# Oral Surgical Treatment of Patients With Chronic Liver Disease: Assessments of Bleeding and Its Relationship With Thrombocytopenia and Blood Coagulation Parameters



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# Oral Surgical Treatment of Patients With Chronic Liver Disease: Assessments of Bleeding and Its Relationship With Thrombocytopenia and Blood Coagulation Parameters

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## Purpose

Cirrhotic patients awaiting liver transplantation require eradication of infectious oral foci to prevent septic episodes after transplantation; however, cirrhosis can hinder hemostasis and can result in severe bleeding. The present study assessed the bleeding risk factors connected with the clinical history of these patients and the characteristics of the extractions.

## Materials and Methods

We retrospectively analyzed 1183 extractions in 318 patients, including 47 with severe end-stage liver disease who were outside of our intention-to-treat bracket (ie, platelet count [PLT] >40 × 103/μL and international normalized ratio [INR] <2.5). Follow-up examinations included inspection of the oral cavity on the first, third, and seventh days, with reparatory surgery in the case of severe bleeding. Continuous variables were compared using the Mann-Whitney U and Kruskal-Wallis tests, and categorical variables were compared using Fisher's exact test. Binary logistic regression analysis was also performed.

## Results

Within the intention-to-treat bracket, 1 of the 271 patients (0.4%) required surgical repair. The bleeding rate for an INR of 2.5 or more was significantly greater than that for a PLT of 40 × 103/μL or less (4 of 10 [40%] versus 2 of 34 [6%]; P = .02]. All 3 patients with both an INR of 2.5 or more and a PLT of 40 × 103/μL or less exhibited severe bleeding. No significant association between the occurrence of bleeding with either liver disease etiology or the number of molars extracted was found. No patient required hospitalization.

Conclusions

Patients with a PLT greater than 40 × 103/μL and an INR of less than 2.5 can be considered relatively low-risk patients. However, an INR of 2.5 or more and, to a minor degree, a PLT of 40 × 103/μL or less represent significant risk factors.

Liver transplantation is the reference standard therapy for patients with chronic decompensated liver disease.1 Infection and rejection represent the most common postoperative transplant complications. Consequently, dental examination is an integral part of the pretransplant evaluations, and the eradication of all oral infectious foci is essential to the prevention of septic episodes of an oral origin in immunosuppressed transplantation patients.2; 3; 4; 5; 6 ;  7 Frequently, the urgency of liver transplantation requires fast and radical treatment, such as the extraction of all compromised elements. However, these patients are exposed to significant postextraction complications because of malnutrition, a compromised immune defense and bleeding diathesis. These conditions, which characterize chronic liver disease, affect the physiologic processes of healing of the extracted socket, thereby exposing the wound to a greater risk of complications.8 Furthermore, hyposyntesis of coagulation factors and thrombocytopenia can compromise the hemostatic process.

The circulation of coagulation factors in the blood is significantly reduced with an increasing severity of liver disease. More than 60% of patients with cirrhosis have reduced levels of factor VII, which results in increased prothrombin times and international normalized ratios (INRs). The need to assess the risk of bleeding in the presence of a high INR has been investigated in several studies of patients undergoing oral anticoagulant therapy.9; 10; 11 ;  12 However, the outcomes of these studies cannot be easily applied to patients with liver disorders for whom an altered hemostasis can derive from chronic anemia, reduced liver production of blood clotting factors, depletion of vitamin K by malnutrition, decreased intestinal absorption or impaired hepatic storage, increased fibrinolytic activity, and/or alcohol-induced bone marrow suppression.13; 14; 15; 16 ;  17

Thrombocytopenia will be observed in 15 to 70% of these patients.18 Its pathogenesis is multifactorial, and its major cause is splenomegaly resulting from portal hypertension, which can lead to an increased sequestration of platelets in the spleen.19

For all these reasons, the hemostasis scenario in these patients is extremely complex and difficult to manage. Furthermore, this issue has become more urgent, because in the past 15 years, the number of patients waiting for liver transplantation and therefore requiring safe teeth extractions has continued to increase. From 2005 to 2014, nearly 1,400 liver transplants were performed at our institution.

In the published data, a general consensus has not yet been reached regarding the pathologic and surgical risks involved in tooth extractions for these particular patients. Few studies have involved such patients, and most included small patient cohorts. We therefore decided to exploit the large numbers of patients available at our institution to perform a retrospective analysis of 1,183 dental extractions on 318 patients who were candidates for liver transplantation. The main topics we investigated were 1) the incidence of severe bleeding requiring reparatory surgery; and 2) the risk factors for bleeding, including both those associated with pre-extraction anamnesis and those more strictly related to the characteristics of the extractions. The present study aimed to provide a broad-based contribution to the search for the most appropriate screening tests and the safest procedures.

## Materials and Methods

### Study Population

The study population was derived from 1,135 patients referred to the Oral Surgery Section by the Liver Transplant Center from June 1, 2013 to June 1, 2015, as a part of the procedure track for candidates to receive a liver transplant. All patients underwent a preliminary visit to assess the following parameters of their oral cavity: hygiene, missing elements, and the presence of caries, periodontal disease, root residue, and osteolysis. Of the 1,135 patients, 318 (28%) required 1 or more tooth extractions because of root or crown fractures, unrestorable caries, residual roots, and/or periodontal disease.

The study had no exclusion criteria for age, gender, or liver pathology. As a first-line precaution against bleeding risks, the intention-to-treat procedure of our institution requires an INR less than 2.5 and a platelet count (PTL) greater than 40 × 103/μL. In 1983, Rose and Kay20 were the first to recommend the necessity of platelet administration for patients with a PTL less than 50 × 103/μL. We reduced this limit to 40 × 103/μL because of more recent data and the need for the rational use of blood transfusions.21 ; 22

Patients with a PTL of 40 × 103/μL or less were given a preoperative platelet transfusion, and patients with an INR of 2.5 or more received a preoperative fresh frozen plasma transfusion. Both values were verified to meet the required thresholds before performing a tooth extraction. However, the requirements for 1 or both thresholds were overruled when an imminent transplantation required immediate intervention. All extractions considered in the present study were performed by the same surgeon (N.C.) with extensive clinical experience in the treatment of these patients.

All patients were informed about the possible use of their data for clinical studies and signed an informed consent form. The patient data were anonymized before analysis.

The present study was a retrospective analysis of surgeries performed in accordance with the protocols of our institution, without any study-related clinical interventions. The analysis was performed in accordance with the local institutional review board standards and conformed to the Declaration of Helsinki of 1975 and subsequent modifications.

### Surgical Protocol

After local anesthesia (mepivacaine 3% without adrenaline), the teeth were extracted in a nontraumatic manner, with rotation and traction movements using dental forceps and an elevator. No procedure required elevation of a mucoperiosteal flap, an osteotomy, or an odontotomy.

The following postextraction protocol was applied to all patients. The alveolar sockets were sutured with 4-0 silk thread followed by local hemostatic measures, such as application of fibrin sponges and tranexamic acid in a rinse form. Analgesic therapy (paracetamol 1,000 mg, 1 tablet twice daily for 2 days) was prescribed. Also, all the patients received postoperative instructions for the management of bleeding. In particular, they were strongly encouraged to telephone their surgeon if the situation could not be resolved by applying local pressure with gauze for 20 minutes.

Follow-up examinations included an objective inspection of the oral cavity on the first, third, and seventh days after extraction. The progression of healing was also evaluated. In the case of severe bleeding that was not manageable, the surgeon performed surgical repair, removing the necrotic coat and application of new sutures. The sutures were removed after 7 days.

## Statistical Analysis

Continuous variables (age, PLT, INR, and white blood cell and red blood cell counts) did not meet normality conditions according to the Shapiro-Wilks W test and Agostino tests; thus, they are reported as the median and 25th to 75th percentile brackets. Statistically significant differences were investigated using nonparametric tests for k independent distributions: the Mann-Whitney U test for $k = 2$ and the Kruskal-Wallis test for $k > 2$.

Binary and categorical variables, reported as counts and percentages, were arranged in contingency tables and analyzed using the $\chi 2$ test (with Yates' correction for $2 \times 2$) or, when appropriate, Fisher's exact test. Binary logistic regression analysis was used to explore the relationship between the occurrence of severe bleeding and the values of the relevant variables.

The threshold for statistical significance was set at $P < .05$. Open source software (www.openepi.com and www.vassarstats.net) was used, along with StatPlus MacPro (AnalystSoft Inc, Walnut, CA).

## Results

Of the 318 patients in our study, 271 (85%) met the intention-to-treat conditions. The remaining 47 patients (15%) required urgent surgery despite the presence of 1 or 2 presumed risk factors (PRFs) because of an imminent transplant. Of the 47 patients, 34 had a PTL of 40 × 103/μL or less, 10 had an INR of 2.5 or more, and 3 had both a PTL of 40 × 103/μL or less and an INR of 2.5 or more.

In our analysis, the liver diseases were grouped as follows. Group 1 included postalcoholic cirrhosis (ALCI). Group 2 included viral hepatitis, such as posthepatitic C cirrhosis, posthepatitic B cirrhosis, and posthepatitic D cirrhosis. Finally, group 3 consisted of other liver diseases, including primary biliary cirrhosis, autoimmune cirrhosis, sclerosing cholangitis, cryptogenic cirrhosis, cirrhosis of unknown cause, Budd-Chiari syndrome, metabolic disease, polycystic liver, epithelioid hemangioendothelioma, and repeat liver transplantation.

Generally, the ALCI and viral hepatitis groups exhibited similar features, which were often significantly different from those of the third group. Men constituted 75% of the ALCI cases and 78% of the viral hepatitis cases compared with 57% of the third group ($P = .009$). The patients in the ALCI group and hepatitis virus group had a mean age of 55 years (range 48 to 60) compared with 52 years (range 43 to 59) for the patients in the third group ($P = .03$). The presence of varices was 71% for the ALCI group, 62% for the viral hepatitis group, and 20% for the third group ($P < .0001$). The PLT was 64 × 103/μL (range 50 to 95) for the ALCI group and 67 × 103/μL (range 51 to 96) for the viral hepatitis group, both significantly lower than the PLT of 92 × 103/μL (range 58 to 175) for group 3 ($P = .0006$). The INR values were comparable ($P = .33$), with a mean of 1.6 (range 1.3 to 2.0) for group 1 (ALCI), 1.5 (range 1.3 to 1.8) for group 2 (viral hepatitis), and 1.4 (range 1.3 to 1.9) for group 3 (other cases).

The baseline values of the intention-to-treat group and of the 2 urgent surgery groups (characterized by a PRF of 1 and PRF of 2) are listed in Table 1. Significant differences among the 3 groups were found in the following important variables: the presence of ALCI pathologic features ($P = .04$), PLT ($P < .0001$), and INR ($P < .0001$).

The 318 patients underwent a total of 1,183 extractions (Table 2), with no significant differences among the 3 groups. Overall, 542 extractions involved molars (46%). Of these 254 were single extractions (47%) and 288 were multiple extractions (53%).

During the 7-day follow-up observation period of the 318 patients (both intention-to-treat and urgent surgery), 12 severe bleeding episodes occurred that required surgical repair in 10 patients. Binary logistic regression analysis showed that bleeding was significantly associated with the INR ($P = .0002$) and, to a minor degree, with the PLT ($P = .04$) but not with the etiology of the liver disease ($P = .96$) or the number of molars extracted ($P = .26$).

Our analysis then focused on the different groups and subgroups. The intention-to-treat-group included only 1 patient who required reintervention. The patient was a 58-year-old man with ALCI who had very poor dental hygiene and widespread periodontitis, which required the extraction of 8 teeth (3 molars). The bleeding rate (BR) for this group was 0.4%.

All 3 patients in the 2-PRF group required surgical repair (BR of 100%). The patient with 3 molar extractions required 2 reinterventions. The patient with a single molar extraction and the patient with nonmolar multiple extractions required 1 reintervention each.

In the 1-PRF group (44 patients), 6 patients underwent 7 reinterventions (BR of 13.6%). The comparison of the 6 bleeding patients with the 38 nonbleeding patients indicated that the INR was the discriminant variable, with a mean value of 2.5 (range 2.4 to 2.6) for the bleeding patients and 1.8 (range 1.6 to 2.0) for the nonbleeding patients (P = .002). The PLT was 42 × 103/μL (range 34 to 53) for the bleeding patients and 38 × 103/μL (range 36 to 39) for the nonbleeding patients, without a statistically significant difference (P = .49). The patient who required 2 surgical repairs (on the third and seventh day) had an INR of 2.5 or more. The overall BR for extractions within this group was 7% (12 of 172): 9.9% (8 of 81) for molars and 4.5% (4 of 89) for nonmolars (P = .29).

To further investigate this issue, we considered separately the case of a PTL of 40 × 103/μL or less and an INR of 2.5 or more. The major features of the 2 subgroups are listed in Table 3. The sample with an INR of 2.5 or more experienced significantly greater BRs, both per patient (40 vs 6%; P = .02) and per extraction (16 vs 4%; P = .02). Furthermore, the 2 patients in the group with a PTL of 40 × 103/μL or less who required reintervention had the greatest INRs in the cohort (2.2 and 2.3). In the group with a PTL of 40 × 103/μL or less, the BR for molars was very similar to the BR for nonmolars (5 vs 3%). However, in the group with an INR of 2.5 or more, the BR was 28% for molars and 8% for nonmolars. Although these values were not significantly different (P = .17), the small number of bleeding events kept the test power to less than 40%. The severe BRs for each of the 4 groups (intention-to-treat, INR ≥2.5, PTL ≤40 × 103/μL, and both INR ≥2.5 and PTL ≤40× 103/μL) are summarized in Figure 1. All surgical repairs were performed in the ambulatory setting. All patients stopped bleeding and could be dismissed within a few hours; no patient required hospitalization.

Discussion

Our data analysis evidenced a very satisfactory outcome for extractions in patients awaiting liver transplantation. The overall severe BR was 3.1% (10 of 318) per patient and 1% (12 of 1183) per extraction. These rates included patients with an INR as high as 2.7 and a PLT as low as 25 × 103/μL.

Our findings support the validity of our intention-to-treat procedure, which requires a PLT greater than 40 × 103/μL and an INR less than 2.5, before proceeding with tooth extraction. Patients who underwent extraction according to our guidelines had a 0.4% BR, comparable to what we have observed in healthy patients. The only patient who required reintervention because of severe bleeding had very advanced periodontitis.23 ;  24

Our low BR can be considered satisfactory, especially because the few available studies have reported safety brackets similar to that of our intention-to-treat procedure. Hong et al25 considered extractions performed on 90 patients with an INR of less than 2.0 and PLT greater than 45 × 103/μL. They reported excessive perioperative bleeding in 1 patient with an INR of 1.6, which caused discontinuation of the procedure, and no postoperative bleeding.

Ward and Weideman,26 in their retrospective study of 35 procedures in patients awaiting transplantation, determined the PLT and INR values to be significant “surgeon-defined risks.” The 10 “high-risk” patients with a PLT of less than 35 × 103/μL and/or an INR greater than 2 were treated with a transfusion of platelets and/or fresh-frozen plasma. Also, their extractions were delayed until the PLT was greater than 80 × 103/μL and the INR was less than 2. Prolonged postoperative bleeding was observed in 7 of 35 procedures (20%). In the high-risk group, 5 of 10 patients (50%) experienced bleeding that required hospitalization for an average of 4 days. A high number of extractions and the quadrants of alveoplasty were found to represent additional risk factors.

Perdigao et al,22 in a prospective study of 23 patients (including 35 dental surgical procedures), reported postoperative bleeding in 1 patient with an INR of 2.5 and PLT of 50 × 103/µL that occurred 3 days after extraction of a maxillary first molar. The bleeding was satisfactorily managed using local hemostatic measures, which allowed them to conclude in favor of a low risk of bleeding (4% per patient and 3% per procedure) in patients with an INR of 2.5 or less and PLT of 30 × 103/µL or more.

The outstanding issue remains the best treatment for patients who do not meet the generally accepted standards of an INR of less than 2 to 2.5 and PLT greater than 30 to 40 × 103/µL but must nevertheless undergo extractions as a necessary step to prevent septic episodes of an oral origin after liver transplantation. Our findings have established that a PLT of 40 × 103/µL or less and/or an INR greater than 2.5 should not be considered "presumed" risk factors. Instead, both are powerful risk factors, with each significantly increasing the BR. Our results identified an INR of 2.5 or greater as the major risk factor, with a 40% BR compared with a 6% BR for a PLT of 40 × 103/µL or less. When both risk factors were present, the BR reached 100%.

Finally, we obtained an indication that molar extraction might be an additional risk factor when associated with an INR of 2.5 or more. However, the difference between the observed BR of 28% for molars and 8% for nonmolars did not reach statistical significance.

In conclusion, patients waiting for liver transplantation with a PTL greater than 40 × 103/µL and an INR of less than 2.5 can be considered to have a relatively low risk of bleeding. If the clinician follows a proper surgical protocol, these patients should have the same risk of postextraction bleeding as any healthy patient. When a patient cannot be stabilized at these values, bleeding must be expected and counterbalanced with careful planning of both the surgical treatment and the follow-up procedures. Also, patients should be informed of any abnormal conditions underlying the surgery to allay their fears regarding the occurrence of postoperative bleeding and to emphasize the importance of the patients following the postoperative instructions.

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Table

Table 1.
Patient Baseline Characteristics

| Characteristic | Intention-to-Treat | Urgent Pre-LT Surgery | | *P* Value |
|---|---|---|---|---|
| | | 1 Presumed RF | 2 Presumed RFs | |
| Patients (n) | 271 | 44 | 3 | |
| Age (yr) | 55 (48-61) | 50 (44-60) | 53 (52-54) | .24 |
| Male gender | 203 (74.9) | 31 (69.6) | 2 (66.7) | .73 |
| PLT (× $10^3$/μL) | 76 (55-110) | 38 (36-40) | 34 (34-35) | < .0001* |
| INR | 1.5 (1.3-1.8) | 1.9 (1.6-2.3) | 2.7 (2.7-2.8) | < .0001* |
| WBC count (× $10^3$/μL) | 5.1 (3.8-6.8) | 4.9 (3.3-7.0) | 6.5 (5.9-7.2) | .39 |
| RBC count (× $10^3$/μL) | 3.8 (3.3-4.5) | 3.8 (3.2-4.4) | 2.8 (2.7-2.9) | .72 |
| ALCI | 61 (22.3) | 16 (34.8) | 2 (66.7) | .04* |
| Viral hepatitis | 163 (60.6) | 25 (54.3) | 0 (0) | .21 |
| Other | 46 (17.1) | 3 (6.5) | 1 (33.3) | .16 |
| Hypertension | 155 (57.6) | 27 (58.7) | 0 (0) | .12 |
| Diabetes | 46 (17.1) | 6 (13) | 0 (0) | .64 |
| Varices | 150 (55.8) | 31 (67.4) | 2 (66.7) | .16 |
| Ascites | 223 (82.9) | 41 (89.1) | 1 (33.3) | .01* |
| Encephalopathy | 26 (9.7) | 8 (17.4) | 1 (33.3) | .11 |
| Liver cancer | 25 (9.3) | 4 (8.7) | 0 (0) | .86 |
| Osteoporosis | 13 (4.8) | 4 (8.7) | 1 (33.3) | .06 |
| Gastric disease | 210 (78.6) | 30 (65.2) | 3 (100) | .25 |
| Poor dental hygiene | 188 (69.9) | 28 (60.9) | 1 (33.3) | .29 |
| Periodontal pathology | 115 (43.1) | 16 (34.8) | 0 (0) | .26 |

Data presented as n (%) or mean (range).

Abbreviations: LT, liver transplantation; RF, risk factor.

*
Statistically significant.

Table 2.
Extractions

| Extraction Type | Intention-to-Treat | Urgent Pre-LT Surgery | | *P* Value |
|---|---|---|---|---|
| | | 1 Presumed RF | 2 Presumed RFs | |
| Single | 299 | 55 | 4 | .27 |
| Molars | 208 (69.8) | 42 (76.4) | 4 (100) | |
| Nonmolars | 91 (30.4) | 13 (23.6) | 9 (0) | |
| Multiple | 702 | 117 | 7 | .87 |
| Molars | 247 (35.2) | 39 (33.3) | 2 (28.6) | |
| Nonmolars | 455 (64.8) | 78 (66.6) | 5 (71.4) | |
| Total | 1,000 | 170 | 11 | .78 |

| Extraction Type | Intention-to-Treat | Urgent Pre-LT Surgery | | *P* Value |
|---|---|---|---|---|
| | | 1 Presumed RF | 2 Presumed RFs | |
| Molars | 455 (45.5) | 81 (47.6) | 6 (54.5) | |
| Nonmolars | 545 (54.5) | 89 (52.3) | 5 (45.4) | |

Data presented as n (%).

Abbreviations: LT, liver transplantation; RF, risk factor.

Table 3.
Severe Bleeding Requiring Surgical Repair in Patients With 1 Presumed Risk Factor

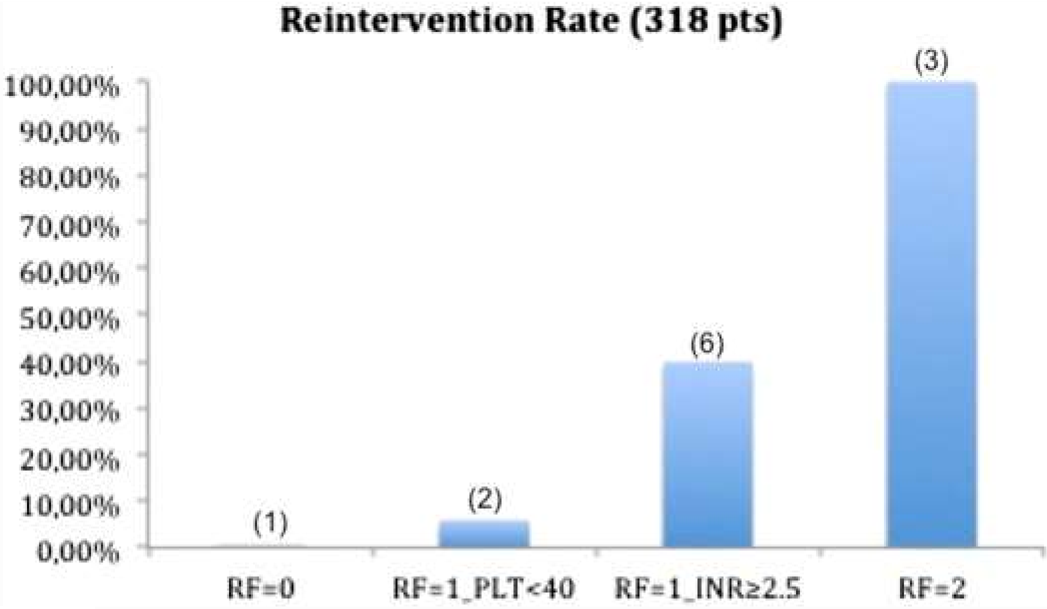
| Variable | INR ≥2.5 | PLT ≤40 × $10^3$/μL | *P* Value |
|---|---|---|---|
| Patients | 10 | 34 | |
| Surgical repair | 4/10 (40) | 2/34 (5.9) | .02* |
| PLT (× $10^3$/μL) | 67 (51-78) | 38 (35-39) | NA |
| INR | 2.5 (2.5-2.6) | 1.8 (1.2-2.0) | NA |
| ALCI | 5 (50) | 11 (32.3) | .52 |
| Viral hepatitis | 4 (40) | 21 (61.8) | .39 |
| Other | 1 (10) | 2 (5.9) | .89 |
| Diabetes | 1 (10) | 5 (14.7) | .40 |
| Poor hygiene | 8/10 (80) | 20/34 (58.8) | .92 |
| Periodontal pathology | 3/10 (30) | 13/34 (39.2) | .92 |
| Extractions (n) | 44 | 126 | |
| Surgical repair | 7/44 (15.9) | 5/126 (4) | .02* |
| Molars | 5/18 (27.8) | 3/63 (4.8) | .01* |
| Nonmolars | 2/26 (7.7) | 2/63 (3.2) | .71 |
| *P* value | .17 | > .9999 | |

Data presented as n (%) or mean (range).

Abbreviations: ALCI, postalcoholic cirrhosis; INR, international normalized ratio; NA, statistical comparison not applicable; PLT, platelet count.

*
Statistically significant.

Figure 1




Reintervention rates for the 4 groups of patients (pts) with different risk factors (RFs): RF 0, patients within the intention-to-treat bracket; RF 1, platelet count (PTL) 40 × $10^3$/μL or less or international normalized ratio (INR) of 2.5 or more; and RF 2, both INR of 2.5 or more and PTL of 40 × $10^3$/μL or less.