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Preoperative platelet count does not predict the occurrence of post-hepatectomy liver failure after partial hepatectomy in a retrospective monocentric cohort study

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Abstract

In humans, thrombocytopenic patients have increased incidence of post-hepatectomy liver failure (PHLF), but existing evidence is heterogeneous. Our objective was to determine if preoperative platelet count or antiplatelet drugs were associated with PHLF.

Patients who underwent hepatic resection in the University Hospitals of Geneva, Switzerland, from 01.12.2009 to 18.12.2018 were identified. Platelet count at day 0, postoperative days (POD) 1, 3, and 5 were retrieved. Occurrence of PHLF according to the ISGLS definition was determined. Logistic regression was performed to determine if platelet count or antiplatelet drug were predictors for PHLF.

Five hundred ninety seven patients were included. Eighty patients (17.8%) had a preoperative platelet count <150 (G/l) and 24 patients (5.3%) had a platelet count <100 (G/l). Thirty five patients (5.9%) were under antiplatelet drug. Platelet count significantly decreased at POD 1 and POD 3 when compared to preoperative platelet count (182 ± 71.61 (G/l) vs 212 ± 85.26 (G/l), $P < .0001$; 162 ± 68.5 (G/l) vs 212 ± 85.26 (G/l), $P < .0001$). At POD 5, post-operative platelet count did not significantly differ from its preoperative value. Forty three patients (11.2%) suffered from PHLF. Their platelet count was not significantly different than patients without PHLF (211 ± 89.7 (G/l) vs 211 ± 83.5 (G/l), $P = .671$). One patient with PHLF had a platelet count <100 (G/l) and 5 had a count <150 (G/l). Univariate logistic regression did not identify preoperative thrombocytopenia (<100 (G/l) or <150 (G/l)), postoperative thrombocytopenia, or the presence of antiagregant drug, as predictors of PHLF. We did not identify preoperative or postoperative thrombocytopenia as predictor of PHLF in a cohort of 597 patients.

Abbreviations: CRM = colorectal metastasis, FFP = fresh frozen platelets, HCC = hepatic cellular carcinoma, PHLF = post-hepatectomy liver failure, POD = post-operative day.

Keywords: liver insufficiency, low platelet count, PHLF, thrombocytopenia

1. Introduction

Post-hepatectomy liver failure (PHLF) constitutes a serious complication of partial hepatectomy that manifests through a failure of the excretory and/or synthetic liver functions. Even though partial hepatectomy is a relatively safe procedure that is also used on living donors for liver transplantation, PHLF still has a documented incidence rate ranging between 1.2 and 32%.[1–4]

PHLF is multifactorial and highly associated with the remnant liver volume and function, and its regenerative capacity. Over the last decades, platelets have been shown to stimulate liver regeneration after partial hepatectomy in rodents and various mechanisms have been postulated.[5–7] Recently, a systematic review and meta-analysis found that preoperative platelet count predicted the occurrence of PHLF (odds ratio: 5.53, 95% CI: 2.85–10.48), also when pooling only patients without liver cirrhosis (odds ratio: 3.13, 95% CI: 1.75–5.58) which could constitute a confounding factor for thrombocytopenia.[8] However, this systematic review and meta-analysis was limited by the heterogeneity of the studies included in terms of definitions of thrombocytopenia (thresholds set at 100 (G/l) or 150 (G/l)) and definitions of PHLF. Further, the effect of thrombocytopenia on the occurrence of PHLF did not constitute the primary outcome of most of the studies included in the meta-analysis. Further, the role played by antiplatelet drugs has been so far not investigated.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Therefore, we have decided to determine if preoperative platelet count or antiplatelet drug administration were associated with PHLF in a retrospective cohort study.

2. Methods

2.1. Ethical clearance

The research project was approved by the Swiss Ethics Committee on research involving humans (BASEC-ID 2018–02074). The study complied with the STROBE guidelines (Supplemental Digital Content (Table S1, http://links.lww.com/MD/F637)).

2.2. Study population

We retrospectively identified patients who underwent hepatic resection in the University Hospitals of Geneva during an 8-year period from 01.12.2009 to the 18.12.2018 through our digital medical records by selecting the surgical coding for "partial hepatectomy". Thereafter, we reviewed medical records and excluded patients with splenectomy and/or administration of fresh frozen plasma (FFP).

2.3. Outcome

Various definitions and criteria coexist and are accepted to define PHLF.[9,10] In the present study, we retained 2 different definitions: the 50 to 50 criterion[1] which defines PHLF as a Quick <50% and a bilirubin value >50 micromol/l on postoperative day (POD) 5, and the less restrictive ISGLS definition,[3] which defines PHLF as an increased INR and an elevated bilirubin concentration on POD 5 according to the local laboratory cut-off.

2.4. Variables

From medical records, we extracted the following variables: gender, age at surgery, length of hospital stay, date of surgery, surgical indication (hepatocellular carcinoma (HCC), colorectal cancer metastasis (CRM) and others (including living donors, hydatic cysts, abscesses, trauma, other tumors, metastases from other origins), platelet count at day 0, POD 1, POD 3, and POD 5, bilirubin value at POD 5, Quick at POD 5 and current medication including antiplatelet drug.

2.5. Statistical analyses

Differences between groups were compared using the two-sided Student's test or the Pearson's Chi-Squared test, as appropriate. Continuous variables were transformed into categorical variables if required. Variables were expressed as proportions for categorical variables and medians for continuous ones; 95% confidence intervals (95% CI) and standard deviations (SD) were reported. Predictors of PHLF were searched using univariate logistic regression, considering as "cases" patients with PHLF and as "controls" other patients. Subgroup analyses were performed per surgical indication. Statistical analyses were performed using the STATA software[11] and Graph Pad Prism version 6 (Graph Pad Software Inc., La Jolla, USA). The null hypothesis was rejected at $P < .05$.

3. Results

3.1. Inclusion process

Six hundred thirty two inpatients were identified from medical records for the studied 8-year period. Duplicate removal allowed obtaining 614 patients. Seventeen patients were further removed for matching at least one of the exclusion criteria (splenectomy, FFP), leaving 597 patients for analysis.

3.2. Patients' demographics

Three hundred and thirty two patients were males (55.4%). The median age was 62 ± 17.6 years. Indications for surgery were CRM in 236 patients (39.5%), HCC in 95 patients (15.9%), and others in 266 (44.6%). Median preoperative platelet count was 212 ± 85.3 (G/l). Eighty patients (17.8%) had a preoperative platelet count <150 (G/l) and 24 patients (5.3%) had a platelet count <100 (G/l). Thirty five patients (5.9%) were under antiplatelet drug. Patients with HCC as surgical indication did not have significantly lower preoperative platelet count than total patients (18 ± -84.09 (G/l) vs 212 ± 85.26 (G/l), $P = .0543$, not shown) or patients with CRM (184 ± 84.09 (G/l) vs 210 ± 68.08 (G/l), $P = .1319$, not shown). Forty eight (50.5%) patients with HCC had liver cirrhosis. Among them, the median hepatic vein pressure gradient was 6 ± 3.4 (mm Hg) and the median MELD score was 8 ± 1.5. Results are summarized in Table 1.

Table 1

Patients demographics in the pre-operative period.

		50–50 criterion		ISGLS definition	
	All patients	PHLF	No PHLF	PHLF	No PHLF
Surgical indication, n (%)					
– All	597 (100%)	3 (0.8%)	382 (99.2%)	43 (11.2%)	342 (88.8%)
– HCC	95 (15.9%)	0 (0%)	68 (100%)	6 (8.8%)	62 (91.2%)
– CRM	236 (39.5%)	0 (0%)	158 (100%)	17 (10.8%)	141 (89.2%)
– Others	266 (44.6%)	3 (1.9%)	156 (98.1%)	20 (12.6%)	139 (87.4%)
Platelet count (G/l), median+/−SD	212+/−85.3	226.5+/−2.12	211+/−84.3	211+/−89.7	211+/−83.5
Platelets <100G/l, n (%)	24 (5.3%)*	0 (0%)†	17 (100%)†	1 (5.9%)†	16 (94.1%)†
Platelets <150G/l, n (%)	80 (17.8%)*	0 (0%)†	55 (100%)†	5 (9.1%)†	50 (90.9%)†
Anti-platelet drug (yes), n (%)	35 (5.9%)*	0 (0%)†	28 (100%)†	4 (14.3%)†	24 (85.7%)†

* Proportion reported to the total number of patients.

† Proportion reported to the number of patients with a positive outcome (thrombocytopenia or anti-platelet drug). Some values are missing.

Median+/−SD or number (proportion) are reported. CRM = colorectal cancer metastasis, HCC = hepatocellular carcinoma, PHLF = post-hepatectomy lifer failure.

3.3. Incidence of PHLF

According to the 50 to 50 criterion, 3 patients (0.8%) suffered from PHLF on POD 5. These 3 patients constituted 1.9% of patients operated for other causes than HCC and CRM. None of them was thrombocytopenic and/or under antiplatelet drugs (Table 1). According to the less restrictive ISGLS definition, 43 patients (11.2%) suffered from PHLF on POD 5. All surgical indications were represented in ISGLS PHLF patients. Among patients with ISGLS PHLF, the number of patients with thrombocytopenia <150 (G/l) and <100 (G/l) only represented, respectively, 9.1% and 5.9% of the total number of patients with thrombocytopenia (Table 1). Only 1 patient (2.6%) with HCC and liver cirrhosis had ISGLS PHLF.

3.4. Dynamics of platelet count after partial hepatectomy

Preoperative distribution of platelets is reported in Supplemental Digital Content (fig. S1, http://links.lww.com/MD/F636). Platelet count significantly decreased at POD 1 and POD 3 when compared to preoperative platelet count (182 ± 71.61 (G/l) vs 212 ± 85.26 (G/l), $P < .0001$; 162 ± 68.5 (G/l) vs 212 ± 85.26 (G/l), $P < .0001$). At POD 5, post-operative platelet count did not significantly differ from its preoperative value (204 ± 82.97 (G/l) vs 212 ± 85.26 (G/l), $P = .1593$). The decrease at POD 3 was observed in all subgroups of patients (Table 2, Fig. 1).

3.5. Preoperative platelet count as predictor of PHLF

According to the 50 to 50 criterion, 3 patients (0.8%) suffered from PHLF on POD 5. Their platelet count was not significantly different from patients without PHLF (226.5 ± 2.12 (G/l) vs 211 ± 84.3 (G/l), $P = .896$). Further, no patient with PHLF had a platelet count <100 (G/l) or <150 (G/l) (Table 3). According to the ISGLS definition, 43 patients (11.2%) suffered from PHLF on POD 5. Their platelet counts were not significantly different from patients without PHLF (211 ± 89.7 (G/l) vs 211 ± 83.5 (G/l), $P = .671$). Further, only 1 patient with PHLF had a platelet count <100 (G/l) and 5 patients had a count <150 (G/l) (Table 3). Univariate logistic regression did not identify a preoperative platelet count <100 (G/l) or <150 (G/l), or the presence of antiagregant drugs, as predictors of PHLF according to the ISGLS definition (Table 3). Subgroup analysis including only patients with HCC reached the same conclusions (Supplemental Digital Content (Table S2, http://links.lww.com/MD/F638)). Then, we investigated if platelet count at POD 1, POD 3, or POD 5 could predict the occurrence of PHLF but did not identify any prediction (Supplemental Digital Content (Table S3, http://links.lww.com/MD/F639)).

4. Discussion

In the present study, we showed that the platelet count dropped after partial hepatectomy, notably at POD 3. This finding was reported in the literature, notably by Takahashi et al,[12] who demonstrated that postoperative decrease in platelet count was associated with PHLF. We hypothesized that, besides being consumed for haemostatic purposes, platelets might also be recruited to the remnant liver sinusoids to initiate liver regeneration.[5–7]

Then, we determined that 0.8% and 11.2% of our patients suffered from PHLF as defined by the 50-50 criterion[1] or the ISGLS definition,[3] respectively. Their platelet counts were not significantly different from patients without PHLF. Further, univariate logistic regression did not identify a platelet count <100 (G/l) or <150 (G/l) as predictors of PHLF according to the ISGLS definition. These results are, however, contrary to the existing literature evaluating the effect of preoperative platelet count on PHLF.[13–15] For instance, Maithel et al.[13] reported in 231 cirrhotic patients that a platelet count <150 (G/l) constituted a risk factor for PHLF (reconstituted odds ratio: 7.33, 95% CI: 3.04–17.65),[8] as defined by a peak bilirubin >7 (mg/dl) or ascites. Tomimaru et al[14] also described in 277 cirrhotic patients that a platelet count <150 (G/l) predicted the occurrence of PHLF (reconstituted odds ratio: 3.81, 95% CI: 1.39–10.48),[8] as defined by the ISGLS definition. Further, Golriz et al[15] recently reported in 231 cirrhotic patients undergoing extended hepatectomy (>4 liver segments) that a preoperative platelet count <150 (G/l) was an independent predictor of PHLF (odds ratio: 4.4, 95% CI: 1.3–15.0), as defined by the ISGLS definition.

Although our cohort constitutes, to our knowledge, the largest published in the field, our results do not indicate that platelet count alone, i.e., thrombocytopenia, predicts the occurrence of PHLF. We suggest that this discrepancy with the existing literature, summarized in 2 recent systematic reviews and meta-analyses,[8,16] might be explained by heterogeneity in the published cohorts of patients (cirrhosis vs no cirrhosis, partial hepatectomy vs extended hepatectomy), and also by a likely underreporting of negative results (publication bias). Further, we did not consider preoperative cross-sectional liver volume estimation for subgroup analysis, as that variable was not available in informatics files. Moreover, a type II statistical error (due to the low number of patients with PHLF in our cohort) cannot be excluded, but this would mean that the association between thrombocytopenia and PHLF is weak. Nevertheless, the results were obtained by careful analysis of a large patient cohort and are therefore of importance for the orientation of future systematic review and meta-analysis.

Table 2

Dynamics of platelet count after partial hepatectomy.

Platelet count (G/l)	All	*P* value*	HCC	*P* value*	CRM	*P* value*	Others	*P* value*
D0	212+/−85.26	–	184+/−84.09	–	210+/−68.08	–	221.5+/−96.99	–
POD 1	182+/−71.61	<.0001	170.5+/−71.42	.0651	177+/−57.29	<0.0001	189+/−81	.0009
POD 3	162+/−68.5	<.0001	159+/−65.81	.0047	152+/−55.34	<0.0001	173.5+/−77.78	<.0001
POD 5	204+/−82.97	.1593	205+/−77.08	.5099	189.5+/−69.34	0.0206	215+/−93.87	.5764

* When compared to platelet count at day 0.

Median+/−SD are reported. CRM = colorectal cancer metastasis, HCC = hepatocellular carcinoma, POD = postoperative day. Some values are missing.

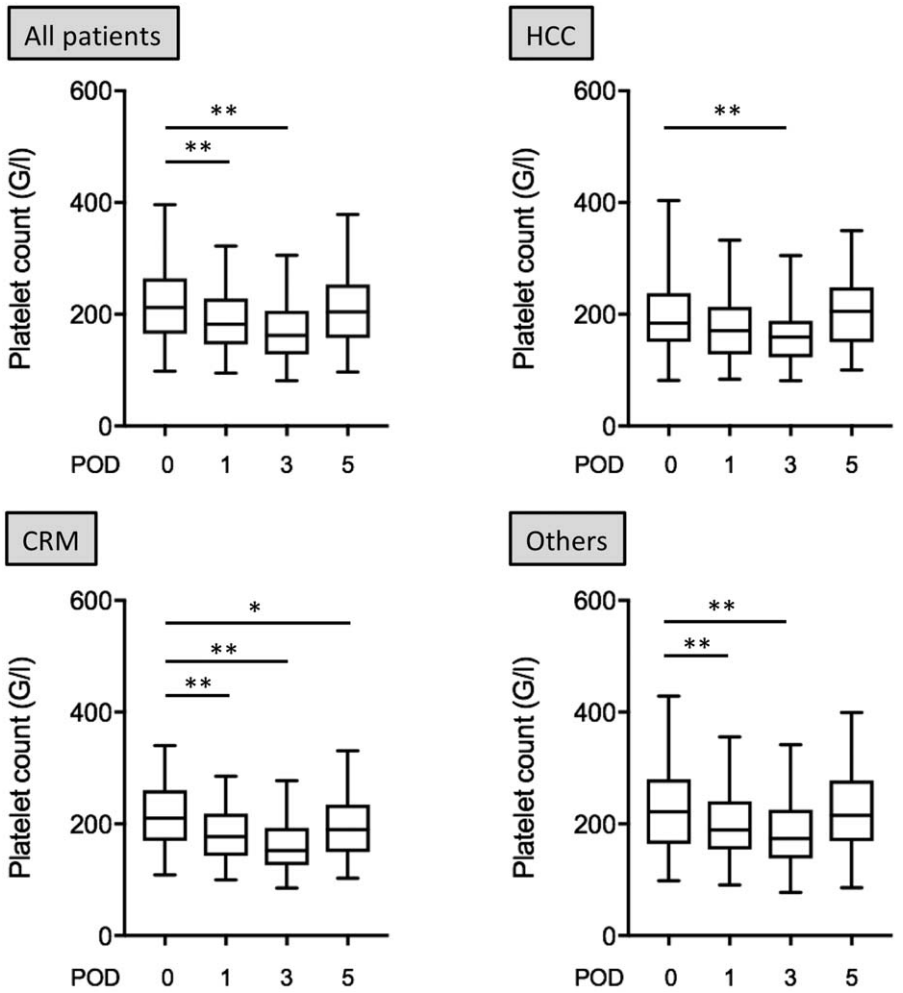

Figure 1. Dynamics of perioperative platelet count. Box-plots reporting the perioperative platelet count in patients undergoing partial hepatectomy. Whiskers represent 95% confidence intervals. CRM = colorectal cancer metastasis, HCC = hepatocellular carcinoma. $^{*}P < .05$; $^{**}P < .001$.

Table 3

Identification of platelet-related predictors of PHLF at day 0.

	50–50 criterion			ISGLS definition			Univariate regression*	
	PHLF (n = 3)	No PHLF (n = 382)	*P* value	PHLF (n = 43)	No PHLF (n = 342)	*P* value	Odds ratio (95% CI)	*P* value
Platelets <100 G/l	0	17	–	1	16	0.533	0.53 (0.07–4.11)	0.54
Platelets <150 G/l	0	55	–	5	50	0.734	0.84 (0.31–2.30)	0.74
Anti-platelet drug (yes)	0	28	–	4	24	0.587	1.36 (0.45–4.12)	0.59

* For PHLF according to the ISGLS definition.
PHLF = post-hepatectomy lifer failure.

In conclusion, we did not identify preoperative or postoperative thrombocytopenia as predictors of PHLF in a retrospective cohort of 571 patients. Further evidence is needed to confirm in humans the effect of platelet on liver regeneration observed in rodent models.

Author contributions

SEH and JM conceived and designed the study. SEH and JM acquired the data. JM analyzed the data. SEH, AB, CT, CGG, LB, and JM interpreted the data. SEH, AB, CT, CGG, LB, and JM contributed to the writing of the manuscript and to its critical revision. SEH, AB, CT, CGG, LB, and JM approved the final version of the manuscript.

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