Title

Assessment of Bleeding in Chronic Liver Disease and Coagulopathy using the IMPROVE Bleeding Criteria

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Abstract

Background: In this study, the authors utilized the IMPROVE bleeding definition to explore the safety profile of pharmacologic VTE prophylaxis in patients with CLD and concurrent coagulopathy (INR≥ 1.5).

Methods: A retrospective study was conducted on 193 adult patient admissions with a diagnosis of CLD and INR ≥1.5 not due to therapeutic anticoagulation. Patients were stratified based on their receipt of pharmacological thromboprophylaxis or not during hospitalization. The rates of overall bleeding defined as the composite of major bleeding and clinically relevant non-major bleeding; major bleeding and; clinically relevant non-major bleeding, within 14 days of admission were evaluated. Secondary endpoints included the rates of thrombosis and mortality.

Results: The composite of overall bleeding occurred in 17.6 % of the admissions. More patients in the group not receiving pharmacological thromboprophylaxis had overall bleeding (18.5% versus 10%), major bleeding (13.3% versus 10%), and clinically relevant non-major bleeding (14.5% versus 5%), with overlapping 95%CI. When stratified per pharmacological thromboprophylaxis status, IMPROVE BRS ≥ 7 was associated with higher rates of overall bleeding, major bleeding, and clinically relevant non-major bleeding as compared to IMPROVE BRS < 7, whether patients received or did not receive pharmacological thromboprophylaxis. The overall incidence of in-hospital mortality among our study population was 15.5%. Receiving pharmacological thromboprophylaxis was markedly associated with higher in-hospital mortality (OR 16.58, 95%CI 4.47 – 61.45).

Conclusion: This study shows that the IMPROVE BRS calculated on admission may serve as a guide for omission of thromboprophylaxis in advanced chronic liver disease.

Key Words: Liver Diseases; Hemorrhage; Anticoagulants; Venous Thrombosis

Short Title: Bleeding Risk in Chronic Liver Disease

Introduction

It is questionable if elevated INR is protective from thrombosis in patients with chronic liver disease (CLD). Initiating thromboprophylaxis in CLD is a complex conundrum of clotting versus bleeding that leads to hesitation in the initiation of venous thromboembolism (VTE) prophylaxis [1]. The risk of VTE in CLD patients has been documented in the literature showing that elevated INR is not protective [2,3]. Risk factors associated with bleeding in patients with CLD are low platelet count, prolonged INR, presence of varices and history of bleeding.

Recent literature evaluating the risk of bleeding in patients with CLD receiving pharmacological thromboprophylaxis identified the following risk factors as independent co-variates associated with bleeding: maximum INR, pharmacological thromboprophylaxis and platelet count [4]. Questionable risk factors associated with an increased risk of bleeding were longer hospital duration, older patients and concomitant administration of antithrombotics [4]. The former study reported on the risk of bleeding in patients with CLD and elevated INR not due to anticoagulation, who are receiving pharmacological thromboprophylaxis [4]. However, the definition of bleeding in previous studies was based on bleeding outcome definitions in cardiology patients, such as the TIMI Bleeding criteria. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) studied medical patients receiving thromboprophylaxis used the bleeding definition of major and clinically relevant non-major

bleeding [5-7]. Recent data has shown that the IMPROVE Bleeding risk score (BRS) calculated at admission predicts major bleeding and clinically relevant bleeding in medical inpatients and may help assess relative risks of bleeding and VTE before the initiation of pharmacological thromboprophylaxis [5,8].

The aim of our study is to assess the safety profile of pharmacologic VTE prophylaxis in terms of bleeding, using the IMPROVE bleeding definition, in patients with CLD and concurrent coagulopathy (INR≥ 1.5). This study adds to previously published literature by reporting on the association of the BRS on admission with bleeding outcomes within 14 days in patients with CLD and INR≥ 1.5 whether or not receiving pharmacological thromboprophylaxis, assessing potential covariates associated with bleeding including antiplatelet therapy on admission, concomitant antiplatelet therapy during hospitalization, minimum platelet count, and maximum INR. Inpatient thrombosis and mortality were also assessed.

Methods

We conducted a retrospective chart review from two university medical centers in Beirut, Lebanon, including the Lebanese American University Medical Center-Rizk Hospital (LAUMC-RH) and Rafik Hariri University Hospital (RHUH), the largest governmental referral hospital in Beirut. Eligible patients were identified by screening patients' medical records with an ICD9 code of liver cirrhosis between the years 2000-2016. Once the patients were identified, all inpatient admissions were screened. Included patients were greater than 18 years of age, diagnosed as having CLD and having an INR of 1.5 or greater during hospitalization not secondary to systemic anticoagulation. Exclusion criteria were defined as thrombosis or bleeding on admission, systemic anticoagulation treatment, indication for therapeutic anticoagulation upon hospital admission and an INR elevated on admission due to anticoagulation. A study

investigator identified patients who met the inclusion criteria and stratified them into those who received or did not receive pharmacological thromboprophylaxis.

Patients' medical records were screened for demographic data, laboratory data, comorbid diseases, variables associated with bleeding and thrombosis on admission, and a diagnosis of liver disease. Antiplatelet use on admission, concomitant antithrombotic therapy including antiplatelet medications and pharmacologic (including unfractionated heparin, enoxaparin, and tinzaparin) or mechanical thromboprophylaxis, time to initiate thromboprophylaxis, minimum platelet count, and maximum INR. For every patient, a Model for End-stage Liver Disease (MELD) sodium score, Child-Pugh class, IMPROVE bleeding risk score (IMPROVE BRS) and PADUA score were calculated [9-11]. Bleeding, thrombosis, mortality and reason for mortality were collected based on the description in the medical charts. The MELD sodium score was calculated using admission INR, admission serum bilirubin, and admission serum creatinine and sodium [1,2].

Patients risk for bleeding on admission was calculated according to the IMPROVE BRS[3]. The IMPROVE BRS was calculated according to the following criteria: one point attributed to moderate renal failure (GFR 30-59 mL/min/m2) or male gender; age between 40 to 84 years corresponding to 1.5 points, two points for current cancer, rheumatic disease, or central venous catheter; severe renal failure (GFR 30 mL/min/m2), ICU/CCU, or hepatic failure (INR. 1.5) attributing to 2.5 points; age >84 years corresponding to 3.5 points; platelet count <50,000 cells/L, bleeding within 3 months prior to admission, 4 points and 4.5 points are assigned to active gastroduodenal ulcer. BRS ≥ 7 points is associated with a higher cumulative incidence of major bleeding within 14 days [5].

Patients risk for developing VTE was calculated according to the PADUA risk score [4]. The score was calculated by attributing, three points to patients with active cancer, previous VTE, reduced mobility, already known thrombophilic condition; two points to recent trauma and/or surgery, and one point to elderly age 70 years, heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity (BMI 30 kg/m2), and ongoing hormonal treatment. Patients were classified as having a high (Padua Prediction Score ≥4) or low (Padua Prediction Score <4) risk of VTE [4].

The co-primary endpoints were overall bleeding defined as the composite of major bleeding and clinically relevant non-major bleeding, major bleeding and clinically relevant non-major bleeding in patients who received or did not receive thromboprophylaxis, within 14 days of admission, according to the IMPROVE bleeding criteria. The bleeding definition was classified as major bleeding contributing to death, hemoglobin drop >2 g/dL, transfusion >2 units of packed red blood cells (PRBCs), bleeding in a critical organ or space including intracranial, retroperitoneal, intraocular, adrenal, spinal, pericardial. Clinically relevant non-major bleeding included overt non-major gastrointestinal bleeding (GI), gross hematuria >24h, epistaxis requiring intervention, lasting >5 min, extensive hematoma >5cm, intra-articular, menorrhagia/metrorrhagia or other bleeding significant enough to be noted in chart [3,5].

Secondary endpoints included the rates of thrombosis or mortality throughout hospital stay. Thrombotic events included both arterial and venous thrombi.

The institutional review board (IRB) of the Lebanese American University (LAU) and RHUH approved this study (IRB#LAU.SOP.NC1.14/Oct/16) and the study was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Given the retrospective study design, no informed consent prior to patient inclusion

in the study was required.

Statistical Methods

The data analysis was based on the compilation of data. Data was entered and analyzed using the SPSS IBM software, version 24. Descriptive statistics were used to report all participants' responses. Continuous variables were described using mean and standard deviation. Categorical variables were described using frequencies. The associations between categorical variables were evaluated using Pearson $\chi 2$ test or Fisher's exact test where the expected cell counts <5. Potential confounder variables that were assessed in the bivariate analysis include age, pharmacological prophylaxis given during hospitalization, IMPROVE BRS score ≥7 or <7, antiplatelet use on admission, concomitant antiplatelet use during hospitalization, minimum platelet count, mean platelet count, minimum platelet count during hospitalization, platelet count < 50,000 x 10^6 /L; mean INR, maximum INR during hospitalization, PADUA score, MELD score, number of anticoagulant doses given, cancer, and hospital length of stay (days). Binary logistic regressions were performed to identify factors that affect dichotomous dependent variables, using Enter method. No formal power calculation was conducted.

Results

A total number of 193 admissions (128 unique patients) were included in the final analysis. Patients' baseline characteristics according to pharmacological thromboprophylaxis status are detailed in **table 1**. Compared to patients not receiving pharmacological thromboprophylaxis, those receiving thromboprophylaxis were older (mean age 64.5 years versus 57.5 years), had higher use of antiplatelet agents on admission (25% vs. 4.6%), and higher PADUA predictive

scores (4.6 +/- 1.5 vs. 3.3 +/- 2.2). Most patients in the study were Child Pugh class C. [Table 1 near here]

During the 20 admissions in which pharmacological thromboprophylaxis was administered, low molecular weight heparin (LMWH) was administered in 17 (85%), while unfractionated heparin (UFH) was administered in 3 (15%). UFH was administered at a dose of 5000 units subcutaneously every 12 h, and LMWH consisted of enoxaparin at doses of 20mg subcutaneously every 24 hours (4 admissions), 40mg subcutaneously every 24 hours (11 admissions), and tinzaparin 3500 units subcutaneously every 24 hours (2 admissions). The mean hospital length of stay (LOS) was 14.1 days for the pharmacological thromboprophylaxis group and 8.8 days for the group not receiving thromboprophylaxis. The mean number of anticoagulation doses received in patients on pharmacological thromboprophylaxis was 5.2 +/- 4.1 doses. Pharmacological thromboprophylaxis was initiated within 24 hours in 50% of the cases (10 admissions out of 20), within 48 hours of admission in 10% of the cases (2 admissions out of 20), and within more than 48 hours in 35% of the cases (7 admissions out of 20).

The composite of overall bleeding occurred in 17.6 % of the admissions (34/193 admissions), with 13% (24/193) incidence of major bleeding, and 13.5% (26/193) incidence of a clinically relevant non-major bleeding. As shown in **table 2**, more patients in the group not receiving pharmacological thromboprophylaxis had overall bleeding (18.5% versus 10%), major bleeding (13.3% versus 10%), and clinically relevant non-major bleeding (14.5% versus 5%), with overlapping 95%CI.

The overall incidence of in-hospital mortality among our study population was 15.5% (30 patients, 29 of whom were Child Pugh class C). When stratified per pharmacological thromboprophylaxis status, mortality rates were 45% of patients receiving pharmacological

prophylaxis (95%CI: 21% - 69%), versus 12.1% of patients not receiving thromboprophylaxis (95%CI: 7% - 17%). In the bivariate analysis, health care coverage was not associated with mortality. The incidence of in-hospital thrombotic events was 2.1% (4 events) occurring within 1.67 +/-0.58 days. No patients who experienced thrombotic events were receiving thromboprophylaxis.

In the bivariate analysis, IMPROVE BRS ≥ 7 was significantly associated with higher rates of overall bleeding (23.6% versus 12.5%), higher rates of major bleeding (19.1% versus 7.7%), and higher rates of clinically relevant non-major bleeding (19.1% versus 8.7%) as compared to IMPROVE BRS < 7. Furthermore, when stratified per pharmacological thromboprophylaxis status, IMPROVE BRS ≥ 7 was associated with higher rates of overall bleeding, major bleeding, and clinically relevant non-major bleeding as compared to IMPROVE BRS < 7, whether patients received or did not receive pharmacological thromboprophylaxis. In patients with low BRS, the rates of bleeding were almost similar in those who received or did not receive pharmacological prophylaxis **(table 3)**.

Table 4 details the results of the multivariable analysis performed on the outcomes of overall bleeding, major bleeding, clinically relevant non-major bleeding, and in-hospital mortality.

[Tables 3 and 4 near here]

In the multivariable analysis, an IMPROVE BRS ≥7 showed higher rates of overall bleeding (OR 1.81, 95% CI 0.82 – 3.98), major bleeding (OR 2.37, 95% CI 0.94 - 5.97), and clinically relevant non-major bleeding (OR 2.08; 95% CI 0.85 – 5.08)

In the multivariable analysis performed on in-hospital mortality, receiving pharmacological thromboprophylaxis was markedly associated with higher in-hospital mortality (OR 16.58, 95%

CI 4.47 – 61.45). Patients' Child Pugh Score was also associated with higher in-hospital mortality (OR 1.48, 95% CI 1.04 – 2.12).

Discussion

Bleeding rates reported in studies published on patients with CLD who received or did not receive pharmacological thromboprophylaxis are variable [6-9]. Moreover, the type of bleeding reported, bleeding definitions used and time frame to assess bleeding are not consistent in these studies, therefore limiting the comparability between them [6,8-10]. In this study, we chose to adopt the definition used in the IMPROVE BRS validation studies [3,11]. The authors opted to select overall bleeding, major bleeding and clinically relevant non-major bleeding as co-primary endpoints in order to facilitate comparison with previous studies published in CLD and to assess the impact of BRS $\geq$ or <7 on bleeding results in patients with CLD.

The rates of bleeding in this study were higher than those observed in the IMPROVE BRS validation studies and original IMPROVE BRS derivation cohort even though the study published by Rosenberg et al included around 1000 patients with liver disease with an INR>1.5 [3,11,12]. In comparison to previous studies in CLD that evaluated the rates of bleeding in patients who received or did not receive pharmacological prophylaxis, the rates were notably higher in this study (Table 5). This may be in part due to the more inclusive definition of bleeding used in our study and the wider time frame for detecting bleeding events.

The apparently higher incidence of bleeding in the group not receiving pharmacological prophylaxis may have been due to the inherent bleeding risk of these patients in comparison to the lower bleeding risk in the group prescribed pharmacological prophylaxis, since

pharmacological prophylaxis itself has not shown to increase patients' risk of bleeding [6,10]. It is well known that the initiation of pharmacological prophylaxis in patients with liver disease is not straightforward. Patients with more risk factors for clotting such as cancer and surgery should have thromboprophylaxis initiated; however, in those with a higher bleeding risk, pharmacologic thromboprophyalxis should be avoided [13]**.** Furthermore, variceal rupture and therefore bleeding, that carries the highest morbidity and mortality risk in patients with cirrhosis and the most significant form of GI bleeding in this patient population is not related to hemostatic dysfunction but rather dependent on severity of portal hypertension[14]. In this study, GI bleeding accounted for 8/25 of the clinically relevant non-major bleeding events in the group not receving pharmacological prophylaxis. Although these bleeds were categorized as non-major GI bleeds, 6 of the 8 patients who experienced non-major bleeds received blood transfusions during their hospital stay. Due to the retrospective nature of the study, the appropriateness of blood transfusions and the compliance with guidelines for transfusions in this patient population could not be assessed. Whether the transfusions given may have caused volume overload and therefore worsened the bleed cannot be ruled out [15].

In our study, 46.11% (89/193) of our admissions had a BRS of >7, showing an elevated risk of bleeding. Based on the IMPROVE validation studies, a BRS >7 predicted a significant two-fold increase in major bleeding and any bleeding within 14 days of admission[11]. The percentage of patients with a BRS≥7 in the IMPROVE BRS derivation cohort and the validation studies ranged between 10-22%. The higher percentage of bleeding found in our study may be attributable to the higher percentage of patients with BRS>7. Moreover, in the validation study by Hostler et.al, which included 1086 patients, the Kaplan-Meier curves showed a higher cumulative incidence of major ($p=0.02$) bleeding and a trend towards an incidence of overall bleeding (major and

clinically relevant non-major) (p=0.06) bleeding within 14 days in patients with an IMPROVE BRS ≥ 7.[3]In the BRS validation study published by Rosenberg et al, which included 15,516 patients, an IMPROVE BRS ≥ 7 on admission was associated with an increased rate of both major bleeding and overall bleeding (major and clinically relevant non-major). Furthermore, the study showed that higher BRS increased the incidence of overall and major bleeding at incremental levels [11].

Although our study did not validate the IMPROVE BRS in patients with CLD, a significant increase in the rate of bleeding was found in those with a BRS≥ 7 versus BRS<7. Moreover, the multivariate analysis confirmed a borderline association between the BRS ≥ 7 and major bleeding as seen in **table 4**. This borderline association may have been due to the small sample size.

Moreover, when bleeding rates were reported taking into consideration both the IMPROVE BRS≥ 7 versus BRS<7 and whether or not patients received pharmacological thromboprophylaxis, patients with a high BRS who did not receive thromboprophylaxis bled more than those who received it. Conversely, in those with a low BRS, even if they did not receive prophylaxis, the risk of bleeding was the same for major or clinically relevant non major bleeding, showing that the BRS could be a useful objective risk assessment tool to assist in guiding the initiation of thromboprophylaxis in CLD patients with an INR>1.5.

The rates of thrombotic events, (2.1%) were similar to previously published retrospective literature ranging between 0.5-8.2% [16-19]. All 4 patients who developed VTE were Child Pugh stage C.

In-hospital mortality was thirty percent in this study population. This is higher than that noted in previous retrospective studies ranging between 7.8-8.5 % [9,10]. This may have been due to patients' poor prognosis as evidenced by a higher mean INR at 2.3, although not supported by the multivariable analysis. Prolonged INR has been shown to be an indicator for hepatic decompensation and a useful prognostic factor in chronic liver disease rather than predicting bleeding or thrombosis[20].

Consistent with other studies, the CPS score predicted mortality in our study [21]. The CPS appeared to be a better predictor of mortality than the MELD-Na, (OR 1.48, 95% CI 1.04 – 2.12). Furthermore, out of the 30 patients that died, 29 (96,7%) were Child Pugh class C, with a mean score of 12.03. In contrast with previous studies, pharmacological prophylaxis was associated with increased mortality in this study [9,10].The cause of death was not documented in charts which makes it harder to assess the reason of higher mortality. The markedly higher mortality reported in the group receiving pharmacological thromboprophylaxis in comparison to the group not receiving thromboprophylaxis was probably accounted for by the fact that there was a high incidence of major bleeding in those receiving prophylactic therapy who had a high IMPROVE score. The latter is based on the presence of a concurrent cancer, renal failure, advanced age and other clinical indicators as well as a prolonged prothrombin time. This finding is in contrast to the work published by Villa et al demonstrating that thromboprophylaxis reduces the incidence of portal vein thrombosis, disease progression and mortality [22]. Whether prophylactic anticoagulation decreases the rates of decompensation and death continues to be a debated clinical question needing additional research.

Although this study was observational, given the high mortality rate, we sought to explore the factors affecting this important clinical outcome. As such, we attempted to evaluate the impact of

the social determinants of health on mortality using health care coverage as a proxy to poor socioeconomic status; however, we were not able to demonstrate a significant association. The lack of statistical significance in health care coverage can be partially attributed to the small sample size and other potential confounders that are not addressed in this study. This patient population being indigent, tends to be less compliant with medical follow-up, generally present in more advanced states of disease, and subsequently has a poor outcome, which may have contributed to the unexpectedly high mortality rate [23]. Another confounder that cannot be overlooked is the quality of healthcare delivered. The fact that patients with high PADUA score received thromboprophylaxis, in fact points to vigilance in medical care delivery and therefore good standard of care [24]. Further prospective studies are needed to investigate this important outcome.

The study has potential strengths and limitations that should be considered.
To the best of our knowledge, this is the first study to report on the rates of bleeding in CLD patients receiving or not receiving thromboprophylaxis, using a bleeding definition adopted by a thromboprophylaxis registry. Furthermore, this study shows that the IMPROVE BRS calculated on admission may serve as a useful guide as to which patients should not receive pharmacological prophylaxis. The findings of this study should be analyzed and applied cautiously, taking into account the retrospective nature of design of the design, the lack of power, and the relatively small sample size of patients who received pharmacological prophylaxis. Further randomized clinical trials or robust real world patient registries are needed to confirm the findings, and the effect of thromboprophylaxis on mortality in CLD.

Transparency section

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***Author contributions*:** N.C, C.L, P.S, E.R, R.C, H.Z, G.G were involved in the conception and design, P.S, R.C, E.R and N.C were involved in the analysis and interpretation of the data. N.C, E.R, C.L, R.C, drafted the manuscript. G.G critically reviewed the manuscript for intellectual content. All authors have approved the final draft submitted and agree to be accountable for all aspects of the work.

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Tables

Table 1: Baseline Characteristics

	Pharmacological Thromboprophylaxis (N= 20)	**No Pharmacological Thromboprophylaxis (N= 173)**
Age (Years), mean ± SD	64.5 ± 9.9	57.5 ± 14.2
Weight (kg), mean ± SD	78.3 ± 20.5	77.9 ± 20.3
BMI (kg/m2), mean ± SD	29.63 ± 7.9	28.04 ± 5.6
Gender		
Males, **N (%)**	11 (55%)	118 (68.2%)
Females, **N (%)**	9 (45%)	55 (31.8%)
Healthcare Coverage		
Public	110 (64.3%)	15 (75%)
Private	55 (32.2%)	5 (25%)
Self	6 (3.5%)	0
CLD Diagnosis, N		
Autoimmune Hepatic Disease	1	4
Liver Cirrhosis		
Viral	1	14
Alcoholic	3	18
Unspecified	15	125
Hepatocellular Carcinoma	0	7
NASH	0	1

	Pharmacological Thromboprophylaxis (N= 20)	No Pharmacological Thromboprophylaxis (N= 173)
Antiplatelet Use on Admission, N (%)	5 (25%)	8 (4.6%)
Antiplatelet Use during Hospitalization, N (%)	5 (25%)	3 (1.7%)
History of Bleeding	0	18 (10.4%)
Cancer	2 (10%)	28 (16.2%)
Previous VTE	1 (5%)	1 (0.6%)
Admission MELD Score, mean ± SD	22.11 ± 5.89	23.30 ± 7.52
Child Pugh Score, mean ± SD	10.15 ± 2.16	10.88 ± 2.35
Child Pugh Class Class A Class B Class C	 2 (10%) 5 (25%) 13 (65%)	 6 (3.5%) 29 (16.8%) 138 (79.8%)
PADUA, (mean), SD	4.6 ± 1.5	3.3 ± 22
PADUA ≥4	18 (90%)	95 (54.9%)
IMPROVE Bleeding Risk Score, mean ±SD	6.4 ± 2.4	6.9 ± 2.9
BRS **<7** **≥7**	 13 (65%) 7 (35%)	 91 (52.6%) 82 (47.4%)
INR upon admission	1.71	2.01

	Pharmacological Thromboprophylaxis (N= 20)	No Pharmacological Thromboprophylaxis (N= 173)
Mean INR, mean ± SD	1.85 ± 0.55	1.96 ± 0.76
Maximum INR During Hospitalization	2.58	2.25

Table 2: Bleeding and Mortality Rates in patients with or without Pharmacological Prophylaxis

	Pharmacological Thromboprophylaxis N= 20 n ; % (95% CI)	No Pharmacological Thromboprophylaxis N= 173 n ; % (95% CI)
Overall Bleeding [a]	2; 10% (0 – 24)	32; 18.5 (13 – 24)
Major Bleeding [b]	2; 10% (0 – 24)	23; 13.3 (8 – 18)
• Retroperitoneal	0	1
• Intraocular	0	1
• Hemoglobin drop	1	7
• Transfusions	1	14
• Death	0	3
Clinically relevant non-major Bleeding [c]	1; 5 (0 – 15)	25; 14.5 (9 – 20)
− Overt non-major GI bleeding	1	8
− Hematuria events	0	4
− Epistaxis	0	4

	Pharmacological Thromboprophylaxis N= 20 n ; % (95% CI)	No Pharmacological Thromboprophylaxis N= 173 n ; % (95% CI)
– Other bleeding significant enough to be reported in the chart	0	12
o Nasogastric tube related bleeding	0	1
o Wound bleeding	0	6
o Rectal bleeding	0	1
o Hemoptysis bleeding	0	3
o Ecchymosis	0	1
Mortality	9; 45 (21 – 69)	21; 12.1 (7 – 17)

[a] During the admission, if patients experienced both a major and clinically relevant non-major bleed, it was reported as 1 bleeding event. [b] If patients experienced 2 different types of clinically relevant non-major bleeds within the admission, it was reported as 1 clinically relevant non-major bleeding event. [c] If patients experienced 2 different types of major bleeds within the admission, it was reported as 1 major bleeding event.

Table 3: Bivariate analysis of IMPROVE BRS with overall, major, and clinically relevant non-major bleeding, stratified per pharmacological thromboprophylaxis

	BRS < 7 (N=104)		BRS ≥ 7 N=89	
	Pharmacological Thromboprophy-laxis (n=13) n ; % (95% CI)	**No Pharmacological Thromboprophy-laxis (n=91) n ; % (95% CI)**	**Pharmacological Thromboprophy-laxis (n=7) n ; % (95% CI)**	**No Pharmacological Thromboprophy-laxis (n=82) n ; % (95% CI)**
Overall Bleeding	1 ; 7.7 (0 – 24)	12; 13.2 (6 – 20)	1 ; 14.3 (0 – 49)	20 ; 24.4 (15 – 34)
Major Bleeding	1 ; 7.7 (0 – 24)	7 ; 7.7 (2 – 13)	1 ; 14.3 (21 – 49)	16 ; 19.5 (11 – 28)
Clinically relevant non-major Bleeding	1; 7.7 (0 – 24)	8; 8.8 (3 – 15)	0	17 ; 20.7 (12 – 30)

Table 4: Multivariable Analysis of Overall Bleeding, Major Bleeding, Clinically Relevant Non-major Bleeding, and Mortality

Overall Bleeding- Multivariable Analysis [a]		
Variable	**ORa[e]**	**95% Confidence Interval**
IMPROVE BRS ≥7	1.81	0.82 – 3.98
Major Bleeding- Multivariable Analysis [b]		

Variable	ORa[e]	95% Confidence Interval
IMPROVE BRS ≥7	2.37	0.94 – 5.97
Clinically Relevant Non-Major Bleeding - Multivariable Analysis [c]		
Variable	**ORa[e]**	**95% Confidence Interval**
IMPROVE BRS ≥7	2.08	0.85 – 5.08
Mortality - Multivariable Analysis [d]		
Variable	**ORa[e]**	**95% Confidence Interval**
Pharmacological Thromboprophylaxis	16.58	4.47 – 61.45
Child Pugh Score	1.48	1.04 – 2.12
MELD-Na Score	1.05	0.96 – 1.14
Maximum INR during Hospitalization	1.09	0.81 – 1.48

[a] Variables with a p-value of 0.2 or less in the bivariate analysis were included in the initial model. Those include: IMPROVE BRS score ≥7 or <7, Antiplatelet use on admission, and Minimum platelet count.

Using ENTER method, the model finally retained the variables shown in this table. Hosmer and Lemshow test for sample adequacy p-value: 0.697.

[b]Variables with a p-value of 0.2 or less in the bivariate analysis were included in the initial model. Those include: IMPROVE BRS score ≥7 or <7, Antiplatelet use on admission, and Minimum platelet count.

Using ENTER method, the model finally retained the variables shown in this table. Hosmer and Lemshow test for sample adequacy p-value: 0.391.

[c] Variables with a p-value of 0.2 or less in the bivariate analysis were included in the initial model. Those include: IMPROVE BRS score ≥7 or <7, Antiplatelet use onadmission, and Minimum platelet count.

Using ENTER method, the model finally retained the variables shown in this table. Hosmer and Lemshow test for sample adequacy p-value: 0.414.

[d] Variables with a p-value of 0.2 or less in the bivariate analysis were included in the initial model. Those include: Pharmacological Thromboprophylaxis during hospitalization, CPS Score, MELD-Na Score, and maximum INR during hospitalization. Using ENTER method, the model finally retained the variables shown in this table. Hosmer and Lemshow test for sample adequacy p-value: 0.257.

[e]ORa: Odds ratio

Table 5: Comparison of bleeding rates in patients with CLD receiving or not receiving thromboprophylaxis

	Bleeding Definition	**No Pharmacological Thromboprophylaxis**	**Pharmacological Thromboprophylaxis**
Barclay[8]	Documented Bleed with no definition	N=1189 123(10.3%)	N=392 8 (2.0%)
Reichart [9]	TIMI Bleeding criteria [a] Overall hemorrhage, Major hemorrhage Minor hemorrhage	N=172 13 (7.4) 5 (2.8) 8 (4.5)	N=80 14 (17.5) 4 (5.0) 10 (12.5)
Shatzel[10]	Overall in hospital bleed (GI & non GI) GI Non-GI	N=304 17 (5.5) 10 (3.3) 7 (2.3)	N=296 24 (8.1) 9 (3.0) 15 (5.1)

[a] TIMI Bleeding criteria

- Overall hemorrhage was a composite endpoint including both major and minor hemorrhage.
- Major hemorrhage was defined as a decrease in hemoglobin of greater than 5.0 g/dl within 10 days or any intracranial hemorrhage.

- Minor hemorrhage was defined as a decrease in hemoglobin 3–5 g/dl with witnessed bleeding or greater than 4 g/dl without witnessed bleeding, both within 10 days.

Hemorrhages were identified by maximum and minimum hemoglobin values across any 10 days during hospitalization, as well as any witnessed hemorrhage during hospitalization not related to surgical procedures.