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Effect of Vitamin K Administration in Cirrhotic Patients with Coagulopathy

Emily Shor, PharmD
PGY-2 Internal Medicine Pharmacy Resident
St. Louis College of Pharmacy/VA St. Louis Health Care System
Project Mentor: Travis Linneman, PharmD, BCPS

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Disclaimer

- This material is the result of work supported with resources and the use of facilities at the VA St. Louis Health Care System.

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- This study was approved by the Institutional Review Board (IRB) at the VA St. Louis Health Care System.

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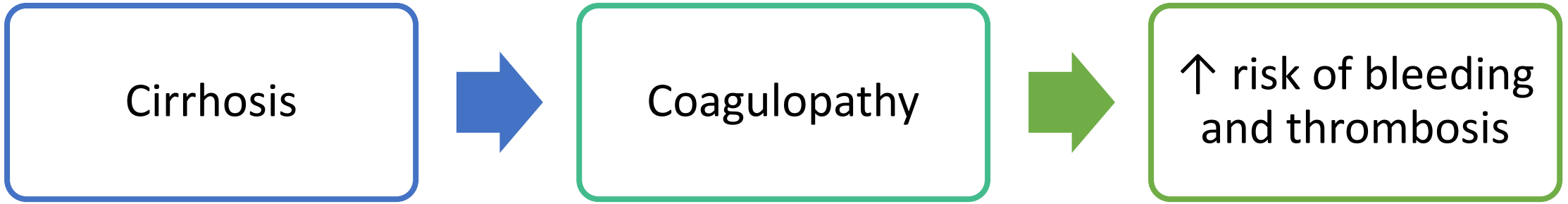
Cirrhosis and Vitamin K



Reduced production of:

- Factors II, VII, IX, X
- Proteins C and S

Providers often administer vitamin K to cirrhotic patients with elevated INRs.

There is a lack of strong evidence to support this practice.

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Literature Review

Study	Cohort	Results
Hambley, et al. Retrospective 2016	Patients with liver disease who received vitamin K n=333 admissions	Mean decrease in INR: 0.08 Change in INR (increase or decrease) > 0.4: 37 encounters
Rivosecchi, et al. Retrospective 2017	Cirrhotic patients with baseline INR > 1.5 receiving vitamin K IV n=96 patients	30% ↓ in INR or reduction of INR to ≤ 1.5: 16.7% Average decrease in INR: 0.31
Meyer, et al. Retrospective 2016	Cirrhotic patients receiving Vitamin K IV, PO, or subQ v. no vitamin K admin n=130 v. 146 patients	INR responders within 72 hours 46.2% v. 32.9% (p=0.03) Bleeding Events: 4.6% v. 0.7% (p=0.05)

Hambley BC. *Blood.* 2016;128(22):2583.
Rivosecchi RM, et al. *Int J Pharm Pract.* 2017;25(6):463-465.
Meyer AV, et al. *Ann Pharmacother*. 2016;50(2):113-7.

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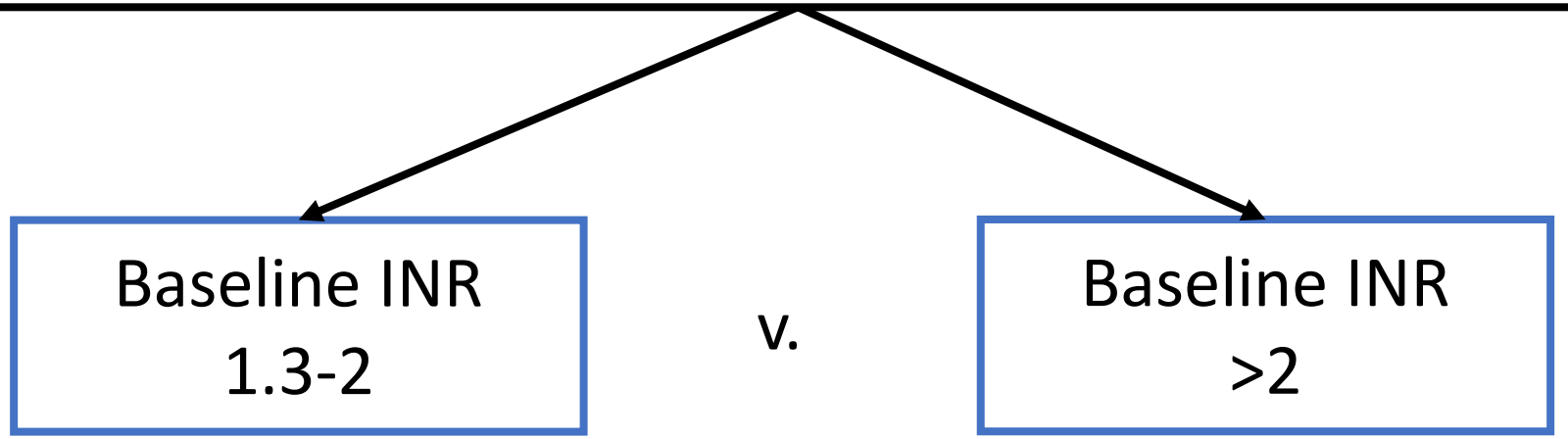
Objective

To compare rates of clinical outcomes (bleeding and thrombosis) post-vitamin K administration in patients stratified by baseline INR.



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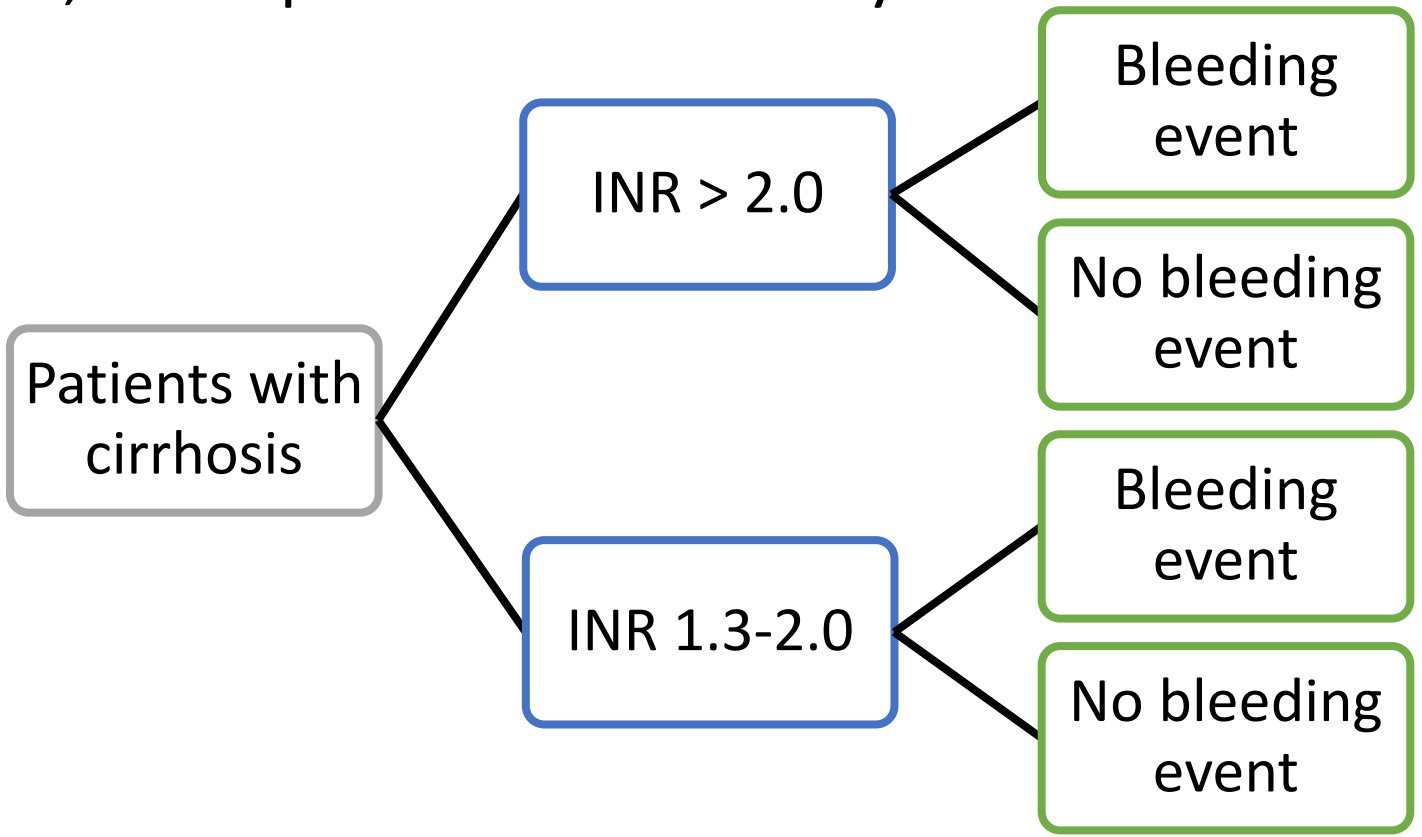
Study Design

- Single-center, retrospective cohort study



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Primary Outcome

- Rate of bleeding events during admission
  - ISTH definition:
    - Bleeding in critical area/organ
    - Confirmed bleeding causing decrease in hemoglobin by ≥2 g/dL
    - Transfusion of ≥ 2 units of PRBCs

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Secondary Outcomes

- Rate of thrombotic events during admission
- Absolute change in INR from baseline to up to 72 hours after last vitamin K administration
- Percent change in INR from baseline to up to 72 hours after last vitamin K administration

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Secondary Analysis

- Multivariate Regression
  - Include variables with $p<0.2$ in univariate analysis

- Univariate Analysis

ICU admission during first seven days of hospitalization	Thrombocytopenia upon admission
Presence of varices	Concurrent infection during admission
Etiology of cirrhosis	Hepatorenal syndrome upon admission
Degree of INR decrease (< 10% v. ≥ 10%)	MELD score (≤20 v. > 20)
Administration of blood products	Vitamin K dose (≤ 5 mg v. > 5 mg)

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Inclusion/Exclusion Criteria

Inclusion Criteria
• 18-89 years old • Cirrhosis diagnosis • Admission to JC VA between January 1, 2003 to December 31, 2018 • Baseline INR > 1.3   • First INR obtained during admit • Vitamin K PO or IV administered within 72 hours of baseline INR

Exclusion Criteria

• ≥ 90 years old
• Home or inpatient use of:
  • DOACs, warfarin
  • Argatroban, fondaparinux, bivalirudin, enoxaparin, heparin
• IM or SQ vitamin K
• History of liver transplant
• Bleeding or thrombotic event during admission but prior to vitamin K admin
• Missing INR data
• Repeat admission

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Statistical Analysis

Baseline Characteristics and Outcomes

- Categorical variables: Chi-square or Fisher's exact
- Continuous variables: independent t-test/Wilcoxon-ranked sum test

Multivariate Regression

- Threshold for univariate $p<0.2$
- Significance after regression $p<0.05$
- Reported as odds ratio

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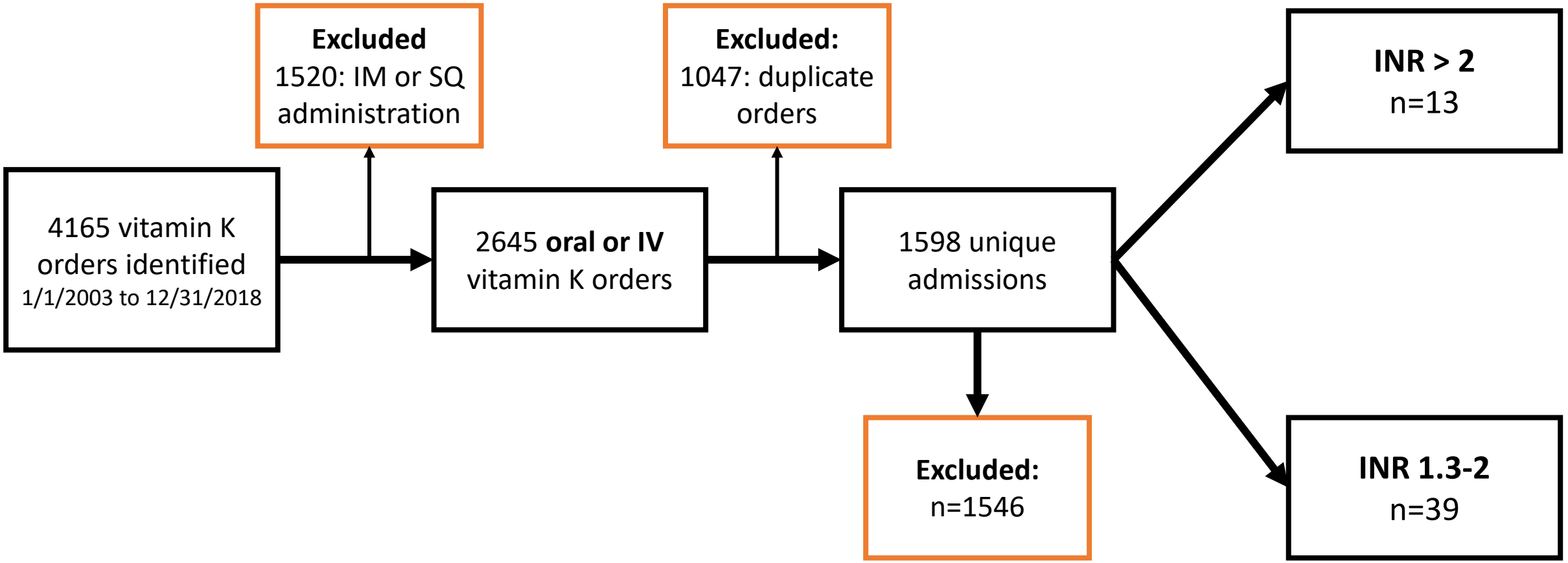
Patient Enrollment



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Baseline Characteristics

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Age, years (mean ± SD)	59.7 ± 7.6	57 ± 8.1	0.28
Race, n (%) Caucasian African American	 26 (66.7) 12 (30.8)	 10 (76.9) 2 (15.4)	0.73
Length of Stay, days (mean ± SD)	7.3 ± 4.1	5.3 ± 4.3	0.15
Baseline INR (mean ± SD)	1.64 ± 0.17	2.36 ± 0.41	<0.001
Heart Failure, n (%)	4 (10.3)	1 (7.7)	1
Dialysis, n (%)	4 (10.3)	1 (7.7)	1
Home/Inpatient Antiplatelet, n (%)	7 (17.9%)	0	0.17
Home/Inpatient Multivitamin, n (%)	14 (35.9)	2 (15.4)	0.3
ICU Admission within 7 days, n (%)	8 (20.5)	5 (38.5)	0.27
Concurrent Infection, n (%)	14 (35.9)	4 (30.8)	1
History of Bleeding, n (%)	10 (25.6)	4 (30.8)	0.73
History of VTE, n (%)	1 (2.6)	1 (7.7)	0.44

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Baseline Characteristics – Labs upon Admission

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Creatinine, mg/dL (mean ± SD)	1.69 ± 1.81	2.25 ± 1.96	0.37
Total bilirubin, mg/dL (mean ± SD)	7.16 ± 6.9	11.38 ± 7.06	0.06
Albumin, g/dL (mean ± SD)	2.73 ± 0.46	2.57 ± 0.64	0.34
Hemoglobin, g/dL (mean ± SD)	10.8 ± 2	10.4 ± 2.3	0.53
Platelets, 10^3/µL (mean ± SD)	130 ± 92	92 ± 56	0.09
Thrombocytopenia, n (%)	15 (38.5)	7 (53.8)	0.33
AST , U/L (mean ± SD)	123 ± 153	189 ± 262	0.4
ALT, U/L (mean ± SD)	62 ± 77	94 ± 149	0.48

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Baseline Characteristics – Cirrhosis Etiology and Complications

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Cirrhosis Etiology, n (%)			
Alcoholic	18 (46.2)	3 (23.1)	0.2
Cholestatic	1 (2.6)	0	1
Viral	8 (20.5)	2 (15.4)	1
NASH	1 (2.6)	2 (15.4)	0.15
Mixed (all alcoholic + viral)	10 (25.6)	6 (46.2)	0.17
Unknown	1 (2.6)	0	1
Cirrhosis Complication History, n (%)			
Ascites	35 (89.7)	12 (92.3)	1
Varices	19 (48.7)	8 (61.5)	0.53
Hepatic Encephalopathy	19 (48.7)	10 (76.9)	0.11
SBP	10 (25.6)	4 (30.8)	0.73
HRS	4 (10.3)	5 (38.5)	0.03
Portal Vein Thrombosis	2 (5.1)	2 (15.4)	0.26
TIPS	1 (2.6)	0	1
Fibrosis-4 Index (mean ± SD)	11.94 ± 15.7	18.47 ± 17.7	0.21

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Baseline Characteristics – Prognosis

	INR 1.3-2 (n=39)	INR > 2 (n=13)	
Child-Pugh Score (mean ± SD)	9.7 ± 1.7	11.5 ± 1.2	<0.001
Child-Pugh Class			
Class A	1 (2.6)	0	
Class B	13 (33.3)	1 (7.7)	
Class C	25 (64.1)	12 (92.3)	
MELD Score (mean ± SD)	23 ± 6.3	32 ± 5.8	0.001

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Vitamin K Use

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Number of Vitamin K Doses per Admission (mean ± SD)	2.62 ± 1.91	2.54 ± 1.27	0.89
Route of Administration, n (%)			1
PO only	34 (87.1)	11 (84.6)	
IV only	5 (12.8)	1 (7.7)	
PO and IV	0	1 (7.7)	
Cumulative Dose during Admission, mg (mean ± SD)	21.9 ± 17.6	22.3 ± 13.4	0.93
Average Daily Dose, mg (mean ± SD)	8.89 ± 3.6	8.85 ±2.2	0.97

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Primary Outcome

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Bleeding Events, n (%)	**14 (35.9)**	**2 (15.4)**	**0.29**
Symptomatic Bleeding	5 (12.8)	1 (7.7)	
Transfusion of > 2 units PRBCs	9 (23.1)	1 (7.7)	

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Secondary Outcomes

	INR 1.3-2 (n=39)	INR > 2 (n=13)	p-value
Thrombotic Events, n (%)	0	0	N/A
All-Cause Death within 30 days, n (%)	12 (30.8)	8 (61.5)	**0.048**
Absolute Change in INR (mean ± SD)	0.045 ± 0.35	0.043 ± 0.82	0.99
Percent Change in INR (mean ± SD)	2.7 ± 20.2	3.6 ± 38	0.91
Any Degree of INR Decrease, n (%)	19 (48.7)	8 (61.6)	0.52

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Univariate Analysis

	Bleeding Event (n=16)	No Bleeding Event (n=36)	p-value
INR >2, n (%)	2 (12.5)	11 (30.6)	0.298
ICU Admission within 7 days, n (%)	7 (43.8)	6 (16.7)	**0.037**
Varices, n (%)	9 (56.3)	18 (50)	0.677
≥ 10% decrease in INR, n (%)	2 (12.5)	12 (33.3)	**0.179**
Thrombocytopenia, n (%)	7 (43.8)	15 (41.7)	0.888
Infection during admission, n (%)	8 (50)	10 (27.8)	**0.12**
HRS during admission, n (%)	5 (31.3)	4 (11.1)	**0.113**
Mean Vit K Dose > 5 mg, n (%)	11 (68.8)	27 (75)	0.639
MELD > 20, n (%)	13 (81.3)	29 (80.6)	1
Etiology – Alcoholic, n (%)	9 (56.3)	12 (33.3)	**0.120**
Etiology – Mixed, n (%)	2 (12.5)	14 (38.9)	**0.102**

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Logistic Regression

Multivariate analysis for independent risk factors associated bleeding events

	OR (95% CI)	p-value
INR >2	0.113 (0.008-1.658)	0.112
ICU Admission within 7 days	2.789 (0.470-16.566)	0.259
Etiology – Alcoholic	1.175(0.214-6.459)	0.853
Etiology – Mixed	0.401(0.054-2.987)	0.373
Concurrent Infection	2.060 (0.441-9.633)	0.358
HRS	6.714 (0.622-72.499)	0.117
≥ 10% decrease in INR	0.359 (0.060-2.145)	0.261

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Discussion

Strengths	Limitations
• Assessed clinical outcomes alongside INR changes • Included patients over 15 year period • Various etiologies of cirrhosis included	• Single-center, retrospective • Bleeding event definition • Missing events due to follow-up period • Underpowered • Variability in vitamin K prescribing

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Conclusions

- No significant difference in clinical outcomes was identified after vitamin K administration regardless of baseline INR.
- No independent risk factors associated with bleeding events were identified in this cohort.
- Hypothesis generating study
  - Ex. Differences between patients whose INR decreased versus increased after vitamin K administration

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