

# Predictors of Non-Variceal Hemorrhage in a National Cohort of Patients with Chronic Liver Disease

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## Research Article

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# Abstract

## Background:

Non-variceal hemorrhage in patients with chronic liver disease (CLD) increases morbidity, mortality, and healthcare costs. There are limited data on risk factors for non-variceal hemorrhage in the CLD population. The aim of this study is to assess the predictive value of various clinical and laboratory parameters for non-variceal hemorrhage in CLD patients.

## Methods:

We conducted a retrospective cohort study of U.S. veterans diagnosed with CLD between 2002 and 2018 within the Veterans Health Administration database. We derived candidate variables from existing risk prediction models for hemorrhage, risk calculators for severity of liver disease, Charlson index of prognostic comorbidities, and prior literature. We used a competing risk analysis to study the relationship between putative risk factors and incidence of non-variceal hemorrhage in patients with CLD.

## Results:

Of 15,183 CLD patients with no history of cancer or anticoagulation use, 674 experienced non-variceal hemorrhage within one year of CLD diagnosis. In multivariable analysis, 11 of the 26 candidate variables independently predicted non-variceal hemorrhage: race, INR > 1.5, bilirubin  $\geq$  2 mg/dL, albumin  $\leq$  3.5 g/dL, anemia, alcohol abuse, antiplatelet therapy, chronic kidney disease, dementia, proton pump inhibitor prescription, and recent infection.

## Conclusions:

In this study of almost 15,000 veterans, risk factors for non-variceal bleeding within the first year after diagnosis of CLD included non-Caucasian race, laboratory parameters indicating severe liver disease and recent infection in addition to the risk factors for bleeding observed in a general non-CLD population.

## Introduction

Hemorrhage is a frequent complication of chronic liver disease (CLD)[1]. Among the 4.5 million Americans with chronic liver disease[2], hemorrhage frequently leads to morbidity, mortality and increased health-care costs [3, 4]. Hemorrhage in patients with CLD is classified as variceal hemorrhage (i.e., originating from gastroesophageal varices)[1], and non-variceal hemorrhage (e.g., epistaxis, procedure-related [5], non-variceal gastrointestinal, and intracranial hemorrhage [6]). Variceal hemorrhage is a consequence of portal hypertension [7], and studies have reported risk factors for variceal

hemorrhage [8–10]. There are, however, sparse data on risk factors of non-variceal hemorrhage in patients with CLD.

Non-variceal hemorrhage can trigger decompensation of liver disease, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy [11]. Although patients with CLD experience non-variceal hemorrhage less frequently than variceal hemorrhage [1], there is no difference between mortality, length of hospital stay and readmission rates between patients presenting with variceal and non-variceal hemorrhage [12]. A better understanding of the risk factors for non-variceal hemorrhage can guide preventive strategies against hemorrhage in patients with CLD, and thus improve clinical outcomes.

Patients with CLD have a unique hemostatic profile [13], and hence, traditional risk factors for hemorrhage, such as low platelet count and increasing International Normalized Ratio (INR) values [14–17], may not predict hemorrhage. Preclinical studies show that thrombocytopenia in CLD patients is compensated for by elevations in von Willebrand Factor (vWF) activity [18], and elevated INR is balanced by a decrease in certain anticoagulant factors (e.g., antithrombin, protein C and protein S), and increases in Factor VIII levels [19]. There is, hence, a need to study the value of these laboratory parameters in predicting hemorrhage in the CLD population.

In this study, we used a national cohort of veterans with CLD to identify the clinical and laboratory parameters that predict non-variceal hemorrhage.

## Methods

The St. Louis Veterans Affairs Medical Center (VAMC) and Washington University School of Medicine Institutional Review Boards (IRB) approved this study.

### Data Source:

Using the national Veterans Health Administration (VHA) data, we conducted a retrospective single-cohort study. Information on demographics, comorbidities, outcomes, vital signs, laboratory values and prescription data for medication (antiplatelets, anticoagulants, proton pump inhibitors) were obtained from the Veterans Informatics and Computing Infrastructure (VINCI). Date and cause of death were obtained from the Veterans Administration Vitals Statistics [20].

### Study Population:

We included patients 18 years or older diagnosed with CLD between October 1, 2002, and September 30, 2016, and followed them until 2018 (Fig. 1). We used International Classification of Diseases (ICD) 9/10 codes to identify CLD. To improve diagnostic accuracy, we used a previously validated algorithm [21] where patients are required to have two ICD-9 or -10 codes to qualify for CLD diagnosis: one for CLD (i.e., hepatitis or cirrhosis) and one for a common clinical presentation associated with CLD (e.g., hepatic encephalopathy, hepatorenal syndrome, etc.) (Table A, Supplementary Appendix).

To exclude patients who could be receiving anticoagulant therapy, we excluded those with a history of artificial heart valve and those with an active prescription for anticoagulant therapy during study period. We also excluded patients with history of malignancy within 5 years prior to CLD diagnosis as these patients have additional risks for bleeding. We followed patients up to the date of hemorrhage, loss to follow-up, or 12-months after CLD diagnosis, whichever came first.

### Detection of Outcomes

The primary outcome was occurrence of a non-variceal hemorrhage within 12-months of CLD diagnosis. A non-variceal hemorrhage was identified using previously validated ICD-9/10 codes in **i)** any position for gastrointestinal bleeding, intracranial bleeding, epistaxis and gross hematuria, and **ii)** in the primary position for hemorrhage at all other sites [22–25](Table B, Supplementary Appendix). We excluded ICD codes for non-specific gastrointestinal bleeding e.g., melena and hematemesis that likely denote variceal hemorrhage in patients with CLD.

### Selection of Candidate Variables

We studied the role of 26 clinical and laboratory parameters in predicting hemorrhage among patients with liver disease. We derived candidate variables from demographic characteristics [age, gender, race], existing risk-prediction models for hemorrhage [14–16, 26], risk-prediction models for severity of liver disease [i.e., Childs-Pugh [27]and MELD [28] scores], Charlson index for prognostic comorbidities [29], and prior literature [30]. Demographic variables were studied as fixed variables and values closest to the date of CLD diagnosis were used for analyses. Comorbidities were identified within 12-months prior to CLD diagnosis and used as fixed variables. Laboratory values (e.g., INR) and prescriptions (e.g., anti-platelet therapy) were used as time-varying variables to account for their temporal association with hemorrhage (Table 1).

Table 1  
Definition and Measurement of Covariates

<b>Risk Factor</b>	<b>Fixed/Time-dependent</b>	<b>Categorical/Continuous</b>	<b>Identification</b>
Age	Fixed (at CLD diagnosis)	Continuous	VINCI
Sex	Fixed (at CLD diagnosis)	Categorical (Male/Female)	VINCI
International Normalized Ratio	Time-dependent	Categorical (2 categories: > 1.5, ≤ 1.5)	Laboratory value
Platelet Count	Time-dependent	Categorical (2 categories: < 50,000 μ/L, ≥ 50,000 μ/L)	Laboratory value
Total bilirubin	Time-dependent	Categorical (2 categories: ≥2 mg/dL, < 2 mg/dL)	Laboratory value
Albumin	Time-dependent	Categorical (2 categories: ≤3.5 mg/dL, > 3.5 mg/dL)	Laboratory value
Chronic kidney disease	Time-dependent	Categorical (2 categories: CrCl < 30 ml/min, CrCl ≥ 30 ml/min)	Laboratory value
Aspirin or antiplatelet use	Time-dependent	Categorical (Yes/No)	PBM
Prior hemorrhage	Fixed (within 5 years prior to CLD diagnosis)	Categorical (Yes/No)	ICD 9/10 codes
Anemia	Fixed (within 12 months prior to CLD diagnosis)	Categorical (Yes/No)	Laboratory value: Hgb < 10 Or ICD 9/10 codes

Risk Factor	Fixed/Time-dependent	Categorical/Continuous	Identification
Hypertension	Fixed (within 12 months prior to CLD diagnosis)	Categorical (Yes/No)	BP > 160 or IC9/10 codes
Alcohol abuse, Ascites, Congestive heart failure, Cardiovascular disease, Dementia, Chronic lung disease, Connective tissue disease, Peptic ulcer disease, Diabetes, Hemi- or paraplegia, HIV	Fixed (within 12 months prior to CLD diagnosis)	Categorical (Yes/No)	ICD 9/10 codes
Infection	Time-dependent	Categorical (Yes/No)	ICD 9/10 codes for sepsis, pneumonia, urinary tract infection, peritonitis
Abbreviations: CLD = chronic liver disease, VINCI = Veterans Informatics and Computing Infrastructure, PBM = Pharmacy Benefits Management, ICD = International Classification of Diseases			
Time-varying variables were used to predict hemorrhage within 30-days after the abnormal value.			

## Statistical Analysis

We analyzed the association between candidate variables and hemorrhage in a time-to-event analysis: time 0 was the date of CLD diagnosis and the outcome of interest was first non-variceal hemorrhage during follow-up. We used competing risk model by the methods of Fine and Gray to perform a multivariable analysis while accounting for the competing risk of non-hemorrhage related death [31]. A p-value of < 0.05 was considered significant. All statistical analyses were performed using SAS version 9.2.

## Results

Most patients were Caucasian males with a median age of 58 years. Of the 15,183 patients with CLD who were included in the study (Fig. 1), 674 (4.4%) experienced non-variceal hemorrhages within 12-months of CLD diagnosis. Patients who experienced hemorrhage were more likely to be younger, non-Caucasian, with a history of congestive cardiac failure, anemia, alcohol abuse, antiplatelet therapy, and recent infection. They were also more likely to have laboratory abnormalities of INR, bilirubin, albumin, and creatinine clearance and to have higher MELD scores (14 versus 12.8,  $p = 0.0004$ ) (Table 2). Of the 674 hemorrhages observed during follow-up, most occurred within the upper gastrointestinal tract followed by the lower gastrointestinal tract, intracranial, and nasal/respiratory sites (Table 3).

Table 2  
Demographic and Clinical Characteristics of Patients with Chronic Liver Disease

Demographic/Clinical Characteristics	Total (N = 15,183)		P-value
	Hemorrhage n = 674	No Hemorrhage n = 14,509	
Age (mean years)	57.3	58.2	0.02†
Male (%)	97.3	97	0.58*
Race (%)			0.02*
White	82.1	85.6	
Black	14.1	11.9	
Other	3.9	2.5	
Prior Bleeding (%)	8.9	8.2	0.48*
Cardiovascular disease (%)	8.3	7.9	0.75*
Congestive heart failure (%)	7.3	5.3	0.03*
Dementia (%)	1	0.5	0.08*
Chronic lung disease (%)	11.6	12.4	0.54*
Connective tissue disease (%)	1.3	0.8	0.11*
Peptic ulcer (%)	1.5	1.6	0.77*
Diabetes mellitus (%)	22.3	24.4	0.21*
Hemi- or paraplegia (%)	0.5	0.4	0.81*
HIV/AIDS (%)	0.6	1	0.32*
Anemia (%)	26	19.2	< 0.001*
Alcohol abuse (%)	38	30	0.001*
Ascites (%)	5.3	4.2	0.15*
NSAID use (%)	23.4	22.4	0.53*
Antiplatelet use (%)	17.4	14.7	0.053*
Median Platelet count (per microl)	119,000	121,000	0.49‡
INR (median)	1.4	1.3	< 0.001‡
Median Albumin (g/dL)	2.8	3.1	< 0.001‡
Median Bilirubin (mg/dL)	1.9	1.6	< 0.001‡

	Total (N = 15,183)		P-value
Demographic/Clinical Characteristics	Hemorrhage n = 674	No Hemorrhage n = 14,509	
Median Creatinine Clearance mL/min	93.4	89.1	< 0.001‡
Infection (%)	45.1	25.2	< 0.001*
MELD score > 20 (%)	14	12.8	0.0004*
* Chi-square test			
† T-test			
‡ Wilcoxon Two-Sample Test			

Table 3: Site of Hemorrhage	Frequency
	N (%)
Total (Any location)	674 (4.4/year)
Upper Gastrointestinal	404 (60.0)
Lower Gastrointestinal	130 (19.3)
Intracranial	67 (9.9)
Nasal/ Respiratory	39 (5.8)
Genitourinary	26 (3.9)
Peritoneum	3 (0.4)
Hemorrhage, unspecified	2 (0.3)
Joint / Soft Tissue	3 (0.4)

In the multivariable analysis, eleven of the 26 candidate variables were found to be independent risk factors for non-variceal hemorrhage: non-Caucasian race, abnormal INR, high bilirubin, low albumin, anemia, alcohol abuse, anti-platelet therapy, chronic kidney disease, dementia, recent infection and use of proton pump inhibitors. Among these risk factors, low serum albumin, chronic kidney disease, dementia and infections predicted the highest risk of hemorrhage (Table 4).



Table 4  
Multivariable Analysis of Risk Factors for Non-Variceal Hemorrhage

Parameter	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Age	0.99	0.985–1.003	0.20
Gender (Ref: Male)	1.36	0.84–2.20	0.22
Race (Ref: Caucasian)	1.04	0.83–1.30	0.74
African American	<b>1.54</b>	<b>1.03–2.28</b>	0.03
<b>Others</b>			
HTN (SBP > 160 mmHg)	1.36	0.98–1.89	0.06
<b>Albumin (<math>\leq 3.5</math> g/dL)<sup>1, 2</sup></b>	<b>3.68</b>	<b>2.84–4.77</b>	< 0.0001
<b>Anemia<sup>1</sup></b>	<b>1.30</b>	<b>1.08–1.57</b>	0.01
<b>Bilirubin (<math>\geq 2</math> mg/dL)<sup>1, 2</sup></b>	<b>1.45</b>	<b>1.19–1.76</b>	0.0002
<b>Chronic kidney disease (CrCl &lt; 30 ml/min)<sup>1, 2</sup></b>	<b>2.63</b>	<b>2.05–3.39</b>	< 0.0001
<b>INR &gt; 1.5<sup>1, 2</sup></b>	<b>1.68</b>	<b>1.39–2.04</b>	< 0.0001
Thrombocytopenia (platelets < 50k/microL) <sup>1</sup>	0.96	0.67–1.34	0.80
<b>Antiplatelet Use<sup>1</sup></b>	<b>1.36</b>	<b>1.02–1.82</b>	0.03
NSAID Use <sup>1</sup>	1.21	0.75–1.96	0.43
<b>PPI Use<sup>1</sup></b>	<b>1.23</b>	<b>1.05–1.43</b>	0.01
Prior Hemorrhage (within 5 years)	0.92	0.70–1.22	0.56
<b>Alcohol abuse</b>	<b>1.29</b>	<b>1.10–1.53</b>	0.002
Ascites <sup>2</sup>	1.01	0.71–1.43	0.95
Cardiovascular disease	0.85	0.62–1.17	0.33
Congestive cardiac failure	1.17	0.84–1.62	0.35
Chronic lung disease	0.85	0.66–1.10	0.23
Connective tissue disease	1.51	0.74–3.08	0.25
<b>Dementia</b>	<b>2.56</b>	<b>1.19–5.51</b>	0.02

Parameter	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Diabetes mellitus	0.93	0.76–1.14	0.51
HIV/AIDS	0.57	0.22–1.51	0.26
Hemi- or paraplegia	0.89	0.27–2.89	0.84
Peptic ulcer disease	0.82	0.43–1.56	0.55
<b>Infections*</b>	<b>2.54</b>	<b>2.12–3.05</b>	<b>&lt; 0.0001</b>

Abbreviations: HTN = hypertension, SBP = systolic blood pressure, CrCl = creatinine clearance, INR = International Normalized Ratio, NSAID = non-steroidal anti-inflammatory drugs, PPI = proton pump inhibitors, <sup>1</sup>=studied as time-varying variables, <sup>2</sup> Collinearity was tested between these variables (Tolerance > 0.92 and Condition index < 5).

## Discussion

In a nationwide cohort of 15,183 veterans with CLD, we found a 4.4% annual incidence of non-variceal hemorrhage, and we identified clinical and laboratory predictors of non-variceal hemorrhage in this population.

We analyzed risk of hemorrhage associated with laboratory parameters that predict severity of liver disease in the MELD [28] and Child Pugh Classifications [27]. We chose the cut-offs of these laboratory parameters (bilirubin, albumin and creatinine clearance) based on the definitions used in the MELD and Child-Pugh classifications. We chose the cut-off for INR based on recent literature showing uniform elevation in risk of hemorrhage at all INR values above 1.5 [17]. All these laboratory abnormalities predicted higher risk of hemorrhage suggesting that the severity of liver disease at diagnosis correlates with the risk of non-variceal hemorrhagic complications in the following year. While low albumin represents severe liver disease, this could also affect the risk of hemorrhage by creating an inflammatory milieu [32, 33]. The association between hypoalbuminemia and hemorrhage should be explored further in future studies. Ascites and hepatic encephalopathy, although components of Child-Pugh classification, did not predict hemorrhage in this study. The lack of association between ascites and hemorrhage could be due to non-specific coding of ascites, which may or may not be a consequence of CLD, as suggested by other administrative database studies [21]. Hepatic encephalopathy was coded in less than 1% of our study cohort, which made it hard to find a putative association with hemorrhage. Our analysis however, found a 2.5-fold increase in the risk of hemorrhage in people with “dementia”, which could represent episodes of hepatic encephalopathy in patients with CLD.

The results from this study support prior preclinical research addressing hemostasis in patients with CLD. For example, patients with CLD did not experience a higher risk of hemorrhage with thrombocytopenia. This lack of association supports the preclinical studies demonstrating rebalancing of hemostasis in CLD

patients with thrombocytopenia by elevated vWF levels [18, 37]. We found 2.5-fold risk of hemorrhage with recent infection in this analysis, which supports the preclinical finding that infections can promote hemorrhage in CLD by producing heparin like effect, detectable on heparinase-modified thromboelastography [30, 38].

Some of the risk factors for hemorrhage in this cohort of CLD patients concur with the risk factors for hemorrhage observed in a general non-CLD population e.g., anemia, alcohol abuse, and antiplatelet therapy [14–16]. Dementia predicted a higher risk of hemorrhage likely due to compromised self-care and an increased risk of falls [34]. Other risk factors for hemorrhage in a general non-CLD population e.g., age and hypertension [14–16] did not predict hemorrhage in CLD patients. The lack of association between age and hemorrhage could be due to survivorship bias where patients with severe liver disease do not live long enough [35] to experience hemorrhage. The restricted age range of our study population with few veterans older than 75 years also makes it harder to find this association. Patients with severe liver disease are more likely to have hypotension than hypertension [36], and this may explain the lack of association between hypertension and hemorrhage in this cohort. Moreover, we identified non-Caucasian race to be at a higher risk of non-variceal hemorrhage, which represents a novel finding.

The most frequent site of non-variceal hemorrhage in patients with CLD was upper gastrointestinal tract (60%). This was followed lower gastrointestinal tract (19.3%) and intracranial (9.9%) sites (**Table 3**). Patients with liver disease are pre-disposed to vascular ectasias [39] and peptic ulcer disease [40], which could explain the higher risk of upper gastrointestinal hemorrhage.

We utilized the VHA database to conduct this study as it provides access to patient charts, vital signs, laboratory parameters and pharmacy data from both inpatient and outpatients encounters. This is helpful for an unbiased determination of risk factors for hemorrhage as outcomes associated with parameters observed during hospitalization alone could be confounded by the reason for hospitalization and interventions performed during hospitalization e.g., transfusions. Moreover, we assessed vital signs, laboratory parameters and medication as time-dependent variables and utilized all values during the study period to determine temporal association of these variables with hemorrhage. We used previously validated methods to identify study population and outcomes [21–25].

This study has several limitations. We relied on ICD-9 and – 10 codes for identification of hemorrhage, so inclusion of events was contingent on accuracy of coding. The coding provider may have misclassified variceal hemorrhage as “non-variceal”. Moreover, we were unable to capture any events outside of the VHA system. VHA database underrepresents females, and thus results should be confirmed in a cohort more inclusive of females. While retrospective analysis establishes association, it is hard to elucidate causation. For example, anemia and prescription for proton pump inhibitors likely represent consequences of hemorrhage rather than “causes” for hemorrhage. Despite these limitations, this study provides a comprehensive assessment of the clinical and laboratory predictors of non-variceal hemorrhage in a national cohort of CLD patients. This study has the potential to guide physicians in risk-stratifying patients for hemorrhage at the time of CLD diagnosis and encourage them to perform a

careful assessment of the risk versus benefit of certain interventions like antiplatelet therapy that predispose to hemorrhage. This study will also generate rationale for future research for example, development of a risk-prediction model for hemorrhage specific to patients with CLD.

In summary, non-Caucasian race, severity of liver disease, anemia, alcohol abuse, antiplatelet therapy, chronic kidney disease, dementia, infections, and prescriptions for proton pump inhibitors are associated with a higher risk of non-variceal hemorrhage in the first year after CLD diagnosis. Knowledge of risk factors for hemorrhage in CLD can inform management of this patient population (e.g., avoidance of anti-platelet therapy without a clear indication) and increase patient awareness regarding possible complications of their disease.

## Declarations

Ethics approval and consent to participate: The St. Louis Veterans Affairs Medical Center (VAMC) and Washington University School of Medicine Institutional Review Boards (IRB) approved this study. Study was performed in accordance with the Declaration of Helsinki. This study analyzed data retrospectively using de-identified electronic medical records so an informed consent was not obtained (in accordance with the VAMC and the Washington University in St Louis IRB policy).

Consent for publication: Not applicable (This publication analyzed de-identified electronic medical records with no identifiable image or information in the final publication).

Availability of data and materials: Datasets used and analyzed during the current study are available in the Veterans Medical Affairs password protected electronic system. Please email the corresponding author to obtain reasonable access (afzalamber@wustl.edu).

Competing interests: All authors declare no competing financial interests to disclose.

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### Authors' contributions:

Conceptualization and Study Design: AA, PK, KMS

Data acquisition: AA, LS, KMS

Data analysis and interpretation: AA, PK, LS, BFG, KK, MS, KMS

Manuscript preparation: AA, PK, LS

Manuscript review: AA, PK, LS, KK, BFG, MS, KMS

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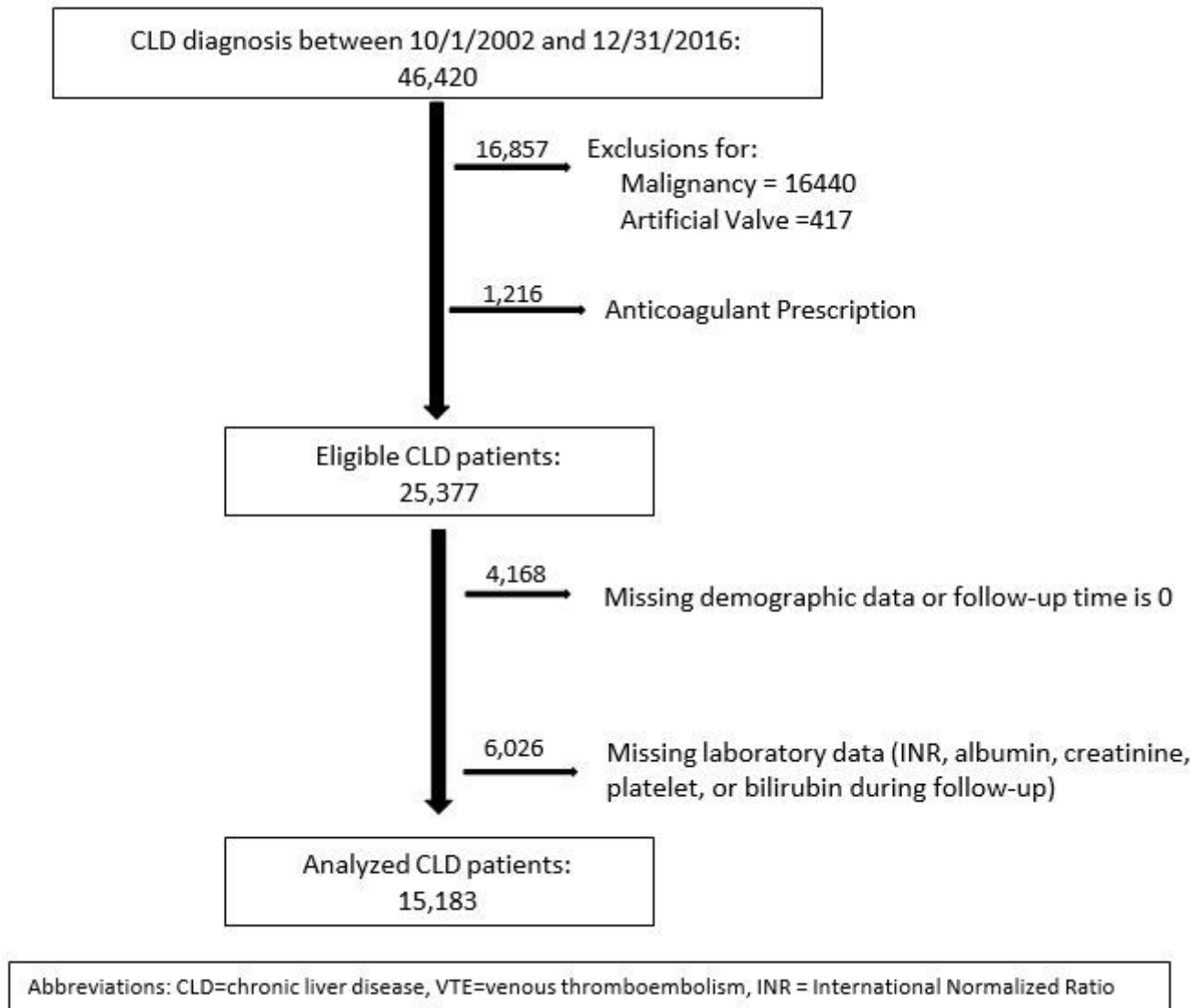
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## Figures



**Figure 1**

CONSORT Diagram

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