MEDS Clinical Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2025.060521
ISSN 2616-1907 Vol. 6 Num. 5

Analysis of Risk Factors for Lower Extremity Deep Vein Thrombosis Following Surgery for Gynecological Malignancies

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Keywords: Deep Vein Thrombosis, Gynecological Malignancies, Surgery, Risk Factors, Thromboprophylaxis, Venous Thromboembolism

Abstract: Lower extremity deep vein thrombosis (LEDVT) represents a significant perioperative complication in patients undergoing surgical management of gynecological malignancies. Despite advances in surgical techniques, anesthesia, and perioperative care, the incidence of LEDVT remains substantial, ranging from 5% to 25% depending on patient characteristics, tumor type, and procedural factors. The present study aimed to systematically analyze the risk factors associated with LEDVT following gynecologic oncologic surgery by reviewing current literature and cohort studies. Key predictors identified include advanced age, obesity, high-stage ovarian cancer, prolonged operative time, significant intraoperative blood loss, extensive lymphadenectomy, perioperative transfusion, and insufficient prophylactic anticoagulation. This analysis underscores the necessity of individualized risk assessment, evidence-based thromboprophylaxis, and early postoperative mobilization to mitigate LEDVT incidence and improve patient outcomes.

1. Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of preventable morbidity and mortality in the postoperative period for patients with gynecological malignancies [1]. Lower extremity DVT (LEDVT) accounts for the majority of postoperative VTE events and is associated with substantial acute and long-term complications, including post-thrombotic syndrome, recurrent VTE, and pulmonary embolism, which may be fatal in certain cases [2].

Epidemiological studies indicate that LEDVT incidence after gynecologic oncology surgery varies from 5% to 25%, depending on tumor type, surgical extent, patient demographics, and prophylactic measures [3]. For example, in a multicenter cohort study involving 1,236 patients undergoing staging laparotomy for ovarian cancer, LEDVT occurred in 12.8% of patients, with 4.1% progressing to PE [4]. Endometrial cancer patients undergoing open hysterectomy with pelvic and para-aortic lymphadenectomy demonstrated an incidence of 6–12%, while cervical cancer patients undergoing radical hysterectomy and pelvic exenteration had a reported incidence of 4–10%, particularly in cases combined with chemoradiation [5].

The clinical consequences of LEDVT are profound. Acute manifestations include lower extremity swelling, pain, and risk of thrombus propagation leading to PE, which carries up to 30% mortality in massive events. Long-term sequelae encompass post-thrombotic syndrome, chronic venous insufficiency, recurrent VTE, and potential delays in adjuvant therapy, which can adversely affect oncologic outcomes [6].

Given these considerations, identifying perioperative risk factors is essential for targeted prophylaxis and early intervention. The present work provides a detailed, academically oriented analysis of LEDVT risk factors in patients undergoing surgery for gynecologic malignancies, integrating epidemiological evidence, mechanistic insights, surgical parameters, laboratory and imaging data, and perioperative management strategies.

2. Methods

2.1 Literature Search

A comprehensive literature review was conducted using PubMed, Embase, and Scopus databases from January 2000 to December 2024. Search terms included "gynecological malignancy," "ovarian cancer," "endometrial cancer," "cervical cancer," "surgery," "deep vein thrombosis," "venous thromboembolism," and "risk factors." Studies were limited to English-language publications involving adult patients undergoing surgical management of gynecologic malignancies.

2.2 Inclusion and Exclusion Criteria

- Inclusion criteria: Adult patients (≥18 years) undergoing primary or cytoreductive surgery for ovarian, endometrial, or cervical malignancy; studies reporting perioperative LEDVT incidence and associated risk factors; cohort studies, randomized controlled trials, and meta-analyses.
- Exclusion criteria: Non-surgical studies, studies including pregnant patients, benign gynecologic surgery only, case reports, and reviews lacking quantitative data.

2.3 Data Extraction and Analysis

Relevant data were extracted including patient demographics, tumor type and stage, surgical approach and duration, intraoperative blood loss, lymphadenectomy extent, perioperative transfusion, prophylactic anticoagulation regimen, laboratory and imaging markers, and postoperative LEDVT incidence [7]. Statistical methods reported in the original studies, such as univariate and multivariate logistic regression or Cox proportional hazards models, were used to identify independent risk factors. Odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs) were recorded where available.

3. Epidemiology

LEDVT prevalence following gynecologic oncologic surgery demonstrates considerable variability, influenced by patient demographics, tumor biology, and surgical factors.

- Ovarian cancer: Advanced-stage disease (FIGO III–IV) is associated with higher LEDVT incidence (10–20%), with higher risk among patients undergoing extensive cytoreductive procedures including bowel resection, diaphragmatic stripping, and splenectomy.
- Endometrial cancer: Incidence of 6–12% is observed in open hysterectomy with comprehensive pelvic and para-aortic lymphadenectomy, with minimally invasive approaches reducing incidence to 3–5%.

• Cervical cancer: Radical hysterectomy and pelvic exenteration, especially when combined with chemoradiation, result in LEDVT incidence of 4–10%.

Population-based studies suggest that Asian cohorts report lower LEDVT rates (5–8%), potentially reflecting lower BMI, differing surgical practices, prophylactic strategies, or genetic factors influencing thrombophilia.

4. Pathophysiology

LEDVT in gynecologic malignancy surgery is explained primarily through **Virchow's triad**:

1) Venous stasis: Prolonged lithotomy and Trendelenburg positions reduce lower extremity venous return. Postoperative immobility exacerbates stasis. Doppler studies indicate femoral vein flow velocity <10 cm/s in patients developing LEDVT.

2) Endothelial injury: Pelvic vessel dissection, lymphadenectomy, and vessel retraction induce endothelial trauma, enhancing platelet adhesion and local thrombin generation.

3) Hypercoagulability: Malignancy elevates tissue factor expression, inflammatory cytokines (IL-6, TNF-α), and procoagulant microparticles. Chemotherapy and hormonal therapy can further amplify coagulation activity. Laboratory correlates include elevated D-dimer (>2 μg/mL), fibrinogen (>4 g/L), shortened aPTT (<26 s), and elevated thrombin-antithrombin complex levels.

Genetic predisposition, including Factor V Leiden and Prothrombin G20210A mutation, though rare, may further enhance risk. LEDVT often occurs in proximal veins (femoral, popliteal, iliac) in high-risk patients, increasing the likelihood of pulmonary embolism.

5. Risk Factors

5.1 Patient-Related

• Age >60 years: OR 2.4 (95% CI 1.3–4.1) in multivariate analysis; decreased venous compliance and comorbidity prevalence contribute to risk.
• Obesity (BMI >30 kg/m ^{2}): OR 2.1; technical challenges and chronic inflammation play a role.
• Comorbidities: Hypertension, diabetes, cardiovascular disease increase risk 1.5–2-fold.
• History of VTE: OR 3.5–4.2.
• Genetic thrombophilia: Factor V Leiden, Prothrombin G20210A mutation, Protein C/S deficiency (4–8%)

5.2 Tumor-Related

• Advanced stage ovarian cancer (FIGO III–IV): HR 3.2 (95% CI 2.0–5.1)
• Clear cell carcinoma: Elevated tissue factor expression
• Tumor bulk >10 cm and ascites: Mechanical venous compression increases stasis

5.3 Surgery-Related

• Open laparotomy: 2.3-fold higher risk than laparoscopy/robotic surgery
• Operative duration >4 hours: OR 2.3 (95% CI 1.2–4.4)
• Blood loss >1000 ml and transfusion >4 units: OR 1.9–2.4
• Extensive lymphadenectomy (>25 nodes): HR 1.8

5.4 Perioperative Management

• Immobilization >48 hours: 2.7-fold risk increase

- Central venous catheter: HR 1.6
- Chemotherapy/hormonal therapy: Prothrombotic effect
- Inadequate prophylaxis: LEDVT incidence 12% vs 4% with extended LMWH

6. Risk Stratification Models

- Caprini score: Patients with scores ≥9 have LEDVT >15%; adapted models including tumor stage and operative time improve AUC to 0.82
- Khorana score: Underestimates perioperative risk; more relevant to medical oncology
- Novel models: Incorporating preoperative D-dimer, thrombin generation, and inflammatory markers

7. Clinical Outcomes

- Pulmonary embolism: 15–20% of untreated LEDVT; perioperative mortality 1–5%
- Post-thrombotic syndrome: 30–40%; chronic leg swelling, pain, pigmentation
- Recurrent VTE: 18–22% within 2 years, particularly with ongoing chemotherapy
- Impact on adjuvant therapy: Potential 1–2 week delay, affecting disease-free survival

8. Prevention and Management

8.1 Mechanical Prophylaxis

- Intermittent pneumatic compression (IPC): Reduces LEDVT by ~40%
- Graduated compression stockings (GCS): Complement IPC for distal protection

8.2 Pharmacologic Prophylaxis

- LMWH: Enoxaparin 40 mg SC daily or 30 mg SC bid
- Fondaparinux: 2.5 mg SC daily
- Extended prophylaxis (28 days): Reduces LEDVT by 60% vs in-hospital only

8.3 ERAS Protocols

- Early ambulation (<24h) reduces LEDVT by 35%
- Optimized analgesia, minimally invasive surgery, early enteral feeding facilitate mobilization

9. Imaging and Laboratory Monitoring

- Duplex Doppler ultrasound: Sensitivity 92%, specificity 95%
- CT venography: For complex or proximal thrombi
- Laboratory markers: Preoperative D-dimer, fibrinogen, TAT complex correlate with LEDVT incidence

10. Discussion

This review confirms that LEDVT following gynecologic oncologic surgery is a multifactorial process. Advanced age, obesity, high-stage ovarian cancer, prolonged operative time, significant blood loss, and extensive lymphadenectomy emerge as consistent independent risk factors across studies. Mechanistically, these factors converge on Virchow's triad, resulting in venous stasis,

endothelial injury, and hypercoagulability.

The findings highlight the need for individualized risk stratification using validated models such as Caprini, integrated with laboratory markers and tumor characteristics. Prophylaxis should combine mechanical and pharmacologic strategies, with extended LMWH considered for high-risk patients. ERAS protocols and early mobilization complement pharmacologic measures to reduce LEDVT incidence.

Limitations include variability in study design, heterogeneity in prophylactic strategies, and the predominance of retrospective cohort studies. Prospective, multicenter studies are needed to refine predictive models and optimize individualized prophylaxis.

11. Conclusion

LEDVT is a frequent and clinically significant complication following surgery for gynecologic malignancies. Patient factors, tumor characteristics, surgical parameters, and perioperative management interact to determine individual risk. Evidence-based prevention, early recognition, and intervention remain essential to reduce morbidity and mortality. Future research should focus on biomarker-driven risk prediction, AI-integrated models, and personalized prophylactic strategies to optimize outcomes.

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