# Impact of Platelet Count on Perioperative Bleeding in Patients With Cirrhosis Undergoing Surgical Treatments of Liver Cancer

Vincenzo Ronca,[1#] Matteo Barabino,[2] Roberto Santambrogio,[2##] Enrico Opocher,[2,3] James Hodson,[4] Emanuela Bertolini,[5] Simone Birocchi,[1] Gaetano Piccolo,[2] PierMaria Battezzati,[5] Marco Cattaneo,[1] and Gian Marco Podda [1]

**In patients with cirrhosis with severe thrombocytopenia (platelet count [PC] <50 × $10^9$/L) and undergoing invasive procedures, it is common clinical practice to increase the PC with platelet transfusions or thrombopoietin receptor agonists to reduce the risk of major periprocedural bleeding. The aim of our study was to investigate the association between native PC and perioperative bleeding in patients with cirrhosis undergoing surgical procedures for the treatment of hepatocellular carcinoma (HCC). We retrospectively evaluated 996 patients with cirrhosis between 1996 and 2018 who underwent surgical treatments of HCC by liver resection (LR) or radiofrequency ablation (RFA) without prophylactic platelet transfusions. Patients were allocated to the following three groups based on PC: high (>100 × $10^9$/L), intermediate (51-100 × $10^9$/L), and low (≤50 × $10^9$/L). PC was also analyzed as a continuous covariate on multivariable analysis. The primary endpoint was major perioperative bleeding. The overall event rate of major perioperative bleeding was 8.9% and was not found to differ significantly between the high, intermediate, and low platelet groups (8.1% vs. 10.2% vs. 10.8%, *P* = 0.48). On multivariable analysis, greater age, aspartate aminotransferase, lower hemoglobin, and treatment with LR (vs. RFA) were found to be significant independent predictors of major perioperative bleeding, with associations with disease etiology and year of surgery also observed. After adjusting for these factors, the association between PC and major perioperative bleeding remained nonsignificant. *Conclusion:* Major perioperative bleeding was not significantly associated with PC in patients with cirrhosis undergoing surgical treatment of HCC, even when their PC was <50 × $10^9$/L. With the limit of a retrospective analysis, our data do not support the recommendation of increasing PC in patients with severe thrombocytopenia in order to decrease their perioperative bleeding risk. (*Hepatology Communications* 2022;6:423-434).**

The unstable balance of primary hemostasis, coagulation, and fibrinolysis in liver cirrhosis may be easily perturbed during invasive procedures and expose patients to bleeding and thrombotic risks.[1,2] Thrombocytopenia (platelet count <150 × $10^9$/L) and severe thrombocytopenia (platelet count <50 × $10^9$/L) are reported in 76% and 10% of patients with liver cirrhosis, respectively.[3,4] Considering the important role of platelets in hemostasis, patients with cirrhosis undergoing invasive procedures may be

*Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinical Liver Cancer; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LR, liver resection; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PT, prothrombin time; RFA, radiofrequency ablation; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist.*

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*[#]Actual affiliation:Liver Transplant and Hepatobiliary Unit, University Hospital of Birmingham National Health Service (NHS) Foundation Trust, Birmingham, United Kingdom; [##]Unità di Chirurgia Generale, ASST Fatebenefratelli Sacco, Milano, Italy.*



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at heightened risk for excessive perioperative bleeding when their platelet count is severely reduced. In national guidelines, a threshold of 50 × $10^9$/L platelets is considered safe in patients with thrombocytopenia undergoing invasive procedures, although this is based on weak evidence.[5-7] The same threshold is recommended in a position paper from the Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine that suggested administering platelet transfusions to patients with cirrhosis with platelet counts <50 × $10^9$/L before undergoing invasive procedures.[8] However, this recommendation is not supported by clear evidence stemming from *ad hoc* experimental studies[8] that show a clear association between the severity of thrombocytopenia and bleeding risk. Hence, there is no evidence that any intervention aiming to increase the platelet count (platelet transfusions or thrombopoietin [TPO] mimetics) has a favorable risk-benefit profile. The aim of this retrospective study was to investigate the association between platelet count and major perioperative bleeding in a cohort of patients at our center between 1996 and 2018 who had cirrhosis and underwent surgical treatments of hepatocellular carcinoma (HCC)[9] by liver resection (LR) or radiofrequency ablation (RFA)[10] without prophylactic platelet transfusions or other therapies to increase the platelet count.

# Patients and Methods

## STUDY POPULATION

Details of all patients referred to the Surgical Unit of Azienda Socio Sanitaria Territoriale Santi Paolo e Carlo in Milan for surgical treatment for HCC in liver cirrhosis from 1996 to 2018 were prospectively recorded in a database. All patients provided written informed consent for their data to be used in research. The database was retrospectively reviewed to extract demographic, clinical, and biochemical data recorded at the time of patient admission.

Liver cirrhosis was diagnosed either by liver biopsy or as a result of clinical/biochemical and instrumental findings.[11] The diagnosis of HCC was based on the Barcelona 2000 European Association for the Study of the Liver conference.[12] The management of HCC in our center is guided by a multidisciplinary team that includes surgeons, radiologists, and hepatologists. The Barcelona Clinical Liver Cancer (BCLC) criteria published in 2012 were used to allocate the patient to the appropriate treatment strategy.[13] Before 2012, LR HCC management was determined according to American Association for the Study of Liver Diseases and BCLC guidelines.[14] Patients who underwent prophylactic platelet transfusions or whose records were unavailable were excluded from the study.

## DEFINITIONS AND OUTCOMES

The cohort of patients was initially stratified into the following three groups for the purpose of the study according to their platelet count at admission and to commonly accepted criteria[15]: high platelet count (platelet count >100 × $10^9$/L), intermediate platelet count (moderate thrombocytopenia; platelet count 51-100 × $10^9$/L), and low platelet count (severe thrombocytopenia; platelet count ≤50 × $10^9$/L).

The primary outcome of the study was the rate of major perioperative bleeding, which was defined according to the criteria of the International Society

**ARTICLE INFORMATION:**

From the [1]Unità di Medicina II, Azienda Socio Sanitaria Territoriale (ASST) Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy; [2]Unità di Chirurgia Epatobilliare, ASST Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy; [3]Unità di Chirurgia II, ASST Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy; [4]Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [5]Unità di Gastroenterologia, ASST Santi Paolo e Carlo, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy.

**ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:**

Gian Marco Podda
Unità di Medicina II, ASST Santi Paolo e Carlo
Dipartimento di Scienze della Salute
Università degli Studi di Milano
Via di Rudinì, 8
20142 Milano, Italy
E-mail: gmpodda@gmail.com
Tel.: +39-(0)2-81844275

on Thrombosis and Haemostasis.[16] Secondary outcomes were the major perioperative bleeding rates within the RFA and LR subgroups separately and mortality within 90 days of surgery.

## STATISTICAL ANALYSIS

Initially, the cohort characteristics were compared between the three platelet count groups. The distributions of continuous variables were assessed graphically before analysis. Those found to be approximately normally distributed were reported as mean ± SD and were compared across groups using one-way analysis of variance tests. Non-normally distributed continuous variables were reported as medians and interquartile ranges (IQRs) and were compared across groups using the Kruskal-Wallis test. Ordinal variables were also analyzed using the Kruskal-Wallis test, with nominal variables compared using the chi-squared test.

Platelet count was then treated as a continuous variable and analyzed using a binary logistic regression model. This analysis was repeated within the subgroups of patients treated with RFA and LR separately. A model was also produced with the platelet count, type of surgery, and an interaction term as covariates such that the interaction term compared the effect of platelet count between the RFA and LR subgroups.

Univariable binary logistic regression models were then produced for the other demographic, clinical, and biochemical factors being assessed to identify other predictors of major perioperative bleeding. For continuous variables, the goodness of fit of the model was assessed using the Hosmer-Lemeshow test with variables being divided into categories based on the quartiles where poor fit was detected. The platelet count was then entered into a multivariable model with a backwards stepwise approach (removal at $P > 0.1$) used to identify other independent predictors of outcomes.

Logistic regression models were summarized using odds ratios (ORs) with 95% confidence intervals (CIs). For continuous variables, the ORs were reported for a unit increase that gave values of a reasonable magnitude; for example, the OR for platelets was reported per 50 × $10^9$/L rather than per 1 × $10^9$/L. All analyses were performed using IBM SPSS 22 (IBM Corporation, Armonk, NY), with $P < 0.05$ deemed to be indicative of statistical significance throughout.

# Results

## CHARACTERISTIC OF THE STUDY POPULATION

The cohort included 1,011 patients admitted to our hospital between 1996 and 2018. Of these, 7 patients were excluded because they received prophylactic platelet transfusions; a further 8 patients were excluded due to missing data for either the platelet count or the primary outcome. Thus, 996 patients were included in the analysis (Fig. 1).

The main characteristics of the patients are summarized in Table 1. The median platelet count for the cohort as a whole was 115 × $10^9$/L (IQR, 80-163). In total, 607 (60.9%) patients belonged to the high platelet count group (median platelet count, 150 × $10^9$/L; IQR, 121-191), 315 (31.6%) to the intermediate platelet count group (77 × $10^9$/L; IQR, 64-89), and 74 (7.4%) to the low platelet count group (39 × $10^9$/L; IQR, 32-46). The patient with the most severe thrombocytopenia had a platelet count of 14 × $10^9$/L. The majority of patients had Child A cirrhosis (n = 897, 90.2%), with only a single patient having Child C liver cirrhosis. RFA was performed in 579 patients (58.1%), of whom 504 (87.0%) underwent laparoscopic procedures; the remaining 417 patients (41.9%) underwent LR, which was performed by a laparotomic approach in 392 cases (94.0%).

Comparisons across the platelet count groups found patient age, liver function (as quantified by alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], prothrombin time [PT], and bilirubin), hemoglobin, and creatinine levels to increase significantly with the severity of thrombocytopenia (Table 1). The median Model for End-Stage Liver Disease (MELD) score, frequency of

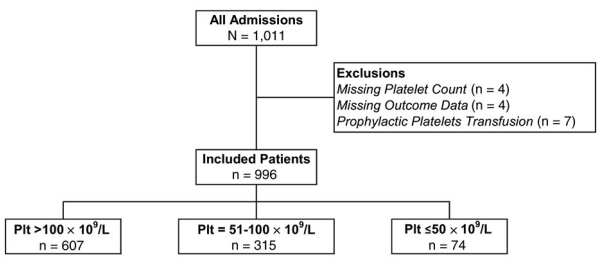


**FIG. 1.** Flow diagram of patients included in the analysis. Abbreviation: Plt, platelet count.

**TABLE 1. COHORT CHARACTERISTICS BY PLATELET COUNT GROUP**

| | | | Platelet Count Group | | | |
|---|---|---|---|---|---|---|
| | Number | Overall | High (>100 × $10^9$/L) | Intermediate (51-100 × $10^9$/L) | Low (≤50 × $10^9$/L) | *P* Value |
| Platelet count (×$10^9$/L) | 996 | 115 (80, 163) | 150 (121, 191) | 77 (64, 89) | 39 (32, 46) | N/A |
| Age at surgery (years) | 995 | 70 (64, 75) | 71 (65, 76) | 69 (63, 74) | 66 (61, 71) | <0.001 |
| Sex (% female) | 996 | 253 (25.4%) | 149 (24.5%) | 86 (27.3%) | 18 (24.3%) | 0.64 |
| Hemoglobin (g/dL) | 992 | 13.5 ± 1.8 | 13.7 ± 1.8 | 13.4 ± 1.7 | 12.9 ± 1.7 | <0.001 |
| PT | 995 | 1.10 (1.04, 1.19) | 1.07 (1.02, 1.14) | 1.16 (1.08, 1.23) | 1.25 (1.13, 1.37) | <0.001 |
| Bilirubin (mg/dL) | 987 | 1.00 (0.70, 1.40) | 0.89 (0.65, 1.15) | 1.21 (0.90, 1.72) | 1.60 (1.10, 2.09) | <0.001 |
| Albumin (g/dL) | 991 | 3.82 ± 0.55 | 3.95 ± 0.51 | 3.66 ± 0.54 | 3.45 ± 0.51 | <0.001 |
| Creatinine (mg/dL) | 877 | 0.83 (0.70, 1.00) | 0.85 (0.70, 1.01) | 0.80 (0.70, 0.98) | 0.84 (0.70, 1.05) | 0.04 |
| ALT (IU) | 995 | 50 (31, 87) | 43 (29, 77) | 60 (36, 97) | 74 (39, 113) | <0.001 |
| AST (IU) | 995 | 52 (33, 88) | 45 (30, 78) | 67 (41, 103) | 73 (41, 122) | <0.001 |
| ALP (IU) | 901 | 139 (89, 235) | 129 (84, 213) | 145 (98, 266) | 183 (128, 291) | <0.001 |
| Cirrhosis etiology | 996 | | | | | <0.001 |
| HCV | | 645 (64.8%) | 359 (59.1%) | 233 (74.0%) | 53 (71.6%) | |
| HBV | | 146 (14.7%) | 114 (18.8%) | 25 (7.9%) | 7 (9.5%) | |
| Cryptogenetic | | 21 (2.1%) | 13 (2.1%) | 4 (1.3%) | 4 (5.4%) | |
| Others | | 184 (18.5%) | 121 (19.9%) | 53 (16.8%) | 10 (13.5%) | |
| MELD score | 932 | 8 (7, 10) | 8 (7, 9) | 9 (8, 11) | 11 (9, 13) | <0.001 |
| Child score | 995 | | | | | <0.001 |
| A | | 897 (90.2%) | 582 (96.0%) | 261 (82.9%) | 54 (73.0%) | |
| B/C | | 98 (9.8%) | 24 (4.0%) | 54 (17.1%) | 20 (27.0%) | |
| Varices | 938 | | | | | <0.001* |
| F0 | | 666 (71.0%) | 477 (83.4%) | 159 (53.0%) | 30 (45.5%) | |
| F1 | | 197 (21.0%) | 77 (13.5%) | 98 (32.7%) | 22 (33.3%) | |
| F2/F3 | | 75 (8.0%) | 18 (3.1%) | 43 (14.3%) | 14 (21.2%) | |
| BCLC | 980 | | | | | <0.001* |
| A1 | | 364 (37.1%) | 307 (51.9%) | 56 (17.8%) | 1 (1.4%) | |
| A2 | | 130 (13.3%) | 35 (5.9%) | 75 (23.9%) | 20 (27.0%) | |
| A3 | | 87 (8.9%) | 19 (3.2%) | 53 (16.9%) | 15 (20.3%) | |
| A4 | | 302 (30.8%) | 148 (25.0%) | 117 (37.3%) | 37 (50.0%) | |
| Other (B, C, D) | | 97 (9.9%) | 83 (14.0%) | 13 (4.1%) | 1 (1.4%) | |
| Number of lesions | 996 | | | | | 0.14* |
| 1 | | 720 (72.3%) | 452 (74.5%) | 217 (68.9%) | 51 (68.9%) | |
| 2 | | 193 (19.4%) | 110 (18.1%) | 70 (22.2%) | 13 (17.6%) | |
| 3 | | 83 (8.3%) | 45 (7.4%) | 28 (8.9%) | 10 (13.5%) | |
| Type of surgery | 996 | | | | | <0.001 |
| Resection | | 417 (41.9%) | 288 (47.4%) | 113 (35.9%) | 16 (21.6%) | |
| RFA | | 579 (58.1%) | 319 (52.6%) | 202 (64.1%) | 58 (78.4%) | |
| Surgical approach | 996 | | | | | <0.001 |
| Laparoscopic | | 529 (53.1%) | 279 (46.0%) | 196 (62.2%) | 54 (73.0%) | |
| Laparotomy | | 467 (46.9%) | 328 (54.0%) | 119 (37.8%) | 20 (27.0%) | |
| Year of surgery | 996 | | | | | <0.001* |
| 1996-2003 | | 197 (19.8%) | 105 (17.3%) | 60 (19.0%) | 32 (43.2%) | |
| 2004-2008 | | 218 (21.9%) | 140 (23.1%) | 67 (21.3%) | 11 (14.9%) | |
| 2009-2013 | | 365 (36.6%) | 212 (34.9%) | 131 (41.6%) | 22 (29.7%) | |
| 2014-2018 | | 216 (21.7%) | 150 (24.7%) | 57 (18.1%) | 9 (12.2%) | |

Data are reported as median (IQR), with *P* values from the Kruskal-Wallis test; mean ± SD, with *P* values from one-way analysis of variance; or as n (column %), with *P* values from the chi-squared test, unless stated otherwise. $P < 0.05$ is considered significant.
**P* value from the Kruskal-Wallis test, as the factor is ordinal.
Abbreviation: N/A, not available.

**TABLE 2. PATIENT OUTCOMES BY PLATELET COUNT GROUP**

| Outcome | Overall | Platelet Count Group | | | *P* Value |
|---|---|---|---|---|---|
| | | High (>100 × $10^9$/L) | Intermediate (51-100 × $10^9$/L) | Low (≤50 × $10^9$/L) | |
| Primary outcome | | | | | |
| Major perioperative bleeding | 89/996 (8.9%) | 49/607 (8.1%) | 32/315 (10.2%) | 8/74 (10.8%) | 0.48 |
| Secondary outcomes | | | | | |
| Major bleeding by type of surgery | | | | | |
| Patients undergoing RFA | 33/579 (5.7%)* | 16/319 (5.0%) | 12/202 (5.9%) | 5/58 (8.6%) | 0.54 |
| Patients undergoing LR | 56/417 (13.4%)* | 33/288 (15.9%) | 20/113 (17.7%) | 3/16 (18.8%) | 0.21 |
| 90-Day mortality† | 35/965 (3.6%) | 14/586 (2.4%) | 17/307 (5.5%) | 4/72 (5.6%) | 0.04 |

Data are reported as n/total n (%), with *P* values from the chi-squared test. $P < 0.05$ is considered significant.
*Rate of bleeding events is significantly higher in LR versus RFA ($P < 0.001$).
†Excludes n = 31 patients who were lost to follow-up.

Child B/C, severity of variceal varices, and tumor staging according to the BCLC staging system increased significantly with the severity of thrombocytopenia. A significant difference in the operative approach was also observed, with patients with thrombocytopenia more commonly treated by RFA and, consequently, having a higher rate of laparoscopic procedures.

## MAJOR PERIOPERATIVE BLEEDING EVENTS BY PLATELET COUNT

Across the cohort as a whole, the rate of major perioperative bleeding was 8.9% (89/996). There was no statistically significant difference in the rate of major perioperative bleeding across the three platelet count groups, with rates of 8.1% in the high, 10.2% in the intermediate, and 10.8% in the low platelet count groups, respectively ($P = 0.48$; Table 2). The major perioperative bleeding rate was significantly higher in patients who underwent LR compared to RFA (13.4% vs. 5.7%, $P < 0.001$). However, subgroup analysis by the type of surgery found no significant differences in major bleeding rates by platelet count group within either the LR ($P = 0.21$) or RFA ($P = 0.54$) subgroups.

Given the relatively small number of cases in the low platelet count group, the platelet count was also analyzed as a continuous variable in an attempt to increase statistical power. Analysis of the cohort as a whole found no evidence of a significant association between platelet count and major perioperative bleeding, with an OR of 0.94 per 50 × $10^9$/L (95% CI, 0.79-1.12; $P = 0.52$), as visualized in Fig. 2A and Table 3. Subgroup analysis by the type of surgery found similar trends in patients undergoing RFA and LR (interaction term, $P = 0.33$), with ORs of 0.75 per 50 × $10^9$/L (95% CI, 0.53-1.06; $P = 0.10$) and 0.92 per 50 × $10^9$/L (95% CI, 0.74-1.13; $P = 0.42$), respectively (Fig. 2B; Table 3).

## RISK FACTORS FOR MAJOR PERIOPERATIVE BLEEDING

A multivariable analysis was then performed to identify significant independent predictors of major perioperative bleeding and to quantify any effect of platelet count after adjusting for these (Table 4). This model identified greater age ($P = 0.04$) and AST ($P = 0.001$), lower hemoglobin ($P < 0.001$), and treatment with LR (vs. RFA, $P < 0.001$) to be significant independent predictors of major perioperative bleeding, with significant differences across etiologies ($P = 0.03$) and the year of surgery ($P = 0.04$) also observed. After adjusting for these factors, the association between platelet count and major perioperative bleeding remained nonsignificant, with an OR of 0.89 per 50 × $10^9$/L (95% CI, 0.71-1.11; $P = 0.30$)

## RISK FACTORS FOR 90-DAY MORTALITY

Analysis of mortality excluded 31 patients who were lost to follow-up before 90 days; for the remaining 965 patients, the 90-day mortality rate was 3.6% (35/965). Comparison across the three platelet count groups found a significant difference in 90-day mortality rates ($P = 0.04$; Table 2), increasing from 2.4% in those with high platelets to 5.5% and 5.6% in the intermediate and low platelet groups, respectively.

On multivariable analysis (Table 5), greater patient age, hemoglobin, bilirubin, BCLC staging and MELD

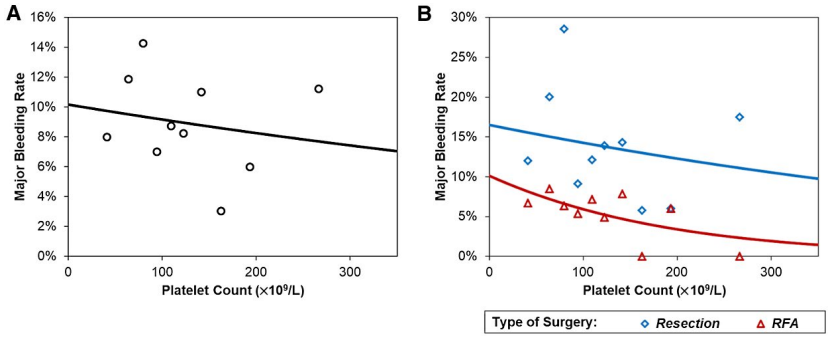


**FIG. 2.** Associations between platelet count and major perioperative bleeding/90-day mortality. Associations with (A) overall major perioperative bleeding and (B) by type of surgery. Trend lines are as per the models described in Table 3. Points represent the observed outcome rates within deciles of the distribution of platelets and are plotted as the mean of the interval.

**TABLE 3. UNIVARIABLE BINARY LOGISTIC REGRESSION OF THE ASSOCIATION BETWEEN PLATELET COUNT AND MAJOR PERIOPERATIVE BLEEDING**

| | Major Perioperative Bleeding | |
|---|---|---|
| | OR per 50 × $10^9$/L (95% CI) | *P* Value |
| Whole cohort | 0.94 (0.79-1.12) | 0.52 |
| By type of surgery | | |
| Patients undergoing RFA | 0.75 (0.53-1.06) | 0.10 |
| Patients undergoing LR | 0.92 (0.74-1.13) | 0.42 |
| | Interaction term, *P* = 0.33 | |

Odds ratios are from univariable binary logistic regression models with the platelet count as a continuous covariate and are reported per 50 × $10^9$/L increase. Separate models were produced for the cohort as a whole and within subgroups defined by the type of surgery. Models were then produced with the platelet count, type of surgery, and an interaction term as covariates. As such, this interaction term represented a comparison between the ORs in the surgical subgroups. $P < 0.05$ is considered significant.

scores, and lower albumin were found to be significant independent predictors of 90-day mortality. In addition, laparotomic surgery and major perioperative bleeding were also significant independent predictors of 90-day mortality. After adjusting for these factors, no significant association between platelet count and 90-day mortality was detected (OR, 0.93 per 50 × $10^9$/L; 95% CI, 0.60-1.45; $P = 0.762$). However, the small number of outcomes included in the multivariable model of 90-day mortality likely resulted in the analysis being underpowered and may have led to a degree of overfitting; hence, these results should be interpreted with caution.

# Discussion

In this retrospective study, we failed to detect a statistically significant association between thrombocytopenia and major perioperative bleeding in a cohort of 996 patients with cirrhosis who underwent RFA or LR for HCC without prophylactic platelet transfusions. In particular, patients with a platelet count <50 × $10^9$/L, for whom platelet transfusions are recommended,[8] had a frequency of major bleeding events not significantly higher than patients with higher platelet counts, with similar trends observed when the subgroups undergoing RFA and LR were assessed separately. Furthermore, when treating the platelet count as a continuous variable, no significant association with major perioperative bleeding was observed either on univariable analysis or after adjusting for the effect of confounding factors on multivariable analysis. To our knowledge, this is the first study to have evaluated the incidence of major perioperative bleeding events in patients with severe thrombocytopenia and cirrhosis undergoing surgery in the absence of prophylactic platelet therapy.

While there is currently limited evidence regarding perioperative bleeding, the association between thrombocytopenia and postprocedural bleeding has previously been evaluated. Napolitano et al.[17] assessed a cohort of 363 patients with cirrhosis who underwent 852 invasive procedures, mostly associated with a low or intermediate bleeding risk, and observed only 10 postprocedural bleeds, none of which were related to the platelet count. Recently, Zanetto et al.[18] showed that a platelet count <50 × $10^9$/L was not associated

**TABLE 4. UNIVARIABLE AND MULTIVARIABLE ANALYSIS OF VARIABLES ASSOCIATED WITH MAJOR PERIOPERATIVE BLEEDING**

| | Univariable Models | | Multivariable Model | |
|---|---|---|---|---|
| | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Platelet count (per 50 × $10^9$/L) | 0.94 (0.79-1.12) | 0.52 | 0.89 (0.71-1.11) | 0.30 |
| Age at surgery (per decade) | 1.48 (1.12-1.96) | 0.006 | 1.39 (1.02-1.90) | 0.04 |
| Sex (female) | 2.53 (1.62-3.95) | <0.001 | - | NS |
| Hemoglobin (per 1 g/dL) | 0.62 (0.55-0.71) | <0.001 | 0.53 (0.45-0.62) | <0.001 |
| PT (>1.5) | 0.68 (0.09-5.24) | 0.71 | - | NS |
| Bilirubin (per 1 mg/dL) | 1.10 (0.83-1.45) | 0.50 | - | NS |
| Albumin (per 1 g/dL) | 0.71 (0.48-1.06) | 0.09 | - | NS |
| Creatinine (mg/dL)* | | 0.08 | | NS |
| <0.70 | - | - | - | - |
| 0.70-0.84 | 1.10 (0.55-2.19) | 0.78 | - | - |
| 0.85-0.99 | 0.57 (0.24-1.38) | 0.21 | - | - |
| 1.00+ | 1.54 (0.78-3.04) | 0.21 | - | - |
| AST (per 10 IU) | 1.04 (1.00-1.07) | 0.05 | 1.08 (1.03-1.13) | 0.001 |
| Cirrhosis etiology | | 0.03 | | 0.03 |
| HCV | - | - | - | - |
| HBV | 0.63 (0.32-1.26) | 0.20 | 1.20 (0.52-2.78) | 0.67 |
| Cryptogenic | 2.03 (0.66-6.21) | 0.22 | 2.64 (0.70-9.93) | 0.15 |
| Others | 0.39 (0.18-0.83) | 0.02 | 0.21 (0.06-0.72) | 0.01 |
| MELD score (per point) | 1.07 (0.98-1.16) | 0.13 | - | NS |
| Child score (B/C) | 1.49 (0.78-2.84) | 0.23 | - | NS |
| Varices | | 0.79 | | NS |
| F0 | - | - | - | - |
| F1 | 1.10 (0.63-1.91) | 0.75 | - | - |
| F2/F3 | 1.30 (0.59-2.84) | 0.51 | - | - |
| BCLC | | 0.11 | | NS |
| A1 | - | - | - | - |
| A2 | 1.57 (0.79-3.11) | 0.20 | - | - |
| A3 | 1.14 (0.48-2.71) | 0.77 | - | - |
| A4 | 1.07 (0.60-1.92) | 0.82 | - | - |
| B-D | 2.38 (1.21-4.69) | 0.01 | - | - |
| Number of lesions | | 0.63 | | NS |
| 1 | - | - | - | - |
| 2 | 0.75 (0.41-1.36) | 0.35 | - | - |
| 3 | 0.88 (0.39-1.99) | 0.77 | - | - |
| Type of surgery | | <0.001 | | <0.001 |
| RFA | - | - | - | - |
| Resection | 2.57 (1.64-4.03) | <0.001 | 5.46 (3.00-9.93) | <0.001 |
| Surgical approach | | <0.001 | | NS |
| Laparoscopic | - | - | - | - |
| Laparotomy | 2.28 (1.44-3.59) | <0.001 | - | - |
| Year of surgery | | 0.45 | | 0.04 |
| 1996-2003 | - | - | - | - |
| 2004-2008 | 0.90 (0.43-1.88) | 0.77 | 0.42 (0.15-1.17) | 0.10 |

**TABLE 4.** *Continued*

| | Univariable Models | | Multivariable Model | |
|---|---|---|---|---|
| | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| 2009-2013 | 1.41 (0.76-2.63) | 0.28 | 1.29 (0.55-3.01) | 0.55 |
| 2014-2018 | 1.31 (0.65-2.61) | 0.45 | 1.30 (0.51-3.31) | 0.58 |

Results for the univariable analysis are from individual binary logistic regression models. Platelet count was then entered into a multivariable model, with a backwards stepwise approach used to select other factors for inclusion. The final model was based on n = 836 (n = 76 outcomes), after excluding cases with missing data for any of the factors considered for inclusion in the model. ORs are reported for the stated number of units increase for continuous variables or for the stated category relative to the reference category for nominal variables. $P < 0.05$ is considered significant.
*Goodness of fit testing indicated poor model fit when creatinine was treated as a continuous variable, hence it was categorized based on the quartiles for analysis.
Abbreviation: NS, not selected by the stepwise procedure for inclusion in the final multivariable model.

with procedure-related bleeding in a prospective cohort of 72 patients with decompensated cirrhosis. There are also several studies assessing postbiopsy bleeding rates. For example, in a retrospective study of 2,740 liver biopsies in patients with chronic liver disease (40% with cirrhosis), Seeff et al.[19] reported a bleeding event rate of 5.3% in patients with a platelet count $<60 \times 10^9$/L, which was greater than in patients with higher platelet counts; presence of any esophageal varices, PT/international normalized ratio ≥1.3, and low serum albumin levels were additionally found to be associated with postbiopsy bleeding on univariable analysis.[19] Similarly, two smaller retrospective studies found significant associations between platelet counts $\leq 70 \times 10^9$/L or $\leq 60 \times 10^9$/L and bleeding risk after liver biopsy.[20,21] On the other hand, Ewe[22] did not report any association between platelet count and the risk of bleeding in 200 patients with hepatic disease undergoing liver biopsy, of whom 29% had liver cirrhosis. As such, evidence in the literature is currently unclear regarding the presence of any association between severe thrombocytopenia and bleeding after liver biopsy.

The lack of association between (severe) thrombocytopenia and major perioperative bleeding in patients with cirrhosis observed in the current study could be explained based on the demonstration that the efficiency of primary hemostasis in liver cirrhosis with severe thrombocytopenia is at least partly counterbalanced by increased concentration and activity of the von Willebrand factor (VWF) and also as a consequence of the presence of low plasma levels of a disintegrin and metalloprotease with thrombospondin type 1 repeats 13 (ADAMTS-13),[23] which cleaves the "supranormal" VWF multimers with high hemostatic activity.[24] We believe that our data support the suggestion that patients with liver cirrhosis who need to undergo invasive procedures do not need to have their platelet count increased above the (arbitrary) level of $50 \times 10^9$/L. This conclusion is reinforced by the research indicating that the two approaches commonly used to increase the platelet count may not necessarily be effective and are potentially associated with adverse effects. The primary treatment for thrombocytopenia is platelet transfusion.[8] However, there is evidence that this may be ineffective in increasing the platelet counts of patients with cirrhosis[17] and could also induce isoimmunization, anaphylactic reactions, and transfusion-related acute lung injury.[25,26] The other common approach to increase platelet counts is the use of TPO receptor agonists (TPO-RAs). Several studies have shown that TPO-RAs are efficacious in increasing the platelet count in patients with chronic liver disease.[4,27-31] However, their use is associated with increased risk of thrombotic events,[32] which may be particularly relevant in patients with liver cirrhosis who are now considered at increased thrombotic risk[33] and prone to developing portal vein thrombosis (PVT), which is associated with unfavorable prognosis.[34] Although there is currently no clear evidence that TPO-RAs are associated with an increased risk of PVT in patients with chronic liver disease undergoing invasive procedures,[4,27-31,35,36] we believe that these drugs should be used with caution until their safety profile in this group of patients can be confirmed.

In our analyses, lower hemoglobin values were found to be a significant independent predictor of

**TABLE 5. UNIVARIABLE AND MULTIVARIABLE ANALYSIS OF VARIABLES ASSOCIATED WITH 90-DAY MORTALITY**

| | Univariable Models | | Multivariable Model | |
|---|---|---|---|---|
| | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Platelet count (per 50 × $10^9$/L) | 0.80 (0.59-1.08) | 0.15 | 0.93 (0.60-1.45) | 0.76 |
| Age at surgery (per decade) | 1.16 (0.77-1.74) | 0.48 | 1.67 (1.01-2.77) | 0.05 |
| Sex (female) | 1.53 (0.75-3.11) | 0.25 | - | NS |
| Hemoglobin (per 1 g/dL) | 0.92 (0.76-1.10) | 0.35 | 1.36 (1.03-1.80) | 0.03 |
| PT (>1.5) | 3.96 (0.86-18.14) | 0.076 | - | NS |
| Bilirubin (per 1 mg/dL) | 1.63 (1.21-2.19) | 0.001 | 2.03 (1.28-3.21) | 0.003 |
| Albumin (per 1 g/dL) | 0.44 (0.24-0.81) | 0.008 | 0.34 (0.14-0.82) | 0.02 |
| Creatinine (per 1 mg/dL) | 1.45 (0.96-2.19) | 0.077 | - | NS |
| AST (per 10 IU) | 1.05 (1.00-1.11) | 0.04 | - | NS |
| Cirrhosis etiology | | 0.43 | | NS |
| HCV | - | - | - | - |
| HBV | 0.91 (0.34-2.42) | 0.85 | - | - |
| Cryptogenic | 2.65 (0.58-12.05) | 0.21 | - | - |
| Others | 0.60 (0.21-1.76) | 0.36 | - | - |
| MELD score (per point) | 1.21 (1.09-1.33) | <0.001 | 1.25 (1.06-1.48) | 0.009 |
| Child score (B/C) | 3.35 (1.52-7.39) | 0.003 | - | NS |
| Varices | | 0.66 | | NS |
| F0 | - | - | - | - |
| F1 | 1.22 (0.53-2.79) | 0.64 | - | - |
| F2/F3 | 1.61 (0.54-4.81) | 0.39 | - | - |
| BCLC | | 0.001 | | 0.01 |
| A1 | - | - | - | - |
| A2 | 2.82 (0.89-8.90) | 0.08 | 2.31 (0.60-8.91) | 0.22 |
| A3 | 2.81 (0.77-10.18) | 0.12 | 1.13 (0.23-5.63) | 0.88 |
| A4 | 1.58 (0.54-4.60) | 0.40 | 0.36 (0.07-1.85) | 0.22 |
| B-D | 7.27 (2.61-20.21) | <0.001 | 4.87 (1.53-15.44) | 0.007 |
| Number of lesions | | 0.62 | | NS |
| 1 | - | - | - | - |
| 2 | 0.69 (0.26-1.83) | 0.46 | - | - |
| 3 | 1.33 (0.45-3.93) | 0.60 | - | - |
| Type of surgery | | 0.004 | | NS |
| RFA | - | - | - | - |
| Resection | 2.84 (1.39-5.77) | 0.004 | - | - |
| Surgical approach | | 0.02 | | 0.009 |
| Laparoscopic | - | - | - | - |
| Laparotomy | 2.30 (1.13-4.67) | 0.02 | 4.20 (1.44-12.27) | 0.009 |
| Major perioperative bleeding | 7.04 (3.41-14.56) | <0.001 | 5.18 (1.96-13.68) | <0.001 |
| Year of surgery | | 0.76 | | NS |
| 1996-2003 | - | - | - | - |
| 2004-2008 | 1.13 (0.44-2.92) | 0.80 | - | - |
| 2009-2013 | 0.73 (0.29-1.86) | 0.51 | - | - |
| 2014-2018 | 0.77 (0.26-2.28) | 0.64 | - | - |

Results for the univariable analysis are from individual binary logistic regression models. Platelet count was then entered into a multivariable model, with a backwards stepwise approach used to select other factors for inclusion. The final model was based on n = 810 (n = 30 outcomes), after excluding cases with missing data for any of the factors considered for inclusion in the model. ORs are reported for the stated number of units increase for continuous variables or for the stated category relative to the reference category for nominal variables. $P < 0.05$ is considered significant.

Abbreviation: NS, not selected by the stepwise procedure for inclusion in the final multivariable model.

major perioperative bleeding. This confirms the results of previous studies that have shown low hematocrit values and anemia to be associated with increased risk of bleeding in patients with cirrhosis,[37,38] likely because anemia is a general marker of frailty and/or due to the role played by red blood cells in hemostasis. On the other hand, there is some evidence that a larger intravascular volume might increase the risk of perioperative bleeding in patients with portal hypertension.[39] It is important to note that none of our patients received a red blood cell transfusion before surgery; hence, there was no iatrogenic effect on the intravascular volume in our cohort of patients.

Regarding the type of HCC surgical treatment, LR was found to be associated with a higher risk of major perioperative bleeding than RFA. This finding is consistent with those reported in similar cohorts[40-42] and is not unexpected considering that LR is a more invasive procedure than RFA. Our analysis found no significant association between PT and major perioperative bleeding events, which is in keeping with what is reported in the literature[43] this confirms the inadequacy of PT to predict bleeding in patients with cirrhosis.

In addition to assessing bleeding events, the current study also analyzed 90-day mortality as a secondary outcome. This found some evidence to suggest that severe thrombocytopenia was associated with increased 90-day mortality. However, this association was not found to be significant on multivariable analysis after adjustment for other confounding factors. This may imply that thrombocytopenia was acting as a surrogate marker of disease severity on univariable analysis; hence, the effect may not have been causal. Alternatively, this may reflect a false-negative error on account of low statistical power of analyses of this outcome due to the relatively small number of deaths in the cohort. In contrast to our finding, other studies have reported thrombocytopenia to be independently associated with adverse outcomes, such as mortality or liver failure, in patients with cirrhosis undergoing surgery,[44-48] although the literature is not conclusive in this regard.[49]

A total of 29.0% of patients in our cohort had clinically significant portal hypertension. Portal hypertension has been reported as a relative contraindication for liver surgery due to an increased risk of short- and long-term mortality. In our cohort, we did not find any significant correlation between the presence of varices and 90-day mortality. It should be noted that no patients in our retrospective cohort underwent measurement of hepatic venous pressure gradient; the presence of varices was instead based on endoscopy reports. Moreover, our overall mortality rate was 3.6%, just above the recommended threshold for the indication of surgical treatment by the most recent European Association for the Study of the Liver guidelines,[50] but it is significantly higher in patients with lower platelet count, which might reflect a worse portal hypertension in this group. It is likely a degree of case-selection bias in selecting for surgical treatment the healthiest patients with portal hypertension; this mitigates its effect on the outcome.

Our study has several limitations. First, it spans our 20 years of experience during which time surgical techniques have changed, and this may have influenced the frequency of bleeding events. However, we adjusted for the year of surgery on multivariable analysis in an attempt to mitigate this effect. Second, the numbers of patients and major perioperative bleeding events in the severe thrombocytopenia group were relatively small. As such, the statistical power of comparisons against this group will have been low, increasing the risk of a false-negative error. To increase the statistical power, the analysis was also repeated treating the platelet count as a continuous covariate, and this approach was used in the multivariable analysis. The analysis of the secondary outcome of 90-day mortality was also affected by this limitation, with the small sample size also increasing the risk of overfitting in the multivariable model of this outcome.

In conclusion, major perioperative bleeding was not found to be significantly associated with the platelet count in patients with cirrhosis undergoing surgical treatment of HCC without therapies to increase platelet count, even when the platelet count was $<50 \times 10^9$/L. With the limit of a retrospective analysis, our data do not support the recommendation of increasing platelet counts (e.g., by platelet transfusion or use of TPO in patients) in an attempt to decrease their perioperative bleeding risk.

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