Precipitation of Occult Lymphomatous Hemorrhage by Early Initiation of Factor Xa Inhibitors: A Pharmacovigilance Case Study and Critical Reappraisal of DOAC Safety

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A B S T R A C T

Background: The concurrent management of cancer-associated thrombosis (CAT) and active malignancy represents a precarious clinical equilibrium, particularly when the neoplasm involves occult extranodal gastrointestinal (GI) sites. While direct oral anticoagulants (DOACs) have largely supplanted low-molecular-weight heparin (LMWH) as the standard of care for CAT, emerging pharmacovigilance data suggest a specific vulnerability in patients with luminal GI malignancies. **Case presentation:** We report the case of a 76-year-old frail female presenting with extensive left iliofemoral deep vein thrombosis (DVT). Diagnostic evaluation identified a perfect storm of pathology: Stage IV diffuse large B-cell lymphoma (DLBCL) with bulky retroperitoneal lymphadenopathy encasing the inferior vena cava (IVC) and a suspicious infiltrative mass in the proximal jejunum. Following standard guidelines, the patient was initiated on rivaroxaban. However, this intervention precipitated a catastrophic upper GI hemorrhage (hemoglobin drop to 6.5 g/dL) within 96 hours. A retrospective pharmacokinetic audit revealed critical predisposing factors: severe hypoalbuminemia (1.6 g/dL) increasing the free drug fraction, and an estimated glomerular filtration rate (eGFR) <30 mL/min, suggesting the patient was effectively overdosed relative to her physiological clearance. **Conclusion:** The empiric use of rivaroxaban in elderly patients with uncharacterized abdominal masses, renal impairment, and cachexia carries unacceptable hemorrhagic risks. We advocate for a systematic bleed-risk stratification protocol, prioritizing LMWH or Apixaban, and the judicious use of IVC filters as bridging therapies in high-risk phenotypes.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) stands as the most prevalent histological subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 40% of cases globally. Characterized by the aggressive, rapid proliferation of large, atypical B-lymphocytes, DLBCL is a systemic disease driven by complex molecular heterogeneity.[1] While lymphadenopathy is the cardinal feature, extranodal involvement occurs in up to 40% of patients, with the gastrointestinal (GI) tract—specifically the stomach and small bowel—being the most frequent site of extranodal disease. The clinical trajectory of DLBCL is often tumultuous, particularly in the geriatric population, where advanced-stage disease frequently co-exists with significant physiological frailty, sarcopenia, and cardiovascular comorbidities.[2]

A major driver of morbidity and mortality in DLBCL is cancer-associated thrombosis (CAT).[3] Patients with hematologic malignancies possess a markedly elevated risk for venous thromboembolism (VTE), estimated between 10% and 15%. This prothrombotic

state is multifactorial, driven by a complex interplay of tumor-mediated cytokine release (particularly Interleukin-6 and tumor necrosis factor-alpha), the constitutive expression of tissue factor by malignant B-cells, and the mechanical compression of major vasculature by bulky tumor masses.[4] The biology of lymphoma-associated thrombosis differs significantly from solid tumors, often involving a higher degree of systemic inflammatory activation and direct vascular invasion.[5]

The therapeutic landscape for CAT has undergone a paradigm shift over the last decade.[6] Direct oral anticoagulants (DOACs), such as rivaroxaban and apixaban, have largely replaced low-molecular-weight heparin (LMWH) as the first-line therapy, endorsed by major guidelines including the NCCN and ASCO. The appeal is clear: fixed oral dosing eliminates the burden of daily injections and laboratory monitoring. However, this shift has introduced new complexities. Pivotal clinical trials, such as SELECT-D (rivaroxaban) and CARAVAGGIO (apixaban), have signaled a "safety warning" regarding the use of factor Xa inhibitors in patients with luminal GI malignancies, citing increased rates of mucosal bleeding. Furthermore, these trials often excluded hemodynamically unstable patients or those with severe renal impairment, leaving a knowledge gap regarding the safety of these agents in "real-world," frail, elderly populations where polypharmacy and organ dysfunction are the norm.[7]

A critical, often overlooked nuance in these guidelines is the distinction between specific DOAC agents. While often grouped as a class, rivaroxaban (a once-daily agent with high peak plasma concentrations) and apixaban (a twice-daily agent with a lower peak-to-trough variance) possess distinct pharmacokinetic profiles that may influence bleeding risk in fragile mucosa.[8] Additionally, the impact of paraneoplastic cachexia—specifically severe hypoalbuminemia—on the protein binding and free-fraction availability of these drugs remains under-discussed in clinical practice.[9] The initiation of high-intensity anticoagulation in a patient with an undiagnosed, friable mucosal tumor represents a high-stakes clinical decision that requires precision beyond simple algorithmic compliance.[10]

This manuscript presents a detailed pharmacovigilance analysis of a case where standard anticoagulation precipitated life-threatening hemorrhage in a patient with occult jejunal lymphoma. The novelty of this study lies in its granular dissection of the intersection between occult malignancy, clinical pharmacokinetics (renal function and protein binding), and hemodynamic management. We aim to challenge the one-size-fits-all approach to anticoagulation in oncology, proposing a novel, integrated risk-stratification model that prioritizes pharmacokinetic suitability and mechanical prophylaxis (IVC filters) over empiric chemical anticoagulation in patients with radiologically ambiguous abdominal masses and metabolic frailty.

2. Case Presentation

The clinical narrative begins with the presentation of a 76-year-old female to the Emergency Department of Wangaya Regional General Hospital, driven by a chief complaint of painful, progressive swelling in her left lower extremity that had relentlessly worsened over a duration of two weeks. While the presenting complaint initially appeared vascular in nature, the surrounding history painted a portrait of a patient in a state of profound, chronic physiological decline. Concurrently with the acute limb symptoms, the patient reported a five-month history of a painless, progressively enlarging mass located in the left cervical region. She had initially neglected this mass, a common phenomenon in geriatric oncology where the absence of pain often leads to a delay in health-seeking behavior, allowing the malignancy to advance unchecked to a stage of substantial systemic burden. A review of her systems and past medical history was conducted to establish the baseline host factors. This inquiry revealed a critical, yet previously uninvestigated, historical detail that would later prove to be the linchpin of the catastrophic event reported herein. The patient disclosed a hospitalization several months prior for an episode of melena—black, tarry

stools indicative of upper gastrointestinal hemorrhage—which was severe enough to necessitate a blood transfusion to maintain hemodynamic stability. Regrettably, due to reasons likely compounded by her frailty and perhaps economic or social constraints, no definitive etiology was established at that time. Crucially, no endoscopic evaluation, such as esophagogastroduodenoscopy (EGD) or colonoscopy, had been performed. This history of "transfusion-dependent melena of unknown origin" served as a silent but ominous harbinger of the underlying fragility of her gastrointestinal mucosal integrity, a factor that remained dormant until provoked by therapeutic intervention. Her medical background was further complicated by a constellation of chronic cardiovascular comorbidities, establishing her as a frail host with limited physiological reserve. She carried established diagnoses of coronary artery disease (CAD) and congestive heart failure (CHF), conditions that predisposed her to venous stasis and altered hepatic perfusion. Her pharmacologic regimen was extensive, consisting of Atorvastatin for lipid management, Nitrokaf (Nitroglycerin) for ischemic symptom control, Spironolactone and Bisoprolol for heart failure management, and Candesartan for afterload reduction. A critical component of the medication reconciliation process involved the verification of antiplatelet usage. It was confirmed that despite her history of coronary artery disease, she was not currently prescribed antiplatelet therapy such as aspirin or clopidogrel. This absence of dual-antiplatelet therapy was a vital piece of data, as it ruled out the synergistic effect of antiplatelet and anticoagulant agents as a potential confounder for the subsequent bleeding risk. Functionally, the patient was severely compromised, meeting the criteria for an ECOG Performance Status of Grade 3. She was capable of only limited self-care and was confined to bed or chair for more than 50% of her waking hours, a level of immobility that significantly exacerbated her risk for venous thromboembolism through the mechanism of venous stasis, detailed in Figure 1.
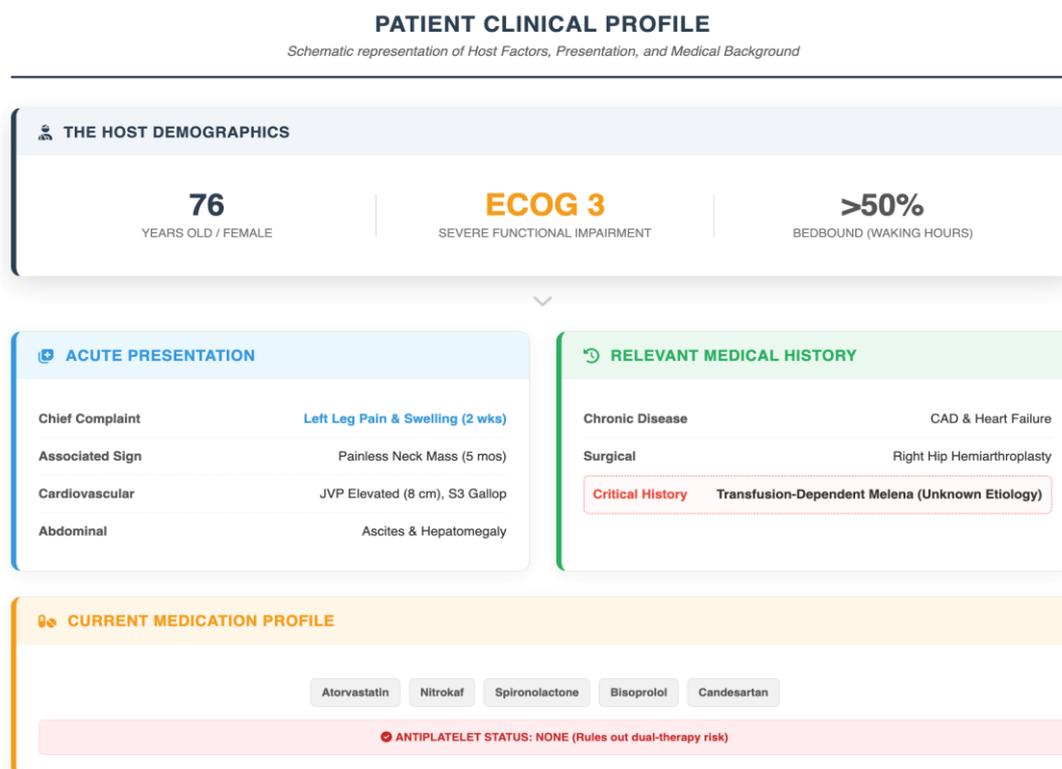

Figure 1. Patient clinical profile.

Upon admission, the patient's physical presentation was that of a frail, elderly woman in mild but evident distress, exhibiting the cachectic features often associated with advanced malignancy. Her general inspection revealed visible conjunctival pallor, a physical sign correlating with significant anemia and chronic disease burden. The cardiovascular assessment provided evidence of decompensated heart failure, which complicated the clinical picture of her edema. Evaluation of the jugular venous pressure (JVP) revealed an elevation estimated at 8 cm H2O, indicating transmitted right heart strain or volume overload. Auscultation of the precordium demonstrated a displaced point of maximal impulse, consistent with cardiomegaly, and a regular rhythm characterized by an audible S3 gallop. This third heart sound, pathological in an elderly patient, suggested ventricular non-compliance and volume overload, reinforcing the diagnosis of uncompensated heart failure. Pulmonary auscultation further corroborated this, revealing fine bibasilar crackles indicative of pulmonary venous congestion. The abdominal examination yielded findings that pointed toward significant intra-abdominal pathology beyond simple heart failure. The abdomen was distended, and the presence of ascites was confirmed by a positive shifting dullness test. While ascites can be a feature of right-sided heart failure, the degree of distension raised suspicion for malignant ascites or peritoneal involvement. Palpation revealed hepatomegaly, with the liver edge felt approximately 3 cm below the right costal margin. This hepatomegaly presented a differential diagnostic challenge, potentially representing hepatic congestion secondary to heart failure, or alternatively, hepatic infiltration by a neoplastic process. The most striking and clinically urgent findings, however, were related to the lymphatic and vascular systems, confirming the suspicion of advanced lymphoproliferative disease and acute vascular compromise. In the left cervical region, a large mass measuring approximately 5 cm by 4 cm was palpable. The mass was firm, fixed to underlying structures, and non-tender, characteristics classically associated with malignancy rather than infectious lymphadenitis. The examination of the left lower extremity confirmed the chief complaint, exhibiting the classic and florid signs of massive venous outflow obstruction. There was significant pitting edema extending from the foot up to the thigh, markedly asymmetrical compared to the contralateral limb. The leg was erythematous and warm to the touch, indicating acute inflammation associated with thrombosis. Deep palpation elicited tenderness over the calf muscles and the femoral vein trajectory. A Homan's sign was elicited and was positive; while this test is historically noted to have low sensitivity and specificity, in the context of this florid presentation, it served to reinforce the clinical probability of deep vein thrombosis (DVT), detailed in Figure 2.

A comprehensive diagnostic workup was initiated to characterize the extent of the thrombosis, the nature of the malignancy, and the patient's baseline metabolic function. The initial laboratory analysis revealed a hematologic triad consistent with a chronic, aggressive inflammatory state: anemia with a hemoglobin of 8.0 g/dL, leukocytosis with a white blood cell count of 14,760/μL, and reactive thrombocytosis with a platelet count of 405,000/μL. The coagulation profile was notable for a critically elevated D-dimer level of 2696.8 ng/mL, a value far exceeding the normal threshold, confirming a massive, ongoing thrombotic burden and active fibrinolysis. However, a retrospective forensic audit of the admission biochemical profile highlights two critical values that were clinically underestimated at the time of anticoagulation initiation, representing the "hidden" risk factors in this case. First, the evaluation of renal function showed a serum creatinine of 1.3 mg/dL. In isolation, this value may appear only mildly elevated. However, when integrated into the context of geriatric pharmacology, it represented significant renal impairment. Utilizing the Cockcroft-Gault equation for a 76-year-old female with an estimated weight of 50 kg—an estimation consistent with her frail, sarcopenic description—the estimated creatinine clearance (CrCl) was calculated to be approximately 29 mL/min.

SYSTEMIC ASSESSMENT MAP

Comprehensive breakdown of clinical findings by organ system

Neck (Left):
Firm, Fixed Mass (5x4cm)
Suspicious for Malignancy

Cardiopulmonary:
S3 Gallop, Crackles
Decompensated Failure

Abdomen:
Ascites & Hepatomegaly
Congestion vs. Infiltration

Left Leg (CRITICAL):
Massive Edema, Erythema
Venous Outflow Obstruction

GENERAL SURVEY

Frailty & Cachexia
Patient appeared frail with diminished physiological reserve, consistent with chronic malignancy.

Conjunctival Pallor ANEMIA
Visible pallor indicating significant anemia (Hgb 8.0 g/dL) and chronic disease burden.

CARDIOVASCULAR & PULMONARY

S3 Gallop & Displaced PMI
Pathological third heart sound indicating ventricular non-compliance and volume overload.

Bibasilar Crackles
Fine crackles at lung bases indicative of pulmonary venous congestion (Left Heart Failure).

Elevated JVP (8 cm H2O)
Sign of right heart strain or transmitted volume overload.

ABDOMINAL ASSESSMENT

Ascites (Shifting Dullness)
Confirmed fluid wave. Differential: Cardiac cirrhosis vs. Peritoneal malignancy.

Hepatomegaly
Liver edge palpable 3cm below costal margin. Indicates congestion or infiltration.

LYMPHATIC & VASCULAR (CRITICAL FINDINGS)

Cervical Mass (Left)
5 x 4 cm, Firm, Fixed, Non-tender.
Classic presentation of lymphomatous involvement.

Left Leg DVT Signs URGENT
- Massive asymmetric edema (Thigh to Foot)
- Erythema and Calor (Heat)
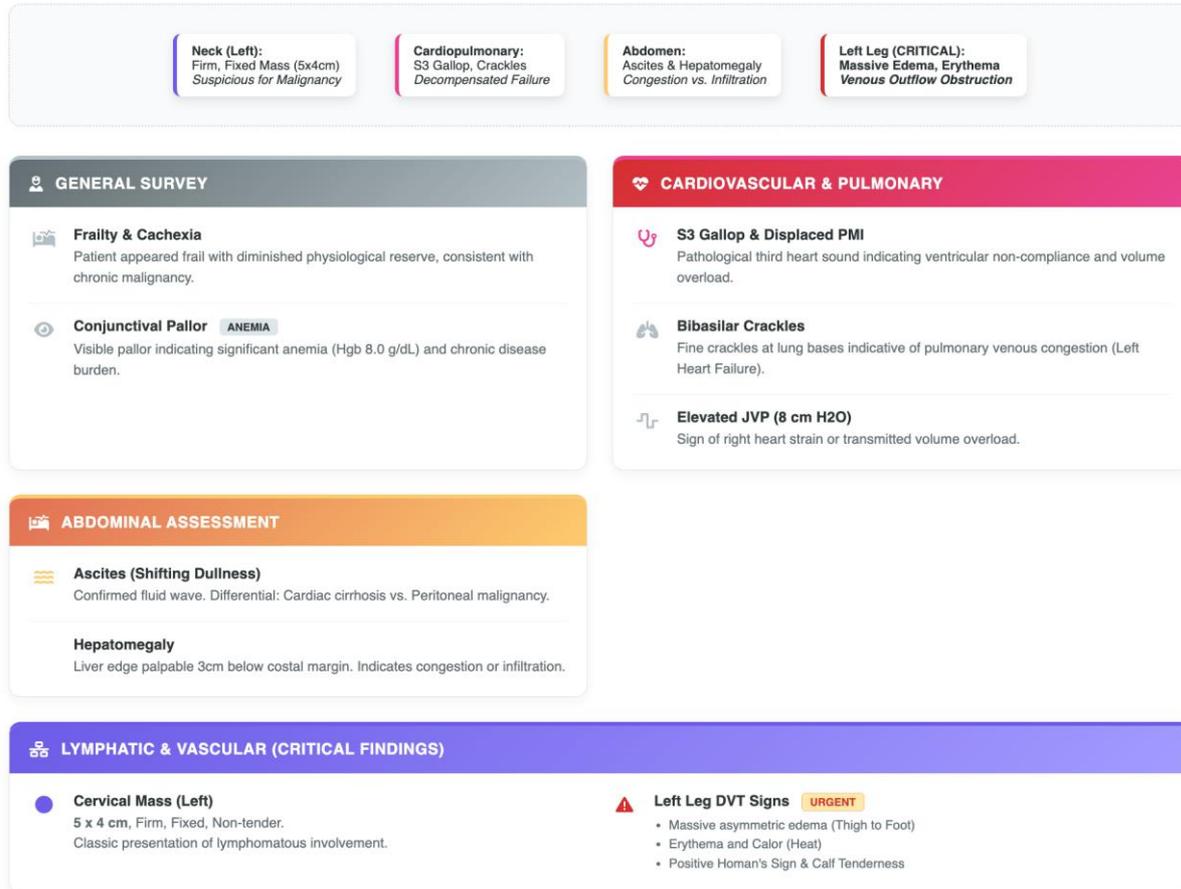- Positive Homan's Sign & Calf Tenderness

Figure 2. Systemic assessment map.

This places the patient in the category of severe renal impairment (CKD Stage 4 equivalent), a critical threshold for the dosing of renally cleared medications. Second, the nutritional assessment revealed severe hypoalbuminemia, with a serum albumin level of 1.6 g/dL. This value indicated profound malnutrition and a chronic catabolic state driven by the malignancy. From a pharmacological perspective, this was a vital finding, as albumin is the primary carrier protein for many drugs, including rivaroxaban. Such severe hypoalbuminemia implies a significant reduction in plasma protein-binding capacity, theoretically leading to higher concentrations of the free, biologically active drug fraction. Imaging studies were pivotal in establishing the definitive anatomic diagnoses and explaining the mechanism of the DVT. Doppler Ultrasonography of the left lower extremity was performed first, confirming the clinical suspicion of extensive acute DVT. The study visualized non-compressible echogenic material—thrombus—occluding a massive segment of the deep venous system, involving the common femoral, deep femoral, superficial femoral, popliteal, and tibial veins. To delineate the etiology of the DVT and the nature of the cervical mass, a Multi-Slice Computed Tomography (MSCT) of the abdomen with intravenous contrast was performed. This imaging modality unveiled the "occult" pathology that would later drive the hemorrhagic complications. The scan identified an irregular, circumferential

thickening of the proximal jejunum, spanning a length of 9.1 cm, accompanied by proximal luminal dilation. This radiographic appearance, characterized by wall thickening without complete obstruction, was highly suspicious for primary small bowel lymphoma. Furthermore, the scan revealed the mechanical cause of the DVT: bulky lymphadenopathy in the retroperitoneum. Extensive paraaortic, paracaval, and mesenteric nodes were seen encasing the abdominal aorta and, critically, the inferior vena cava (IVC). This "iliocaval syndrome" resulted in partial stenosis of the IVC lumen due to extrinsic compression, creating a hemodynamic dam that prevented venous return from the lower extremities. Additionally, the scan confirmed extravascular signs of advanced disease, including bilateral pleural effusions and the previously noted significant ascites. To obtain a tissue diagnosis, a fine needle aspiration biopsy (FNAB) was performed on the accessible left cervical mass. Cytopathological examination of the aspirate revealed a highly cellular specimen composed of a monomorphous population of large, atypical lymphoid cells. These cells exhibited vesicular chromatin and prominent nucleoli, arranged in a diffuse pattern. These cytomorphological findings were diagnostic of Diffuse Large B-Cell Lymphoma (DLBCL), confirming the aggressive nature of the systemic malignancy, detailed in Figure 3.

LABORATORY AND IMAGING FINDINGS

Figure 3. Laboratory and imaging findings.

The therapeutic management of this patient involved a dynamic and ultimately perilous response to evolving complications. The initial strategy was directed toward the immediate management of the massive DVT to prevent the potentially fatal complication of pulmonary embolism. Upon admission (Days 1-2), the patient was started on a bridging regimen of subcutaneous unfractionated heparin at a dose of 5000 IU twice daily. This initial choice allowed for a degree of flexibility and rapid reversibility while the diagnostic workup was being completed.

On Day 3, following the confirmation of the DVT and the establishment of the DLBCL diagnosis, the decision was made to transition the patient to oral anticoagulation to facilitate long-term management. Following current standard guidelines for the treatment of cancer-associated thrombosis (CAT), specifically those from the NCCN, which endorse direct oral anticoagulants (DOACs), the patient was switched to Rivaroxaban. She was initiated on the standard acute-phase loading dose of 15 mg twice daily. This therapeutic decision, while compliant with general algorithms for DVT treatment, failed to account for the specific pharmacokinetic vulnerabilities of this patient phenotype—specifically the combination of occult jejunal pathology, severe renal impairment, and hypoalbuminemia. The consequences of this intervention manifested rapidly. Within 96 hours of initiating the high-dose oral factor Xa inhibitor (Day 4), the patient suffered a catastrophic adverse event. She developed massive melena, passing copious amounts of black, tarry stool, accompanied by signs of hemodynamic instability. Urgent laboratory testing revealed a precipitous drop in hemoglobin from the admission baseline of 8.0 g/dL to a critical level of 6.5 g/dL. This signaled a major upper gastrointestinal hemorrhage. The timing of the bleed, occurring shortly after the introduction of the potent oral anticoagulant, strongly implicated the drug as the precipitating factor that unmasked the fragility of the underlying jejunal lymphoma. The emergency response was immediate. Rivaroxaban was permanently discontinued. The patient was managed aggressively with a protocol for major upper GI bleeding, receiving an intravenous bolus of pantoprazole (80 mg) followed by a continuous infusion at 8 mg/hour to stabilize clot formation via gastric acid suppression, alongside oral sucralfate suspension. To restore oxygen-carrying capacity and hemodynamic stability, she was transfused with two units of packed red blood cells (PRBCs), with furosemide premedication to prevent volume overload given her history of heart failure. A critical juncture in the case occurred regarding the definitive management of the bleeding source. An esophagogastroduodenoscopy (EGD) was strongly recommended by the medical team to visualize the bleeding site and potentially perform endoscopic hemostasis. However, the patient and her family refused the procedure, likely due to the patient's frailty and fear of invasive interventions. Consequently, a definitive endoscopic visualization of the bleeding vessel was not achieved. This refusal left the diagnosis of "jejunal lymphoma hemorrhage" as a clinical and radiographic diagnosis of exclusion. While the jejunal mass identified on CT was the most probable source due to the nature of lymphomatous neovasculature, the differential diagnosis theoretically included variceal bleeding secondary to portal hypertension (suggested by ascites and hepatomegaly), though the specific imaging findings of the jejunal mass made the tumor the primary suspect. Following the cessation of anticoagulation and the administration of blood products, the bleeding clinically resolved over Days 6 and 7. The patient remained hemodynamically stable, and her hemoglobin stabilized post-transfusion. The final therapeutic plan required a complex multidisciplinary consensus. Given the "fatal paradox" where anticoagulation was contraindicated due to the recent life-threatening bleed, yet the DVT posed a risk of PE, the decision was made to prioritize the treatment of the underlying malignancy. The rationale was that systemic chemotherapy would act as the ultimate hemostatic and antithrombotic agent by shrinking the tumor burden. Thus, on Day 8, the patient was scheduled for the initiation of the R-CHOP

chemotherapy regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), proceeding without concurrent anticoagulation and accepting the thrombotic risk in favor of preventing further exsanguination, detailed in Figure 4.

THERAPEUTIC INTERVENTIONS: THE PRECIPITATION OF CRISIS
Timeline of clinical management, adverse event, and emergency response

ADMISSION — Day 1-2
Status: Extensive DVT Confirmed
Action: Initiated bridging anticoagulation.
Subcutaneous Heparin 5000 IU BID

TRANSITION TO ORAL — Day 3
Decision: Switch to standard DOAC loading dose.
Rivaroxaban 15 mg BID
(Guideline compliant, but high risk for this phenotype)

⚠ ADVERSE EVENT — Day 4
Event: Massive Melena
Lab Critical: Hemoglobin drop 8.0 → **6.5 g/dL**
STOP RIVAROXABAN IMMEDIATELY
Emergency Rx: IV Pantoprazole + Sucralfate

STABILIZATION — Day 5-7
Resuscitation: Transfusion of 2 units PRBCs
Status: Hemodynamically Stable. Bleeding Controlled.
Patient Refused Endoscopy

FINAL PLAN — Day 8+
Diagnosis: Stage IV DLBCL
Strategy: "Chemotherapy as Hemostat"
Initiate R-CHOP Protocol
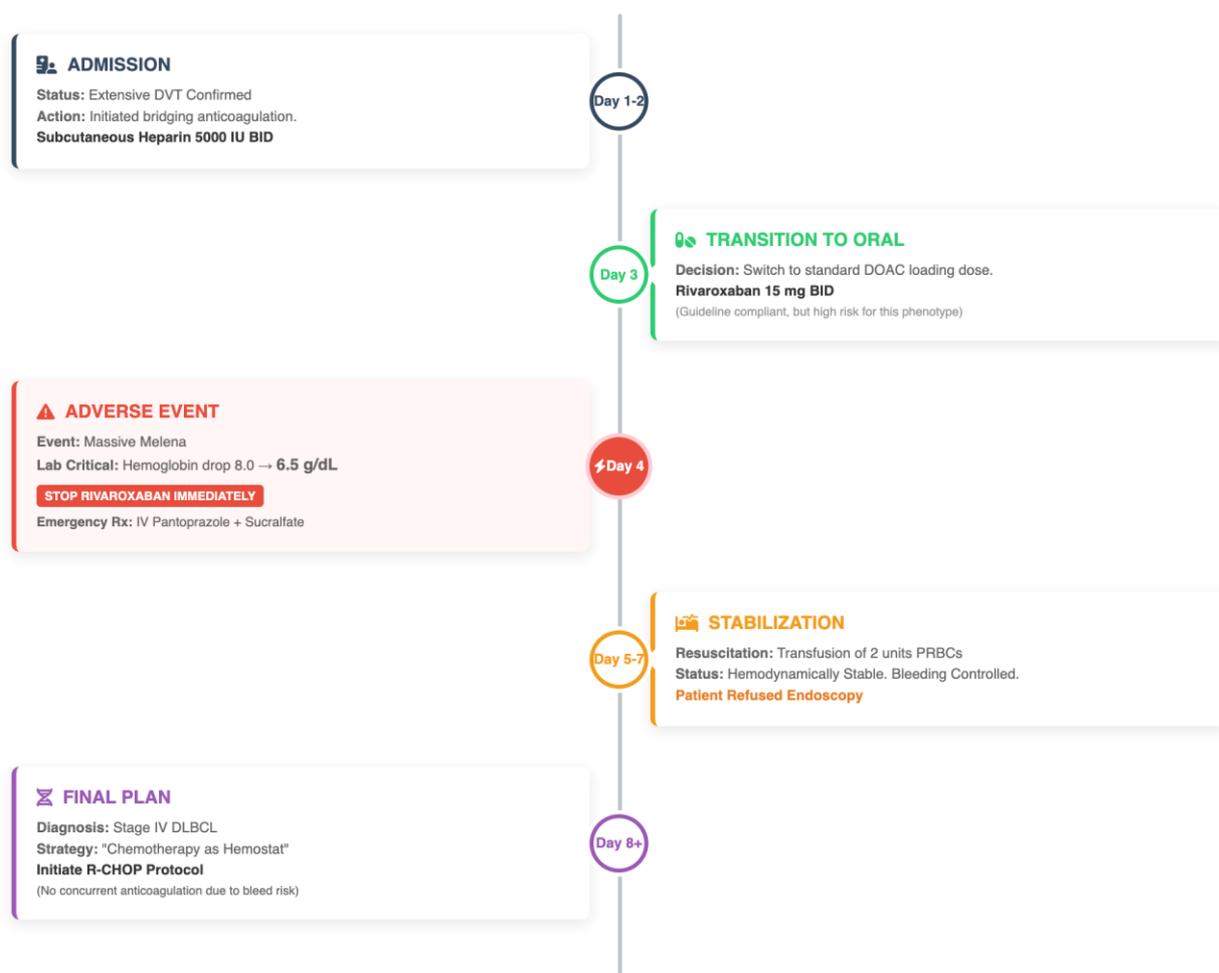(No concurrent anticoagulation due to bleed risk)

Figure 4. Therapeutic interventions: the precipitation of crisis.

3. Discussion

The clinical narrative presented in this case report transcends the traditional scope of a simple adverse drug event. It details a catastrophic convergence of three distinct pathological vectors: active high-grade malignancy, profound hypercoagulability, and fragile mucosal vascularity.[11] However, beyond the immediate pathology, this case serves as a stark illustration of pharmacokinetic failure and the limitations of rigidly applying general clinical practice guidelines to the nuanced physiology of geriatric oncology patients. The development of extensive deep vein thrombosis (DVT) in this patient was not a stochastic or random event but the deterministic result of a "perfect storm" of prothrombotic mechanisms inherent to advanced diffuse large B-cell

lymphoma (DLBCL).[12] We observed a complete fulfillment of Virchow's Triad, amplified by the specific and aggressive biology of the lymphoma. Figure 5 illustrates the multidimensional Perfect Storm that culminated in the catastrophic clinical outcome observed in this case. The schematic is conceptually divided into three hierarchical layers: the pre-existing disease biology (The Vectors), the specific patient vulnerability (The Substrate), and the precipitating intervention (The Trigger).[13] The upper tier of the schematic dissects the components of Virchow's Triad as they specifically manifest in advanced diffuse large B-cell lymphoma (DLBCL). The Mechanical Vector (Hemodynamic Stasis) is characterized by the iliocaval syndrome. The schematic visualizes how bulky retroperitoneal lymphadenopathy exerts extrinsic compression on the inferior vena cava (IVC). This mechanical obstruction creates a physical dam, leading to a precipitous drop in venous flow velocity and stasis in the lower extremities, forming the nidus for deep vein thrombosis. The systemic vector (Hypercoagulability) represents the biochemical engine of thrombosis. It highlights the Cytokine Storm (IL-6, TNF-alpha) driven by the high-grade malignancy. These cytokines act systemically to downregulate natural anticoagulants (Protein C/S) while the tumor cells constitutively express tissue factor, driving a relentless prothrombotic state quantified by the massive D-dimer elevation (~2700 ng/mL). The local vector (Endothelial Injury) is often overlooked but critical. It depicts the direct invasion of vascular structures by the tumor and the hypoxic activation of the endothelium, creating a raw, adhesive surface that promotes clot propagation.[14] Central to the figure is the unique anatomical pathology of the patient's gastrointestinal tract. It highlights the Occult Jejunal Mass (9.1 cm). Crucially, the description focuses on the concept of Aberrant Angiogenesis. Unlike healthy tissue, the lymphoma-infiltrated jejunum is supplied by friable, immature neovasculature that lacks a muscular coat. This aneurysmal growth pattern allows the tumor to expand silently without obstruction, hiding a fragile

vascular network that is prone to rupture. The lower tier visualizes the fatal interaction between the drug and the host's physiology. It frames Rivaroxaban not just as a medication, but as a stress test that the patient's physiology failed. Renal clearance failure underscores the calculated eGFR of ~29 mL/min, a critical value often masked by a normal serum creatinine in sarcopenic elderly patients. This impairment led to the accumulation of the drug to supratherapeutic levels. Protein binding failure connects severe hypoalbuminemia (1.6 g/dL) to pharmacokinetics. With insufficient albumin to bind the drug, the free fraction (biologically active drug) increased disproportionately, effectively overdosing the patient even at standard dosages. Direct mucosal contact identifies the local effect of the active oral drug eroding the already fragile, aberrant vessels of the jejunal mass. Figure 5 culminates in a unified outcome: Catastrophic Hemorrhage. This is not presented as an accidental side effect, but as the inevitable deterministic result of applying a potent anticoagulant (The Trigger) to a fragile anatomical substrate (The Occult Mass) in a patient with compromised metabolic clearance (The Host Factors).[15]

The multi-slice computed tomography (MSCT) findings revealed a critical anatomical disruption: massive retroperitoneal lymphadenopathy encasing the inferior vena cava (IVC) and iliac veins. This phenomenon, often termed iliocaval syndrome, creates a physical dam that significantly impedes venous return from the lower extremities. As the lumen of the IVC was stenosed by extrinsic tumor compression, the velocity of blood flow decreased precipitously. According to fluid dynamics principles, specifically the Bernoulli principle and Poiseuille's law, this stasis creates zones of low shear stress within the deep femoral and popliteal veins. These stagnant pools are ideal environments for the accumulation of activated clotting factors and platelets, protecting them from the natural washout effect of laminar flow and leading to fibrin deposition and thrombus propagation.

THE PATHOPHYSIOLOGICAL "PERFECT STORM"

Schematic representation of the convergence of Disease Biology, Anatomy, and Pharmacokinetics

HEMODYNAMIC STASIS
(MECHANICAL VECTOR)

- "Iliocaval Syndrome"
- Bulky Retroperitoneal Nodes
- IVC Compression & Stenosis
- Reduced Venous Velocity

HYPERCOAGULABILITY
(SYSTEMIC VECTOR)

- Cytokine Storm (IL-6, TNF-α)
- Tissue Factor Expression
- Downregulation of Protein C/S
- D-Dimer: ~2700 ng/mL

THE "OCCULT" SUBSTRATE
(ANATOMICAL VULNERABILITY)

- Jejunal Infiltration (9.1 cm)
- "Aneurysmal" Growth Pattern
- **Aberrant Angiogenesis**
- Friable, Immature Vessels

THE PHARMACOKINETIC TRIGGER
(INTERACTION: RIVAROXABAN + FRAIL HOST)

eGFR ~29	Alb 1.6	Direct Contact
RENAL CLEARANCE FAILURE	PROTEIN BINDING FAILURE	MUCOSAL EROSION
Leading to Drug Accumulation	Increased Free Drug Fraction	Active Drug in Lumen

CATASTROPHIC HEMORRHAGE
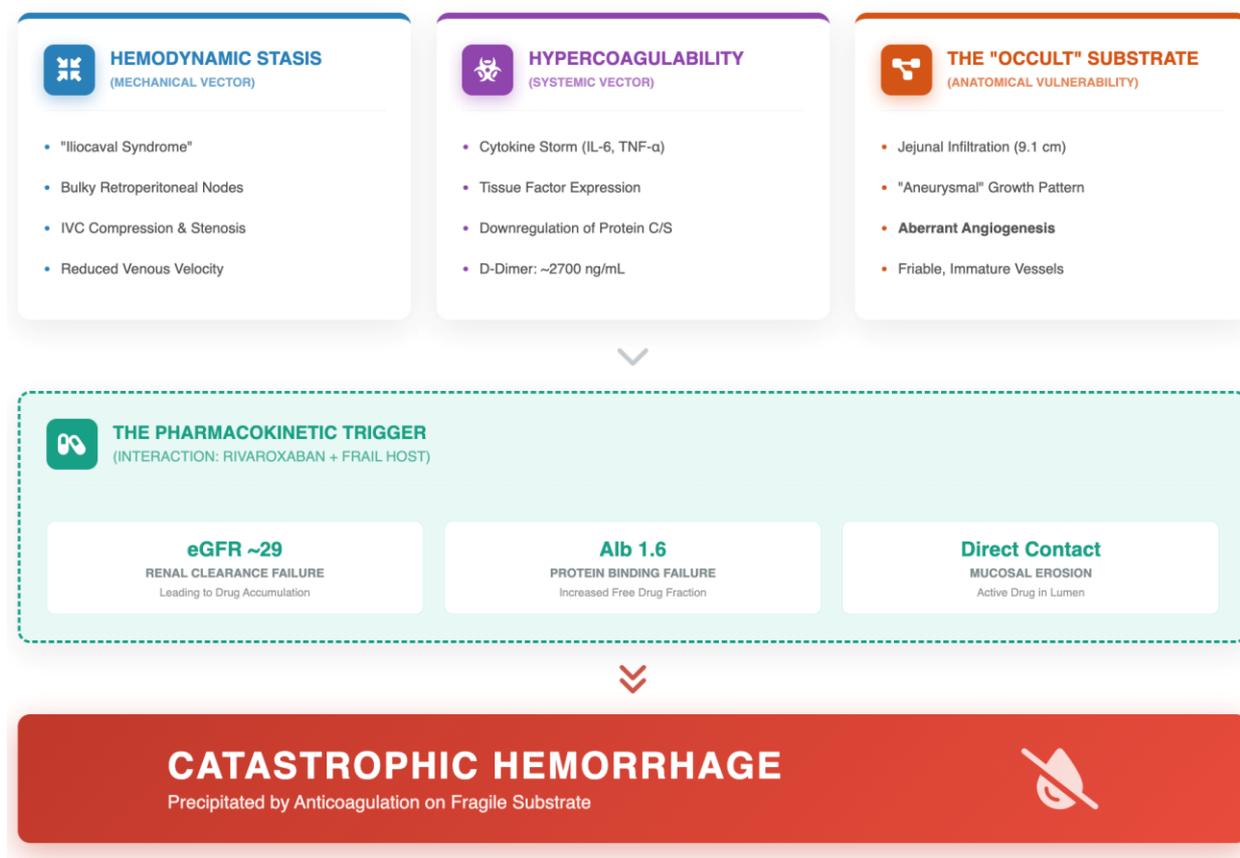Precipitated by Anticoagulation on Fragile Substrate

Figure 5. Pathophysiology related study findings.

In such cases of mechanical obstruction, chemical anticoagulation alone is often insufficient because it addresses the clotting cascade but not the hydrostatic obstruction.[16] The thrombus in this patient was likely a mix of acute fibrin-rich clot and older, organized material, reflecting the chronicity of the external compression.

The cytokine cascade of DLBCL is biologically potent and inherently thrombogenic. The patient's elevated lactate dehydrogenase (LDH) and leukocytosis reflect a high tumor burden and rapid cell turnover. Malignant B-cells do not merely occupy space; they are metabolically active factories of thrombosis. They constitutively express tissue factor (TF), the primary initiator of the extrinsic coagulation cascade. Furthermore, aggressive lymphomas secrete a milieu of inflammatory cytokines, primarily Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines exert a systemic effect on the liver and endothelium: they downregulate the synthesis of natural anticoagulant proteins (such as Protein C, Protein S, and Antithrombin III) and simultaneously upregulate the production of acute-phase reactants like fibrinogen and factor VIII. The patient's D-dimer level of nearly 2700 ng/mL serves as a quantitative biomarker of this aggressive fibrinolytic overdrive and ongoing thrombin generation. This systemic hypercoagulability means that the patient's blood was primed to clot, requiring higher-than-standard levels of anticoagulation to achieve

therapeutic efficacy, yet this very requirement clashed with her bleeding risk.[17]

While there was no history of recent trauma, the invasion of the vascular adventitia by direct tumor extension creates a raw, thrombogenic surface. Additionally, the hypoxic microenvironment induced by the massive tumor burden can lead to endothelial activation. Hypoxia-inducible factor 1-alpha (HIF-1α) upregulation in the tumor microenvironment promotes the expression of adhesion molecules (P-selectin, E-selectin) on the endothelial surface. This recruits platelets and leukocytes to the vessel wall, creating a self-perpetuating cycle of thrombosis that is resistant to standard therapy.[18] A critical finding in this study was the 9.1 cm circumferential thickening of the proximal jejunum. Primary gastrointestinal involvement in DLBCL often exhibits an "aneurysmal" pattern of growth—infiltrating the submucosa expansively without immediately occluding the lumen. This growth pattern allows the tumor to reach a significant size while remaining clinically "occult," presenting only with vague constitutional symptoms or intermittent bleeding, like the patient's historical melena.

The pathophysiology of bleeding in GI lymphoma is distinct from carcinoma and centers on aberrant angiogenesis.[19] Unlike normal physiologic vessels, the tumor neovasculature induced by lymphoma is tortuous, immature, and crucially, lacks the smooth muscle coat and pericyte coverage of normal arterioles. These vessels are exceptionally friable and prone to rupture. Furthermore, the tumor cells invade and erode the mucosal barrier, exposing these fragile vessels to the intraluminal environment. When the patient was subjected to systemic anticoagulation, specifically a potent direct inhibitor of factor Xa, like rivaroxaban, the delicate hemostatic plugs sealing these fragile micro-vessels were dissolved. The tumor vessels became the path of least resistance for blood loss, leading to the catastrophic hemorrhage observed on Day 4. The direct mucosal contact of the oral anticoagulant, combined with its systemic effect, likely exacerbated local tissue injury, turning a silent lesion into a life-threatening hemorrhage.

It is imperative to acknowledge a limitation in this study: the lack of endoscopic confirmation due to patient refusal. While the jejunal lymphoma is the most probable bleeding source given the CT findings, the patient's clinical signs of ascites and hepatomegaly raise the differential diagnosis of portal hypertension. It is theoretically possible that the bleeding originated from esophageal or gastric varices, which would also be exacerbated by anticoagulation. However, the specific finding of the jejunal mass on CT, combined with the history of melena, strongly implicates the lymphoma as the primary culprit. The distinction is critical because variceal bleeding requires different management (octreotide, banding) compared to tumor bleeding (radiation, chemotherapy).[20] Nevertheless, in the absence of endoscopy, the management strategy had to pivot to systemic control of the malignancy and cessation of the precipitating drug.

The decision to use Rivaroxaban 15 mg BID was the pivotal moment in this case. While guideline-compliant for general CAT, a forensic pharmacological analysis reveals why this specific regimen was hazardous for this specific patient phenotype. This failure highlights the gap between population-based guidelines and individualized precision medicine in geriatrics. Rivaroxaban relies significantly on renal excretion, with approximately 33% of the active drug being eliminated unchanged in the urine. In geriatric patients, serum creatinine is notoriously unreliable as a marker of renal function due to sarcopenia (low muscle mass). A frail, bedbound 76-year-old woman produces very little creatinine, masking significant renal impairment. While a creatinine of 1.3 mg/dL might appear only mildly elevated to the casual observer, our calculation of the eGFR using the Cockcroft-Gault equation revealed a value of approximately 29 mL/min. In the treatment of acute DVT, rivaroxaban labeling advises extreme caution in patients with CrCl < 30 mL/min. The use of the high-intensity loading dose (15 mg BID) in a patient with this level of renal impairment likely led to drug accumulation. As the kidneys failed to clear the drug

efficiently, the plasma concentration rose with each successive dose, eventually reaching supratherapeutic levels that vastly exceeded the therapeutic window necessary for anticoagulation. This accumulation pushed the patient into a hemorrhagic state, effectively turning a therapeutic dose into a toxic overdose.[17,18]

Rivaroxaban is a highly protein-bound drug (92-95%), binding primarily to serum albumin. This high protein binding acts as a reservoir, limiting the amount of free (pharmacologically active) drug in the circulation. This patient, however, had severe hypoalbuminemia (1.6 g/dL) due to cancer cachexia and chronic inflammation. In states of severe protein deficiency, the binding capacity of the plasma is saturated or reduced. This leads to a significant increase in the free fraction of the drug. For a drug with a narrow therapeutic index in high-risk patients, a doubling of the free fraction can have devastating consequences. This pharmacokinetic phenomenon implies that even if the total drug concentration was within standard limits, the active concentration was likely toxic. The combination of reduced clearance (low eGFR) and high free fraction (low albumin) created a "toxic pharmacokinetic environment" that standard guidelines do not adequately account for. This interaction is rarely discussed in clinical trials, which often exclude patients with severe malnutrition, yet it is a daily reality in oncology wards.

The introduction of DOACs as a monolithic class often obscures important differences between agents. Rivaroxaban is administered once daily (after the initial loading phase), which necessitates a higher peak plasma concentration to maintain efficacy over 24 hours. Apixaban, conversely, is administered twice daily, resulting in a flatter pharmacokinetic curve with lower peak-to-trough variance. Clinical trials reflect this difference. The CARAVAGGIO trial (Apixaban) showed non-inferiority to Dalteparin regarding major GI bleeding, whereas the SELECT-D trial (Rivaroxaban) showed a marked increase in GI bleeding compared to LMWH, particularly in esophageal and gastric cancers. Had a DOAC been

absolutely necessary, Apixaban (at a renally adjusted dose) might have offered a safer safety profile than Rivaroxaban for this fragile patient due to its metabolic profile (less reliance on renal excretion) and dosing schedule.

Following the hemorrhage, the patient faced a fatal paradox: anticoagulation was absolutely contraindicated due to active GI bleeding, yet the massive thrombus in the iliofemoral segment remained a lethal threat, capable of dislodging and causing a massive Pulmonary Embolism (PE). This scenario represents a classic, albeit controversial, indication for a retrievable Inferior Vena Cava (IVC) Filter. An IVC filter acts as a mechanical sieve, preventing large emboli from reaching the pulmonary circulation without exacerbating the GI bleeding. We acknowledge that the use of IVC filters is debated, with trials like PREPIC-2 showing mixed long-term survival benefits and risks of filter thrombosis. However, those trials largely focused on patients who *could* receive anticoagulation. In the acute setting of absolute contraindication to anticoagulation, guidelines still support their use as a bridging strategy. In developing nations like Indonesia, the logistics of filter retrieval can be challenging, creating a risk of long-term filter complications (such as IVC thrombosis or filter migration). Nonetheless, in this specific precipice scenario, the immediate risk of fatal PE outweighed the long-term risks of the device. An IVC filter would have allowed the team to aggressively resuscitate the patient and initiate chemotherapy with a safety net in place, effectively buying time for the mucosa to heal and the tumor to shrink.[19,20]

Ultimately, the pathophysiology of both the thrombosis and the hemorrhage in this patient was driven by the lymphoma. Therefore, the definitive treatment for both complications is not anticoagulation or embolization, but the eradication of the malignancy itself. The R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) is the gold standard for DLBCL. Rituximab: Targets CD20+ B-cells, inducing direct lysis. Cyclophosphamide/Doxorubicin:

Cytotoxic agents that rapidly debulk the tumor mass. Vincristine/Prednisone: Induces apoptosis and reduces peritumoral edema. While cytotoxic chemotherapy induces thrombocytopenia (increasing bleed risk), it is the only therapy capable of shrinking the retroperitoneal nodes (relieving the iliocaval compression and restoring venous flow) and healing the jejunal mucosa (stopping the bleed source). Thus, in this context, chemotherapy acts as the ultimate anticoagulant and hemostat. A staged approach— perhaps starting with a steroid pre-phase or reduced-intensity chemotherapy (R-miniCHOP)—might be necessary to stabilize the patient before full-dose R-CHOP, mitigating the risk of tumor lysis syndrome and profound pancytopenia in this frail host.

4. Conclusion

This case report serves as a rigorous pharmacovigilance signal regarding the use of Factor Xa inhibitors in the complex landscape of geriatric oncology. The convenience of oral therapy must never supersede the imperative for pharmacokinetic safety. Before initiating DOACs in elderly cancer patients, clinicians must calculate the eGFR (not just look at serum creatinine) and assess serum albumin. In patients with eGFR <30 mL/min or severe hypoalbuminemia (<2.0 g/dL), standard loading doses of rivaroxaban should be avoided due to the risk of drug accumulation and high free-fraction toxicity. In patients presenting with CAT and anemia, a thorough screening for occult GI malignancies is essential. If a luminal mass is suspected, LMWH or Apixaban are preferred over Rivaroxaban due to superior mucosal safety profiles supported by clinical trial data. In the precarious setting of active bleeding and proximal DVT, the IVC filter should be re-embraced not as a relic, but as a sophisticated bridging tool. Its use allows for the cessation of anticoagulation during the acute hemorrhagic phase while protecting the patient from fatal pulmonary embolism, providing a window for oncologic stabilization.

5. References

1. Kanazawa M, Sugaya T, Takenaka K, Tsuchida K, Tominaga K, Majima Y, et al. Diffuse large B-cell lymphoma identified during diagnostic testing for gastrointestinal bleeding. Prog Dig Endosc. 2019; 94(1): 93–5.

2. Kim MS, Park JH, Kim JY, Lim S-N, Lee J. Upper gastrointestinal bleeding caused by direct invasion of diffuse large B-cell lymphoma into the stomach in a patient with HIV infection: a case report. Medicine (Baltimore). 2019; 98(28): e16363.

3. Sunggoro AJ, Dwianingsih EK, Utomo BP, Purwanto I. A complicated case of diffuse large B-cell lymphoma in an elderly presenting with massive gastrointestinal bleeding successfully treated with R-mini CHOP. Case Rep Oncol. 2021; 14(1): 262–8.

4. Reis G, Nunes J, Gaspar N, Teixeira S, Espinheira M do C, Trindade E. Upper digestive tract bleeding as presentation of diffuse large B-cell lymphoma. J Pediatr Gastroenterol Nutr. 2023; 76(1): e20.

5. Cai J, Parnall T, Tomassetti S, Qing X. Diffuse large B-cell lymphoma presenting as postmenopausal bleeding. Clin Case Rep. 2023; 11(11): e8173.

6. Paglia H, Noriega M, Kher KR. Upper gastrointestinal bleeding secondary to gastric invasion by diffuse large B-cell lymphoma. Cureus. 2025; 17(10): e94594.

7. Amor Costa C, Fisac Vázquez J, Martín-Arranz MD. Diffuse large B-cell lymphoma and gastrointestinal Kaposi's sarcoma: a rare cause of upper gastrointestinal bleeding. Rev Esp Enferm Dig. 2025; 117(6): 338–9.

8. Lemoine J, Bachy E, Cartron G, Beauvais D, Gastinne T, Rubio MT, et al. Causes and risk factors of early and late non-relapse mortality after CD19 CAR T-cell therapy for diffuse large B-cell lymphoma (DLBCL): a Lysa study from the descar-T registry. Blood. 2022; 140(Suppl_1): 1859–61.

9. Rajic AS, Kogoj TK, Kocjan T. Addison's disease due to bilateral adrenal hemorrhage as the first presentation of diffuse large B-cell lymphoma. Endocr Abstr. 2018.

10. Rajic AS, Kogoj TK, Kocjan T. Addison's disease due to bilateral adrenal hemorrhage as the firstpresentation of diffuse large B-cell lymphoma. Endocr Abstr. 2018.

11. Duclaux-Loras R, Novak J, Belot A, Dijoud F, Heissat S, Bertrand Y, et al. Polymorphic gastric lesions and hemorrhage after first dose of chemotherapy in a child with diffuse large B-cell lymphoma. Clin Res Hepatol Gastroenterol. 2018; 42(3): 175–7.

12. Bureta C, Higa N, Makino R, Takajo T, Yonezawa H, Uchida H, et al. Diffuse large B-cell lymphoma of the central nervous system manifesting with intratumoral hemorrhage: a case report and literature review. World Neurosurg. 2020; 143: 490–4.

13. Torres F, Suárez U, Pizano P. Diffuse large B-cell lymphoma presenting as acute adrenal hemorrhage. Blood Res. 2025; 60(1): 18.

14. Punnachet T, Cressey TR, Apiwatnakorn P, Koonarat A, Norasetthada L, Tantiworawit A, et al. Pharmacodynamics of rivaroxaban and dabigatran in adults with diffuse large B-cell lymphoma receiving R-CHOP immunochemotherapy. Pharmaceutics. 2024 Oct 11; 16(10): 1319.

15. Katsura H, Hori T, Yamamoto H, Harada H, Yamamoto M, Yamada M, et al. Diffuse large B-cell lymphoma in the liver accompanied by primary biliary cholangitis: a rare and difficult-to-diagnose tumor with portal venous thrombosis. Int J Surg Case Rep. 2021; 82(105936): 105936.

16. Sağlam B, Albayrak M, Yıldız A, Tıplıoğlu P, Tığlıoğlu M, Aras MR, et al. The relationship between ferritin level and thrombosis in patients with diffuse large B-cell lymphoma. Hematol Transfus Cell Ther. 2022; 44: S31.

17. Cape HT, Gupta L, Blanchard CC, Raslau FD, Timoney PJ. Tumor versus bland thrombus: diffuse large B-cell lymphoma presenting as cavernous sinus and left superior ophthalmic vein thrombosis. Orbit. 2025; 44(3): 348–52.

18. Yokoyama K, Murata M, Ikeda Y, Okamoto S. Incidence and risk factors for developing venous thromboembolism in Japanese with diffuse large B-cell lymphoma. Thromb Res. 2012; 130(1): 7–11.

19. Abdel-Razeq H, Ma'koseh M, Mansour A, Bater R, Amarin R, Abufara A, et al. The application of the ThroLy risk assessment model to predict venous thromboembolism in patients with diffuse large B-cell lymphoma. Clin Appl Thromb Hemost. 2021; 27: 10760296211045908.

20. Hantrakun N, Phinyo P, Tantiworawit A, Rattarittamrong E, Chai-Adisaksopha C, Rattanathammethee T, et al. Incidence of venous thromboembolism and predictive ability of age-adjusted international prognostic index for prediction of venous thromboembolism in Asian patients with diffuse large B-cell lymphoma. J Thromb Thrombolysis. 2024; 57(3): 473–82.