	$n=47$	1.0 (1.0, 1.1)[a]	1.4 (1.3, 1.6)	1.2 (1.1, 1.2)[a]	1.1 (1.1, 1.2)[a,c]
NAFLD	$n=26$	1.0 (1.0, 1.1)	1.4 (1.2, 1.5)[a]	1.4 (1.1, 1.5)[b,e]	1.2 (1.1, 1.4)
Chemotherapy	$n=92$	1.0 (1.0, 1.0)	1.5 (1.3, 1.6)[a]	1.4 (1.1, 1.5)[b,e]	1.1 (1.0, 1.3)
Cirrhosis	$n=668$	1.0 (1.0, 1.1)[a,d]	1.3 (1.2, 1.5)[a,b,d]	1.2 (1.1, 1.3)	1.2 (1.1, 1.2)

[a]Significant pairwise difference with healthy donor (Benign Preop INR $p=0.042$) (Cirrhosis Preop INR $p<0.001$) (Benign POD1 T-bili $p=0.005$) (Chemotherapy POD1 T-bili $p<0.001$) (Cirrhosis POD1 T-bili $p<0.001$) (NAFLD POD1 INR $p=0.026$) (Chemotherapy POD1 INR $p=0.030$) (Cirrhosis POD1 INR $p<0.001$) (Benign POD3 T-bili $p=0.003$) (Cirrhosis POD3 T-bili $p<0.001$) (Benign POD3 INR $p<0.001$) (Benign POD5 INR $p=0.004$)

[b]Significant pairwise difference with benign disease (Cirrhosis POD1 INR $p=0.013$) (NAFLD POD3 INR $p=0.002$) (Chemotherapy POD3 INR $p<0.001$)

[c]Significant pairwise difference with NAFLD (Cirrhosis POD1 T-bili $p=0.004$) (Benign POD3 T-bili $p=0.019$) (Cirrhosis POD3 T-bili $p=0.004$) (Healthy donor POD5 T-bili $p=0.003$) (Benign POD5 T-bili $p<0.001$) (Cirrhosis POD5 T-bili $p=0.014$) (Benign POD5 INR $p=0.025$)

[d]Significant pairwise difference with chemotherapy (Healthy donor Preop T-bili $p<0.001$) (Benign Preop T-bili $p=0.002$) (Cirrhosis Preop T-bili $p<0.001$) (Cirrhosis Preop INR $p=0.002$) (Cirrhosis POD1 INR $p<0.001$) (Cirrhosis POD3 T-bili $p=0.008$) (Healthy donor POD5 T-bili $p=0.002$) (Benign POD5 T-bili $p<0.001$) (Cirrhosis POD5 T-bili $p=0.015$)

[e]Significant pairwise difference with cirrhosis (Healthy donor POD3 INR $p<0.001$) (NAFLD POD3 INR $p=0.027$) (Chemotherapy POD3 INR $p<0.001$)

T-bili total bilirubin, *POD* postoperative day, *IQR* interquartile range, *INR* international normalized ratio

bilirubin on POD1 (1.45, IQR 1.1–2.1), but a slower rate of recovery (decreased by 0.4 from POD1 to POD5). The NAFLD group had the highest median total bilirubin on POD3 and 5, compared to the lowest values observed in the benign group ($p<0.001$ overall, at each timepoint).

Across all groups, the highest median INR was observed on POD1 (Fig. 1, Table 2), with the healthy donor group having the highest (1.5, IQR 1.4–1.7), and the cirrhotic group having the lowest INR (1.3, IQR 1.2–1.5). On POD5, the highest INR value was seen in the NAFLD group at 1.2 (IQR 1.1–1.4), compared to the lowest value of 1.1 in the benign and chemotherapy groups ($p=0.003$ overall on POD5, $p<0.001$ overall, all other timepoints).

The highest bilirubin level was observed on POD1 for 56.8% ($n=562$) of individuals, while the highest INR was observed on POD1 for 76.3% ($n=755$) of individuals. There was a statistically significant association between day of highest value for bilirubin and INR ($p<0.001$).

Stratification by extent of hepatic resection

Among patients who underwent resection of 3–4 segments, statistically significant elevations in bilirubin and INR were observed in the healthy donor group ($p<0.001$) on POD1 (Fig. 2). In comparison, among those who underwent resection of at least 5 segments, the chemotherapy group was observed to have the highest median INR on POD1 and 3, which returned to levels below the donor and cirrhosis groups by POD5. For total bilirubin among ≥ 5 segment resection, the healthy donor group had the highest level on POD1, while the chemotherapy group had the highest levels on POD3 and 5. Of note, the benign and NAFLD categories were omitted from stratified analysis due to insufficient sample size.

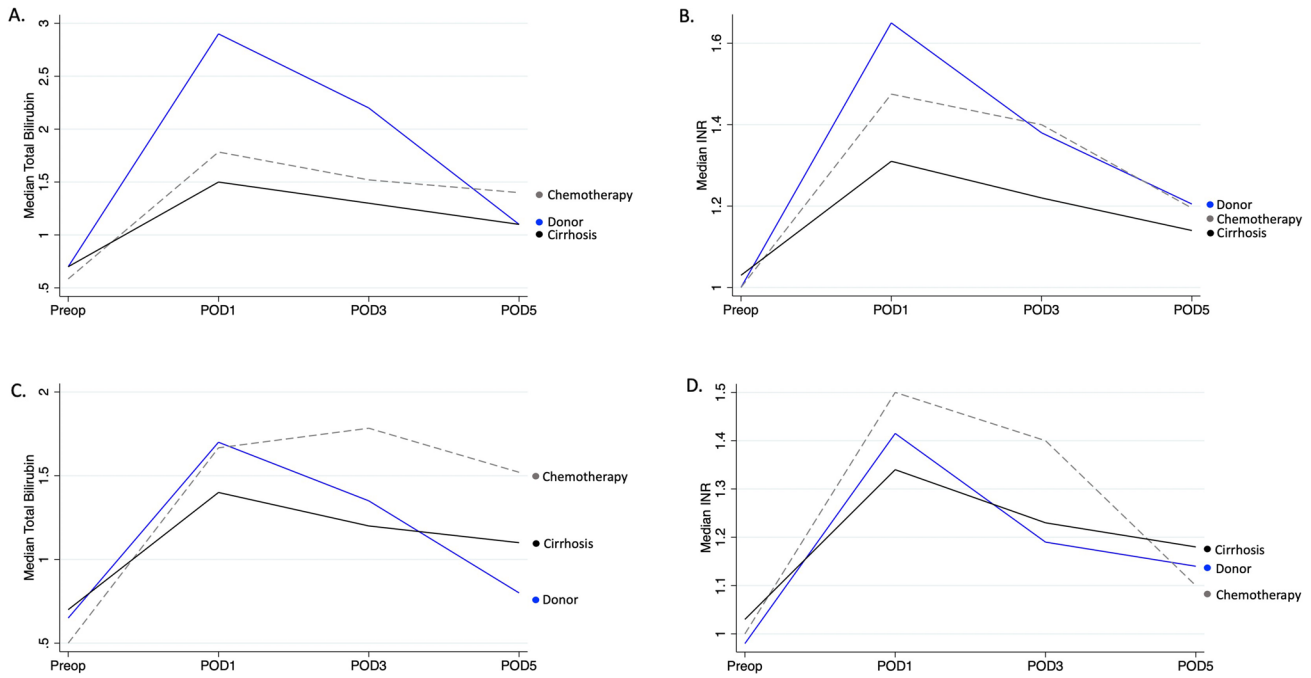

Fig. 2 **A** Postoperative total bilirubin by pre-existing liver pathology, 3–4 segment [a] resection ($n=713$). **B** Postoperative INR by pre-existing liver pathology, 3–4 segment [a] resection ($n=713$). **C** Postoperative total bilirubin by pre-existing liver pathology, 5 or more segment resection ($n=203$). **D** Postoperative INR by pre-existing liver pathology, 5 or more segment resection ($n=203$). "This figure displays total bilirubin and INR preoperatively and then on postoperative days 1, 3, and 5, by pre-existing liver pathology (donor, chemotherapy, cirrhosis), and further stratified by extent of hepatic resection (3–4 segment resection vs. 5 or more segments). *INR* international normalized ratio. [a]2-segment resection included for patients with cirrhosis"

Discussion

This study characterizes the kinetics of total bilirubin and INR following major hepatic resection in a large international cohort of hepatectomy patients. Overall, both biochemical values reached their highest levels on POD1. Interestingly, the highest elevations in bilirubin and INR were seen among healthy living donor patients, although they also had a more rapid normalization of values. In contrast, cirrhotic patients had more modest elevations in biochemical tests. When stratifying by extent of resection, elevations in the healthy donor group were found to be specific to 3–4 segment resection.

Our study distinguishes itself from previous studies because of the diverse, multi-center cohort as well as the stratification of results by pre-existing liver pathology [6, 7]. Much of the existing work on this topic was conducted on small samples of patients and many years ago [2, 4, 5, 8]. More recently, Reissfelder et al. conducted an analysis of 835 patients from a single institution and investigated differences in postoperative laboratory values by extent of hepatic resection. They found greater elevations in bilirubin and INR following major hepatic resection compared to minor resection, and that values returned to the normal range by postoperative day 5. Of note, only 288 of the patients in the cohort had complete lab data and were included in the biochemical blood test analysis [6]. Roberts et al. conducted a similar analysis of the kinetics of postoperative liver function tests, but in a more homogenous sample of 73 patients who underwent hepatic resection for colorectal liver metastasis. The authors compared bilirubin and INR levels and stratified by grade of liver failure per the International Study Group for Liver Surgery criteria [7]. While some analyses have focused on specific patient populations [7], our study adds to existing literature by directly comparing across categories of liver pathology in a large cohort.

Higher initial INR and total bilirubin levels among healthy living donor patients was a surprising finding. It is possible that these elevations reflect a greater proportion of resected functional parenchyma among healthy donors, as this is the only group in which volume loss exactly corresponds to functional parenchyma. This may stand in contrast to those with malignant indications for surgery, where much of the resected volume has been previously rendered non-functional by the presence of tumor. In patients with cirrhosis, the observed blunted elevations in biochemical tests may be due to increased intrahepatic shunting leading to decreased ischemia. In contrast, the more rapid normalization of these markers in healthy donors, and to a lesser extent in those with a benign indication for surgery, is likely

to reflect the robust potential for recovery of healthy liver parenchyma. It is possible that the more modest elevations seen in cirrhotic patients reflect less aggressive resection in this population, particularly as 2 segment resections were included in this group. However, this is unlikely to entirely explain differences as the lowest total bilirubin and INR levels were seen in patients with cirrhosis even when considering 5 or more segment resection. Furthermore, the more rapid return to normal observed among healthy donor and benign indication groups may have clinical implications in terms of the ability of these patients to tolerate additional stressors or complications in the postoperative period.

The present findings have the potential to serve as an educational resource to surgical trainees as well as inform clinical practice. It is common to check markers of hepatic function frequently in the first postoperative week. When results are outside of the normal range, further work up and testing may be triggered. These practice patterns may be partially due to uncertainty around interpretation of markers of hepatic function. Our characterization of the early kinetics of these markers provides a framework with which to interpret these laboratory tests. It is our hope that a shared understanding of normal postoperative elevations in bilirubin and INR, with the expectation of some differences based on pre-existing liver pathology, may help to decrease unnecessary testing, and serve as a cost reduction measure. By reducing unnecessary testing, this knowledge could prevent further costs associated with subsequent workup and intervention—for example, potentially increased length of stay to follow lab values until they normalize. Furthermore, eliminating unnecessary testing may prevent undue distress for patients who worry about the implications of abnormal results.

Limitations of this analysis include the proportion of patients with missing laboratory data. As the intent of this analysis is descriptive, we chose to include patients missing only one lab parameter as detailed in the methods section. Furthermore, it is possible that the presence of missing data, in combination with the exclusion of individuals with other liver pathology when defining NAFLD, underestimated the number of patients with this preoperative pathology ($n=26$). Similarly, substantial missing data on future liver remnant volume precluded our ability to examine the extent to which observed differences across pre-existing liver pathology could be explained by differences in future liver remnant volume. Another limitation is the inclusion criteria allowing for two segment resections among cirrhotic patients. Therefore, it is possible that cirrhotic patients in the <5 segment resection group had smaller volumes of liver parenchyma resected compared to other categories of liver pathology. We chose to include these patients as cirrhotic patients tend to undergo more conservative resections and expanding our inclusion criteria allows for a significantly larger sample size.

Conclusions

Overall, our study characterizes the kinetics of bilirubin and INR in the first week following major hepatic resection. We observed both the highest initial enzyme peaks, and fastest rates of return to normal among healthy donor patients. In contrast, cirrhotic patients had more modest elevations in biochemical tests. We believe this description could serve as a resource for surgical learners as they care for patients following major hepatic resection and, in doing so, help to decrease unnecessary testing.

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Author contributions LC, JW, KMP and NR contributed to the conception and design of the study, to the analysis of the results and to the writing of the manuscript. ABC, PCC, TH, DH, MAH contributed to the acquisition of data, and critically revised the manuscript for important intellectual content. MAA and AA contributed to the conception and design of the study, acquisition of data, and critically revised the manuscript for important intellectual content. The International Post-Hepatectomy Liver Failure Study Group is comprised of authors responsible for data collection and cleaning at their respective sites. All authors critically revised the manuscript for important intellectual content and gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability Available from authors upon reasonable request.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics approval This study was approved by the Institutional Review Board of the University of California San Francisco (IRB No: 20–31911).

Consent This study used retrospective de-identified data, as such informed consent was not obtained for the present analysis.

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