A nomogram model for predicting lower extremity deep vein thrombosis after gynecologic laparoscopic surgery: a retrospective cohort study

Yuping Zhao [1], **Renyu Wang** [1], **Shuiling Zu** [1], **Yanbin Lin** [1], **Ying Fu** [1], **Na Lin** [1], **Xiumei Fang** [1], **Chenyin Liu** [Corresp. 1]

[1] Nursing Department, Fujian Maternity and Child Health Hospital, Fuzhou, Fujian, China

Corresponding Author: Chenyin Liu
Email address: 965912481@qq.com

Objective: To investigate the risk factors associated with lower extremity deep vein thrombosis (LEDVT) and to establish a predictive model for patients who undergo gynecologic laparoscopic surgery. **Methods:** A review of clinical data was conducted on patients who underwent gynecologic laparoscopic surgery between November 1, 2020, and January 31, 2022. Patients who developed LEDVT after surgery were included as the observation group, while the control group comprised patients who did not experience complications. Multivariate forward stepwise logistic regression models were used to identify independent risk factors associated with LEDVT. A nomogram model was then developed based on these risk factors. **Results:** A total of 659 patients underwent gynecologic laparoscopic surgery during the study period, and 52 (7.89%) of these patients developed postoperative LEDVT. Multivariate logistic regression analysis showed that older age (adjusted OR, 1.085; 95% CI, 1.034-1.138; P <0.05), longer operation duration (adjusted OR, 1.014; 95% CI, 1.009-1.020; P <0.05), shorter activated partial thromboplastin time (APTT) (adjusted OR, 0.749; 95% CI, 0.635-0.884; P <0.05), higher D-dimer (adjusted OR, 4.929; 95% CI, 2.369-10.255; P <0.05), higher Human Epididymis Protein 4 (HE4) (adjusted OR, 1.007; 95% CI, 1.001-1.012; P <0.05), and history of hypertension (adjusted OR, 3.732; 95% CI, 1.405-9.915; P <0.05) were all independent risk factors for LEDVT in patients who underwent gynecologic laparoscopic surgery. A nomogram model was then created, which had an area under the curve of 0.927 (95% CI, 0.893-0.961; P <0.05), a sensitivity of 96.1%, and a specificity of 79.5%. **Conclusions:** A nomogram model that incorporates information on age, operation duration, APTT, D-dimer, history of hypertension, and HE4 could effectively predict the risk of LEDVT in patients undergoing gynecologic laparoscopic surgery, potentially helping to prevent the development of this complication.

A nomogram model for predicting lower extremity deep vein thrombosis after gynecologic laparoscopic surgery: a retrospective cohort study

Running Head: Predictive Model for LEDVT

Yuping Zhao, Renyu Wang, Shuiling Zu, Yanbin Lin, Ying Fu, Na Lin, Xiumei Fang, Chenyin Liu

[a]Nursing Department, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China

*Corresponding author: Chenyin Liu

E-mail: 965912481@qq.com

Tel：+86-15806063518

ORCID: 0009-0007-5536-9621

Abstract

Objective: To investigate the risk factors associated with lower extremity deep vein thrombosis (LEDVT) and to establish a predictive model for patients who undergo gynecologic laparoscopic surgery.

Methods: A review of clinical data was conducted on patients who underwent gynecologic laparoscopic surgery between November 1, 2020, and January 31, 2022. Patients who developed LEDVT after surgery were included as the observation group, while the control group comprised patients who did not experience complications. Multivariate forward stepwise logistic regression models were used to identify independent risk factors associated with LEDVT. A nomogram model was then developed based on these risk factors.

Results: A total of 659 patients underwent gynecologic laparoscopic surgery during the study period, and 52 (7.89%) of these patients developed postoperative LEDVT. Multivariate logistic regression analysis showed that older age (adjusted OR, 1.085; 95% CI, 1.034-1.138; P <0.05), longer operation duration (adjusted OR, 1.014; 95% CI, 1.009-1.020; P <0.05), shorter activated partial thromboplastin time (APTT) (adjusted OR, 0.749; 95% CI, 0.635-0.884; P <0.05), higher D-dimer (adjusted OR, 4.929; 95% CI, 2.369-10.255; P <0.05), higher Human Epididymis Protein 4 (HE4) (adjusted OR, 1.007; 95% CI, 1.001-1.012; P <0.05), and history of hypertension (adjusted OR, 3.732; 95% CI, 1.405-9.915; P <0.05) were all independent risk factors for LEDVT in patients who underwent gynecologic laparoscopic surgery. A nomogram model was then created, which had an area under the curve of 0.927 (95% CI, 0.893-0.961; P <0.05), a sensitivity of 96.1%, and a specificity of 79.5%.

Conclusions: A nomogram model that incorporates information on age, operation duration, APTT, D-dimer, history of hypertension, and HE4 could effectively predict the risk of LEDVT in patients undergoing gynecologic laparoscopic surgery, potentially helping to prevent the development of this complication.

Keywords

Gynecological surgery; Laparoscopy; Lower extremity deep vein thrombosis; Risk factors; Nomogram model

1 Introduction

Deep vein thrombosis (DVT) is a common complication that typically occurs within one week after surgery. If venous thrombosis dislodges, it can cause acute pulmonary embolism, which poses a serious threat to the patient's life (Gutzeit et al. 2020; Hui et al. 2020; Kaya et al. 2021). Recently, with the advancements in surgical technology and equipment, laparoscopic surgery has gained popularity in gynecology due to its advantages such as lesser physical damage, reduced stress response, lower blood loss, and faster recovery (Vedantham 2020). However, the incidence of lower extremity deep vein thrombosis (LEDVT) after gynecological laparoscopic surgery is 4.0%, which is not lower than that of open surgery due to factors like surgical posture and pneumoperitoneum (Chan & Weitz 2019; Chong et al. 2020; Qu et al. 2015). Gynecological disease is a high risk factor for developing venous thromboembolism (Abu Saadeh et al. 2013). The occurrence of LEDVT can negatively affect the limb motor function of patients and decrease their quality of life, making it crucial to accurately identify high-risk patients for LEDVT (Han et al. 2021; Liu et al. 2006; Moragon-Ledesma et al. 2020).

In current practice, the diagnosis and prediction of Lower Extremity Deep Vein Thrombosis (LEDVT) primarily rely on the Caprini score and Padua score, alongside laboratory examination and ultrasonic imaging examination (Willan et al. 2019). These scoring systems were initially published in the 1990s and early 21st century and were found to be valuable in predicting the onset of LEDVT in open surgery. However, their predictive efficacy in laparoscopic surgery remains uncertain (Lu et al. 2021; Yang et al. 2019b).

Many previous studies have reported that their model has considerable predictive value for

LEDVT (Hu et al. 2022; Tian & Li 2021; Wu & Cheng 2020). However, they did not take into account the relevant preoperative biochemical indicators. Some studies have revealed that D-dimer is an independent risk factor for LEDVT (Yago et al. 2020; Zhao et al. 2021). However, the influence of other biochemical indicators on LEDVT remains unclear. Gynecological patients undergo blood biochemical tests before laparoscopic surgery, which makes it convenient to investigate the relationships between biochemical indicators and LEDVT.

The aim of this study was to identify independent risk factors and develop a predictive model for the occurrence of LEDVT in patients who underwent gynecological laparoscopic surgery.

2 Methods

2.1 Study design and cohort

This retrospective study was approved by the Institutional Review Board of Fujian Provincial Maternity and Children's Hospital (2022YJ028). The requirement of informed consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki.

The clinical records and data of patients who underwent gynecologic laparoscopic surgery at our institution between November 1, 2020 and January 31, 2022, were collected and reviewed. This study included patients if they met the following criteria: 1) age ≥ 20 years; 2) underwent elective gynecologic laparoscopic surgery; 3) had complete clinical data; 4) had a normal preoperative color ultrasound examination of lower limb veins or normal D-dimer indicators within three days before surgery; 5) did not use any hormonal drugs before surgery. Patients were excluded if they met any of the following criteria: 1) had a prior diagnosis of LEDVT or pulmonary

85 embolism before admission; 2) were preoperative patients with severe underlying diseases or
86 intolerance to general anesthesia; 3) had liver or kidney dysfunction; 4) were perinatal women.
87 A total of 659 patients were included in the study. Out of these, 52 patients developed LEDVT
88 after surgery, and were classified as the observation group. The remaining 607 patients who did
89 not develop any complications were chosen as the control group.

90 ***2.2 Data collection and variables***

91 The clinical records and data of patients were collected by members of the research team. The
92 diagnostic criteria for LEDVT states that the vascular ultrasound must show low echo with a
93 disappearance of blood flow signal in the vascular lumen, and no change should be found after
94 applying pressure with a probe to the blood vessel. The variables in the study include age, height,
95 weight (measured at admission), body mass index (BMI), history of varicose veins, history of
96 hypertension, history of diabetes, operation duration, abdominal air pressure, white blood cell
97 count, neutrophil count, lymphocyte count, platelet count, platelet accumulation, hemoglobin,
98 hematocrit, activated partial thromboplastin time (APTT), thrombin time, international
99 standardized ratio, apolipoprotein A1, apolipoprotein B, high-density lipoprotein cholesterol, low-
100 density lipoprotein cholesterol, triglyceride, D-dimer, carbohydrate antigen 125 (CA125),
101 carbohydrate antigen 199 (CA199), Carbohydrate antigen 153 (CA153), carcinoembryonic
102 antigen (CEA), alpha-fetoprotein (AFP), squamous cell carcinoma antigen (SCCA), and human
103 epididymis protein 4 (HE4).

104 ***2.3 Statistical analysis***

105 Data analyses were performed using SPSS version 26.0 (IBM Inc., Chicago, IL, USA). Categorical

106 variables were compared with the chi-squared test. The Student's t-test was used to compare the
107 continuous variables between the two groups when measurement data met normal distribution and
108 homogeneity of variance. It was described by the median (P25, P75) and the non-parametric rank
109 sum test was used when measurement data didn't meet normal distribution and homogeneity of
110 variance. Independent prognostic factors for LEDVT were identified using multivariate full entry
111 logistic regression models. The criterion value for LEDVT prediction was determined through
112 receiver operating characteristic (ROC) curve analysis. The criteria from other studies (age, APTT,
113 D-dimer and history of hypertension) were applied to the entire patient population of this study as
114 to determine a reference predictive model (Han et al. 2021; Liu & Peng 2022; Liu et al. 2021; Liu
115 et al. 2006). This is followed by Cohen's kappa coefficient (κ) analysis to compare predictive value
116 between the criteria from other studies and the predictive model suggested by this study (Morrison
117 et al. 2013). The RMS program package of R software (v3.6.2; The R Foundation, Vienna, Austria)
118 was used to build the nomogram predictive model, and the consistency coefficient (C-index) was
119 used to evaluate the predictive value of the predictive model for LEDVT. The bootstrap method
120 was used to sample the data randomly 500 times for internal verification, grab the calibration
121 curve, and evaluate the model's compliance. A two-sided P-value <0.05 was considered
122 statistically significant.

123 **3 Results**

124 ***3.1 Participants' characteristics and univariate analysis***

125 The clinical characteristics of the 659 patients were summarized in Table 1. The univariate analysis
126 revealed no significant difference in height, air abdominal pressure, white blood cell count,

neutrophil count, lymphocyte count, platelet count, platelet accumulation, thrombin time, international standardized ratio, low-density lipoprotein cholesterol, apolipoprotein B, triglyceride, CA-199, CA-153, CEA, AFP, and SCCA between the two groups (P>0.05). However, compared to the control group, the observation group had significantly higher age, weight, BMI, operation time, history of varicose veins, hypertension, diabetes, D-dimer, CA125, and HE4 (P<0.05). In contrast, the observation group had a lower rate of hemoglobin, hematocrit, APTT, high-density lipoprotein cholesterol, and apolipoprotein A1 than those in the control group (P<0.05).

3.2 Logistic regression analysis

Based on the statistically significant indicators in the univariate analysis above, the factors with significant differences between the two groups were analyzed for collinearity. The results indicated that the variance inflation factor (VIF) was 13.404 for hemoglobin, 13.457 for hematocrit, and less than 10 for the remaining indicators. Consequently, due to the collinearity issue, the two indicators of hemoglobin and hematocrit were excluded from the subsequent multivariate logistic regression analysis.

Multivariate logistic regression analysis revealed that older age (adjusted OR, 1.085, 95% CI, 1.034-1.138, P<0.05), longer operation duration (adjusted OR, 1.014, 95% CI, 1.009-1.020, P<0.05), shorter APTT (adjusted OR, 0.749, 95% CI, 0.635-0.884, P<0.05), higher D-dimer (adjusted OR, 4.929, 95% CI, 2.369-10.255, P<0.05), higher HE4 (adjusted OR, 1.007, 95% CI, 1.001-1.012, P<0.05), and history of hypertension (adjusted OR, 3.732, 95% CI, 1.405-9.915, P<0.05) were independent risk factors for patients with LEDVT (Table 2).

3.3 A nomogram model for predicting postoperative LEDVT

A nomogram predictive model was established for postoperative LEDVT in patients who underwent gynecological laparoscopic surgery according to independent risk factors (Figure 1). Additionally, a receiver operating characteristic (ROC) curve of the predictive model was established and is shown in Figure 2. The area under the curve (AUC) was 0.927 (95% CI, 0.893-0.961; P<0.05), and the value of the Youden index was 0.720, with corresponding sensitivity of 96.1% and specificity of 75.9%. The calibration curve of the nomogram predictive model demonstrated that the C-index was 92.4% (Figure 3).

Comparison of reference stander and predictive model

The criteria of (age, APTT, D-dimer and history of hypertension) was applied to the entire patient population of this study to determine a reference predictive model(Han et al. 2021; Liu & Peng 2022; Liu et al. 2021; Liu et al. 2006). Cohen's kappa coefficient (κ) was 0.375 (P <0.001) when comparing the prediction of low-risk group between the criteria from other studies and the predictive model suggested by this study were compared.

We also compared the performance of the nomogram model, Caprini score and biochemical indicators (Table 3). The current nomogram model had a better value than Caprini score in sensitivity and specificity. When another model included biochemical indicators (APTT, Thrombin time, D-dimer, CA125 and HE4), it didn’t have advantage than the current nomogram model.

4 Discussion

This research has shown that patients who have undergone gynecological laparoscopic surgery are

169 at risk of lower-extremity deep vein thrombosis (LEDVT) due to several factors. These risk factors
170 include older age, longer operation duration, shorter activated partial thromboplastin time (APTT),
171 higher D-dimer, higher HE4, and a history of hypertension. To prevent the occurrence of LEDVT
172 in clinics, a nomogram model was established with a sensitivity of 96.1% and a specificity of
173 75.9%.

174 Laparoscopic surgery is a commonly employed minimally invasive technique within
175 gynecology. Nonetheless, the incidence of postoperative lower extremity deep vein thrombosis
176 (LEDVT) remains high due to the utilization of pneumoperitoneum and the patient's position
177 during surgery (Hu et al. 2022; Wu & Cheng 2020). A previous study displayed the incidence of
178 LEDVT subsequent to gynecologic laparoscopic surgery to be 7.6-11.55% (Tian & Li 2021).
179 Consistently, our current study discovered that the incidence of LEDVT following gynecologic
180 laparoscopic surgery was 7.89%. A previous study found various independent risk factors for
181 LEDVT in perinatal women, such as older age, mode of delivery, hypertension, diabetes, history
182 of thrombosis, short activated partial thromboplastin time (APTT), high D-dimer, and fasting
183 blood glucose (Zhao et al. 2018). Additionally, another previous study determined several distinct
184 independent risk factors for LEDVT in patients, such as older age, extended bed rest, high blood
185 viscosity, high D-dimer, and intraoperative blood loss (Evans et al. 2022). These two studies,
186 however, didn't examine the value of these risk factors specifically for patients undergoing
187 gynecologic laparoscopic surgery. A previous study established a 16-point evaluation scale for
188 venous thrombosis in gynecological surgery patients. This evaluation scale includes secondary
189 indicators such as age, body mass index (BMI), immobilization preoperatively, specific factors for

190 women, current high-risk disease, past and family medical history, treatment and medication
191 history, surgery and anesthesia duration and mode, special conditions during surgery, posture
192 during surgery, D-dimer, fibrinogen (FIB), APTT, and platelet count (Yang et al. 2019a).
193 However, this study failed to disclose the risk factors specifically for laparoscopic surgery patients
194 and could not predict the risk of LEDVT.

195 In the present study, we determined that prolonged duration of surgery is a significant risk
196 factor for LEDVT independent of other factors. This prolonged surgical time can result in extended
197 periods of laying down for patients, leading to the relaxation of lower limb muscles along with
198 blood stasis in veins, thereby increasing the chance of LEDVT. Researchers have identified an
199 elevated D-dimer level as a reliable indication of an abnormal blood coagulation system.
200 Furthermore, previous studies have indicated that increased D-dimer levels hold immense
201 importance in identifying LEDVT among peripheral diseases (Komatsu et al. 2020; Li et al.
202 2019a).

203 D-dimer, a primary index of coagulation function, holds great significance in the diagnosis,
204 curative effect, and prognosis of thrombotic diseases. The elevation of D-dimer levels indicates
205 active thrombosis or fibrinolytic activity in the blood vessels of patients. This study revealed that
206 an increase in D-dimer is another independent risk factor for LEDVT, which is consistent with
207 several previous studies (Jiang et al. 2021; Li et al. 2019b). However, a previous study showed
208 that D-dimer is a risk factor for venous thromboembolism but not an independent risk factor due
209 to the inclusion of fibrinogen degradation products, which interact with D-dimer (Shen et al. 2020).
210 APPT, a vital indicator for screening the endogenous coagulation system, can reflect the status of

coagulation factors in the body. In a hypercoagulable state or thrombosis, a decrease in APTT value indicates that the coagulation and fibrinolysis systems are unbalanced, leading to a hypercoagulable state and a higher risk of LEDVT (Zhang et al. 2019). Hypertension is another risk factor for LEDVT. Most patients with hypertension exhibit dysfunction of the renin-angiotensin-aldosterone system, leading to an increase in water and sodium retention, interstitial fluid, and decreased plasma content in blood vessels, which raises blood viscosity (Barber & Clarke-Pearson 2016). In hypertension, vascular endothelial cell function is disordered, producing more oxygen-free substances, inactivating more vasodilators, causing vascular inflammation, activating the blood coagulation system, and promoting the onset of LEDVT (Laws et al. 2018). HE4, a member of the whey acidic protein domain-putative extracellular protease inhibitor protein family, serves as a biomarker for malignancy risk evaluation in various neoplastic diseases, especially ovarian cancer (Chhikara et al. 2012; Scaletta et al. 2017). HE4 produced by epithelial or fibroblast-derived cells can exacerbate tissue fibrosis and result in tissue damage (LeBleu et al. 2013; Zhang et al. 2020). An activity could represent an important factor in promoting thrombosis.

A nomogram model was developed in this research to predict the risk of lower extremity deep venous thrombosis (LEDVT) in gynecological patients. The model demonstrated a significant predictive capability, with a sensitivity of 96.1% and a specificity of 75.9%. It has been observed that the predictive performance of the model is higher than that of previous studies.

This study had several limitations. Firstly, due to the retrospective nature of this study, selection bias was inherent. Secondly, the model's external validation was not performed despite the high predictive value for LEDVT, which restricted its application. Thirdly, the application of

the model is restricted to patients undergoing gynecological laparoscopic surgery due to a limited number of patients.

Conclusion

The present study, for the first time to our knowledge, identified the independent risk factors for LEDVT in gynecological laparoscopic surgery patients as old age, prolonged surgical duration, shortened APTT, elevated D-dimer levels, a history of hypertension, and high HE4. Our nomogram model utilizing these factors accurately predicts the likelihood of LEDVT and may be applied to prevent its occurrence.

Competing Interests

No potential conflict of interest relevant to this article was declared.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Fujian Provincial Maternity and Children's Hospital (2022YJ028).

Availability of data and materials

The following information was supplied regarding data availability: The clinical raw data is available in the Supplemental File.

Funding

This work was supported by the National Research Foundation for the Prevention and Treatment of Pulmonary Embolism and Deep Vein Thrombosis (Y101).

Acknowledgements

We are grateful to the patients who made this study possible.

Authors' contributions

LC conceived the idea of the study. YZ designed the study and wrote the manuscript. SZ, RW and YL performed the data collection and analysis. YF, NL and XF reviewed the manuscript and modified the figures and tables. All authors read and approved the final manuscript.

Figure legends

Figure 1. Nomogram prediction model of postoperative LEDVT in patients undergoing gynecologic laparoscopic surgery

Figure 2. Receiver operating characteristic curve for the LEDVT prediction model after gynecological laparoscopy

Figure 3. Calibration curve of the nomogram predictive model

References

Abu Saadeh F, Norris L, O'Toole S, and Gleeson N. 2013. Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival. *Eur J Obstet Gynecol Reprod Biol* 170:214-218. 10.1016/j.ejogrb.2013.06.004

Barber EL, and Clarke-Pearson DL. 2016. The limited utility of currently available venous thromboembolism risk assessment tools in gynecological oncology patients. *Am J Obstet Gynecol* 215:445 e441-449. 10.1016/j.ajog.2016.04.034

Chan NC, and Weitz JI. 2019. Rivaroxaban for prevention and treatment of venous thromboembolism. *Future Cardiol* 15:63-77. 10.2217/fca-2018-0076

Chhikara N, Saraswat M, Tomar AK, Dey S, Singh S, and Yadav S. 2012. Human epididymis protein-4 (HE-4): a novel cross-class protease inhibitor. *PLoS One* 7:e47672. 10.1371/journal.pone.0047672

Chong W, Bui AH, and Menhaji K. 2020. Incidence and risk factors for venous thromboembolism events after different routes of pelvic organ prolapse repairs. *Am J Obstet Gynecol* 223:268 e261-268 e226. 10.1016/j.ajog.2020.05.020

Evans VJ, Lawrence M, Whitley J, Johns C, Pillai S, Hawkins K, Power K, Morris K, Williams PR, and Evans PA. 2022. The treatment effect of rivaroxaban on clot characteristics in patients who present acutely with first time deep vein thrombosis. *Clin Hemorheol Microcirc* 80:139-151. 10.3233/CH-201030

Gutzeit O, Lauterbach R, Loberman Z, Sachner R, Karram T, and Lowenstein L. 2020. Laparoscopic sacrocolpopexy complication: Ilio-femoral deep vein thrombosis. *Eur J Obstet Gynecol Reprod Biol* 247:270-271. 10.1016/j.ejogrb.2020.02.040

Han S, Yang B, Feng Y, Zhao L, Feng Q, Guan H, Song D, Yin F, and Zhuang L. 2021. The Correlation Between FGB Promoter Polymorphism and Clotting Function in Patients With Idiopathic Lower Extremity Deep Venous Thrombosis. *Clin Appl Thromb Hemost* 27:1076029620967108. 10.1177/1076029620967108

Hu J, Geng Y, Ma J, Dong X, Fang S, and Tian J. 2022. The Best Evidence for the Prevention and Management of Lower Extremity Deep Venous Thrombosis After Gynecological Malignant Tumor Surgery: A Systematic Review and Network Meta-Analysis. *Front Surg* 9:841275. 10.3389/fsurg.2022.841275

Hui Y, Zhao S, Gu J, and Hang C. 2020. Analysis of factors related to fertility after endometriosis combined with infertility laparoscopic surgery. *Medicine (Baltimore)* 99:e20132. 10.1097/MD.0000000000020132

Jiang YR, Niu LL, Feng N, Fan HL, Jin QQ, Du QX, Cao J, Wang YY, and Sun JH. 2021. Correlation between the Polymorphism of Coagulation-Related Genes and Lower Extremity Deep Venous Thrombosis. *Fa Yi Xue Za Zhi* 37:145-150. 10.12116/j.issn.1004-5619.2019.491213

Kaya AC, Radosa MP, Zimmermann JSM, Stotz L, Findeklee S, Hamza A, Sklavounos P, Takacs FZ, Wagenpfeil G, Radosa CG, Solomayer EF, and Radosa JC. 2021. Intraoperative and postoperative complications of gynecological laparoscopic interventions: incidence and risk factors. *Arch Gynecol Obstet* 304:1259-1269. 10.1007/s00404-021-06192-7

Komatsu H, Shimada M, Osaku D, Deura I, Sato S, Oishi T, and Harada T. 2020. Deep vein thrombosis and serum D-dimer after pelvic lymphadenectomy in gynecological cancer. *Int J Gynecol Cancer* 30:860-864. 10.1136/ijgc-2019-000914

Laws A, Anderson K, Hu J, McLean K, Novak L, Dominici LS, Nakhlis F, Carty M, Caterson S, Chun Y, Duggan M, Barry W, Connell N, Golshan M, and King TA. 2018. Implementation of a Venous Thromboembolism Prophylaxis Protocol Using the Caprini Risk Assessment Model in Patients Undergoing Mastectomy. *Ann Surg Oncol* 25:3548-3555. 10.1245/s10434-018-6696-y

LeBleu VS, Teng Y, O'Connell JT, Charytan D, Muller GA, Muller CA, Sugimoto H, and Kalluri R. 2013. Identification of human epididymis protein-4 as a fibroblast-derived mediator of fibrosis. *Nat Med* 19:227-231. 10.1038/nm.2989

Li N, Zhang FB, Li BJ, and Wang RT. 2019a. Combination of Preoperative D-Dimer and Platelet

Distribution width Predicts Postoperative Deep Venous Thrombosis in Patients with Cervical Carcinoma. *Asian Pac J Cancer Prev* 20:1025-1029. 10.31557/APJCP.2019.20.4.1025

Li Q, Xue Y, Peng Y, and Li L. 2019b. Analysis of risk factors for deep venous thrombosis in patients with gynecological malignant tumor: A clinical study. *Pak J Med Sci* 35:195-199. 10.12669/pjms.35.1.365

Liu H, and Peng Y. 2022. Analysis of Risk Factors for Postoperative Lower Extremity Deep Venous Thrombosis and its Treatment and Nursing. *Emerg Med Int* 2022:9180696. 10.1155/2022/9180696

Liu W, He L, Zeng W, Yue L, Wei J, Zeng S, Wang X, and Gong Z. 2021. Peripherally inserted central venous catheter in upper extremities leads to an increase in D-dimer and deep vein thrombosis in lower extremities. *Thromb J* 19:24. 10.1186/s12959-021-00275-w

Liu YZ, Zhang ZY, Guo SL, He W, Zhang XR, Wang SZ, Liu CD, Li JF, and Li L. 2006. [Prospective investigation of postoperative lower extremity deep venous thrombosis in gynecological procedures]. *Zhonghua Fu Chan Ke Za Zhi* 41:107-110.

Lu X, Zeng W, Zhu L, Liu L, Du F, and Yang Q. 2021. Application of the Caprini risk assessment model for deep vein thrombosis among patients undergoing laparoscopic surgery for colorectal cancer. *Medicine (Baltimore)* 100:e24479. 10.1097/MD.0000000000024479

Moragon-Ledesma S, Galeano-Valle F, Calleja-Carton E, Del-Toro-Cervera J, and Demelo-Rodriguez P. 2020. Bilateral Deep Vein Thrombosis, Vena Cava Agenesis, and Renal Abnormalities: KILT Syndrome-A Case Report and Literature Review. *J Cardiovasc Transl Res* 13:629-631. 10.1007/s12265-019-09935-9

Morrison RE, Bryant CM, Terejanu G, Prudhomme S, and Miki K. 2013. Data partition methodology for validation of predictive models. *Computers & Mathematics with Applications* 66:2114-2125. 10.1016/j.camwa.2013.09.006

Qu H, Li Z, Zhai Z, Liu C, Wang S, Guo S, and Zhang Z. 2015. Predicting of Venous Thromboembolism for Patients Undergoing Gynecological Surgery. *Medicine (Baltimore)* 94:e1653. 10.1097/MD.0000000000001653

Scaletta G, Plotti F, Luvero D, Capriglione S, Montera R, Miranda A, Lopez S, Terranova C, De Cicco Nardone C, and Angioli R. 2017. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: a systematic review. *Expert Rev Anticancer Ther* 17:827-839. 10.1080/14737140.2017.1360138

Shen C, Ge B, Liu X, Chen H, Qin Y, and Shen H. 2020. Predicting the occurrence of venous thromboembolism: construction and verification of risk warning model. *BMC Cardiovasc Disord* 20:249. 10.1186/s12872-020-01519-9

Tian Q, and Li M. 2021. Risk factors of deep vein thrombosis of lower extremity in patients undergone gynecological laparoscopic surgery: what should we care. *BMC Womens Health* 21:130. 10.1186/s12905-021-01276-7

Vedantham S. 2020. Using it wisely: catheter-directed thrombolysis for deep vein thrombosis. *Lancet Haematol* 7:e6-e7. 10.1016/S2352-3026(19)30205-4

Willan J, Katz H, and Keeling D. 2019. The use of artificial neural network analysis can improve

the risk-stratification of patients presenting with suspected deep vein thrombosis. *Br J Haematol* 185:289-296. 10.1111/bjh.15780

Wu L, and Cheng B. 2020. Analysis of perioperative risk factors for deep vein thrombosis in patients with femoral and pelvic fractures. *J Orthop Surg Res* 15:597. 10.1186/s13018-020-02131-5

Yago H, Yamaki T, Sasaki Y, Homma K, Mizobuchi T, Hasegawa Y, Osada A, and Sakurai H. 2020. Application of the Caprini Risk Assessment Model for Evaluating Postoperative Deep Vein Thrombosis in Patients Undergoing Plastic and Reconstructive Surgery. *Ann Vasc Surg* 65:82-89. 10.1016/j.avsg.2019.10.082

Yang T, Tian S, Wang Y, Zhao J, Pei M, Zhao M, Wang L, Guo Y, and Yang X. 2019a. Evaluation of Risk Factors for Venous Thromboembolism in Patients Who Underwent Gynecological Surgery and Validation of a Fast-Rating Assessment Table. *Med Sci Monit* 25:8814-8819. 10.12659/MSM.920198

Yang Y, Wang X, Huang Y, Chen N, Shi J, and Chen T. 2019b. Ontology-based venous thromboembolism risk assessment model developing from medical records. *BMC Med Inform Decis Mak* 19:151. 10.1186/s12911-019-0856-2

Zhang L, Liu L, Bai M, Liu M, Wei L, Yang Z, Qian Q, Ning X, and Sun S. 2020. Hypoxia-induced HE4 in tubular epithelial cells promotes extracellular matrix accumulation and renal fibrosis via NF-kappaB. *FASEB J* 34:2554-2567. 10.1096/fj.201901950R

Zhang W, Huai Y, Wang W, Xue K, Chen L, Chen C, and Qian A. 2019. A Retrospective cohort study on the risk factors of deep vein thrombosis (DVT) for patients with traumatic fracture at Honghui Hospital. *BMJ Open* 9:e024247. 10.1136/bmjopen-2018-024247

Zhao CM, Zhang Y, Yang SD, Huang AB, Liang ZM, Wu J, and Chen Q. 2018. Risk Factors for Lower Limb Deep Vein Thrombosis in Patients With Single-Level Lumbar Fusion: A Prospective Study of 710 Cases. *Clin Appl Thromb Hemost* 24:157S-162S. 10.1177/1076029618798940

Zhao Z, Tian Q, and Zhang B. 2021. Effects of rehabilitation nursing care on deep vein thrombosis of the lower limbs following spinal fractures. *Am J Transl Res* 13:1877-1883.

Figure 1

Nomogram prediction model of postoperative LEDVT in patients undergoing gynecologic laparoscopic surgery

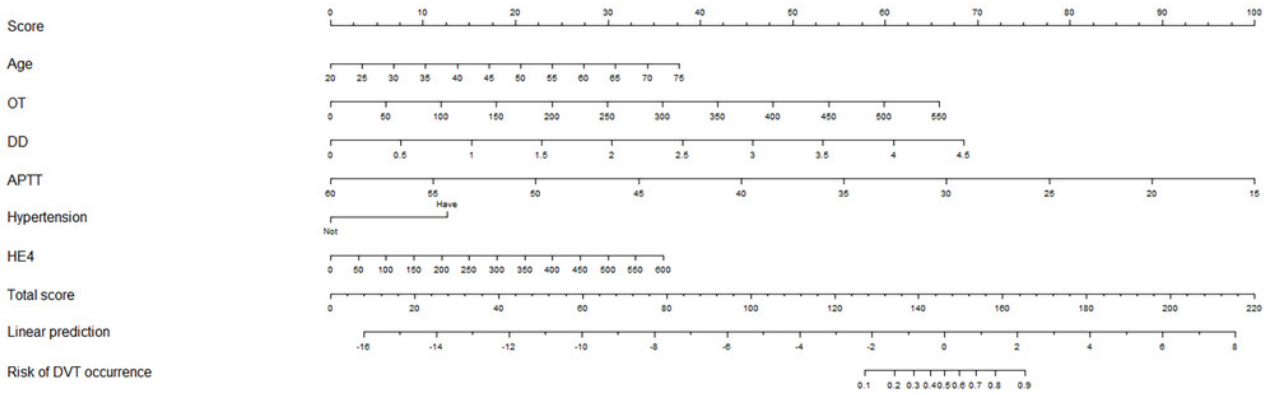

Figure 2

Receiver operating characteristic curve for the LEDVT prediction model after gynecological laparoscopy

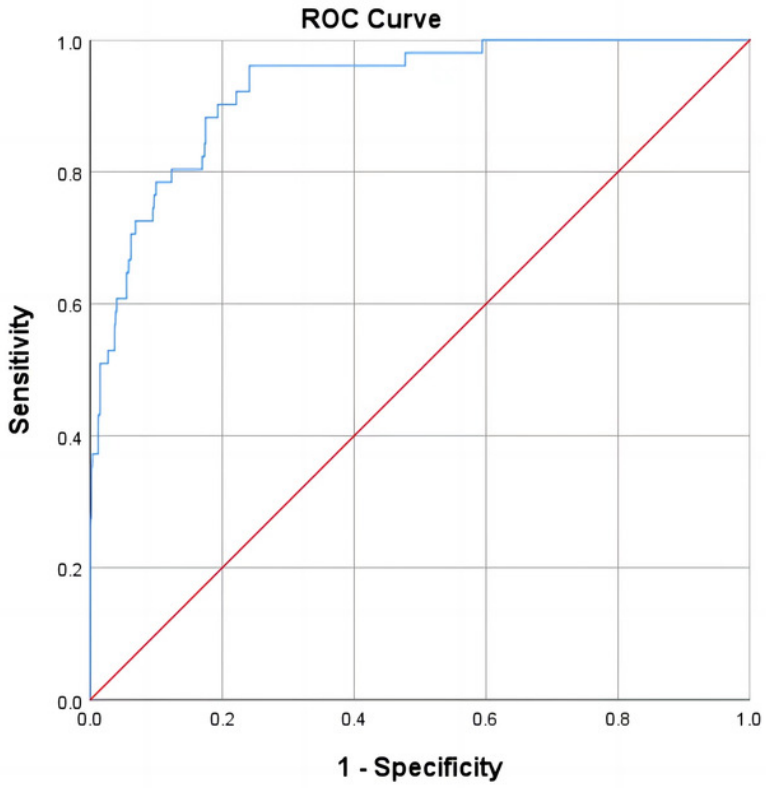

Figure 3

Calibration curve of the nomogram predictive model

Calibration curve of the nomogram predictive model

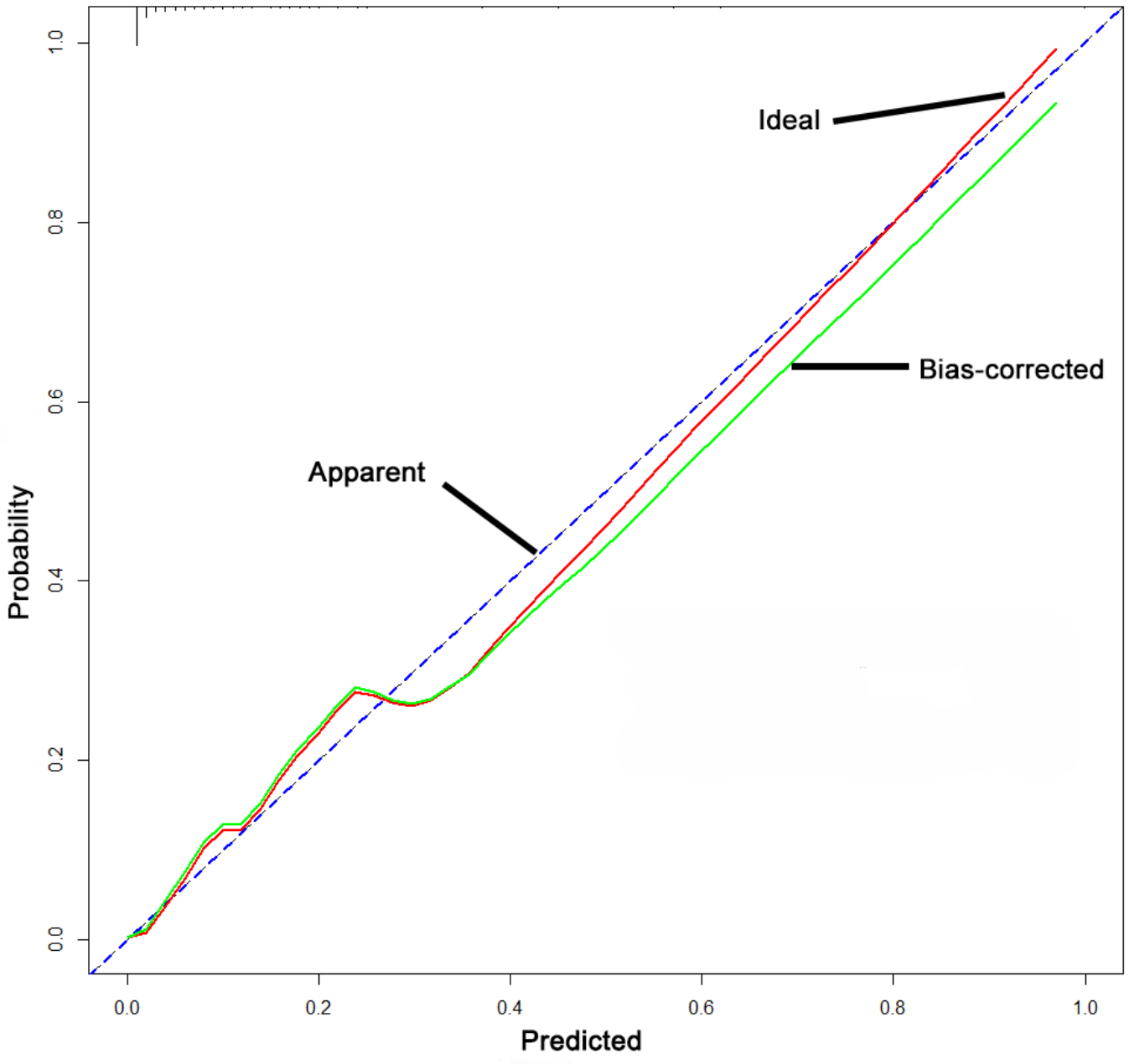

Table 1(on next page)

The characteristics of included patients

1 Table 1 The characteristics of included 659 patients

Characteristics	Non-LEDVT group	LEDVT group	P
Number (%)	607 (92.1)	52 (7.9)	
Age, mean (SD), years	39.66 (10.31)	50.79 (7.55)	< 0.001
Weight, mean (SD), kg	57.16 (8.16)	60.09 (8.02)	0.013
Height, mean (SD), meters	1.59 (0.05)	1.59 (0.05)	0.365
BMI, mean (SD), kg/m2	22.51 (3.07)	23.85 (2.99)	0.003
Operation duration, mean (SD), min	126.12 (53.32)	210.19 (98.40)	< 0.001
Air abdominal pressure, mean (SD), mmHg	13.98（0.478）	14.06（0.574）	0.319
History of varicose vein, n (%)			0.033
Yes	2 (0.33)	2 (3.85)	
No	605 (99.67)	50 (96.15)	
Hypertension, n (%)			< 0.001
Yes	34 (5.60)	17 (32.69)	
No	573 (94.4%)	35 (67.31)	
Diabetes, n (%)			0.036
Yes	12 (1.98)	4 (7.69)	
No	595 (98.02)	48 (92.31)	

White blood cell count, Median (25%, 75%), $\times 10^9$/L	5.67 (4.74, 6.63)	5.64 (4.48, 6.97)	0.965
Neutrophil count, Median (25%, 75%), $\times 10^9$/L	3.06 (2.55, 3.98)	3.09 (2.42, 4.40)	0.970
Lymphocyte count, Median (25%, 75%), $\times 10^9$/L	1.82 (1.52, 2.13)	1.77 (1.28, 2.18)	0.196
Platelet count, Median (25%, 75%), $\times 10^9$/L	268 (227, 314)	276 (231, 339)	0.503
Platelet accumulation, Median (25%, 75%), %	0.28 (0.24,0.31)	0.28 (0.24,0.32)	0.792
Hemoglobin, mean (SD), g/L	124.2（16.724）	116.73（19.879）	0.002
Hematocrit, Median (25%, 75%), %	38.10 (35.70, 40.10)	36.80 (33.30, 39.35)	0.013
APTT, Median (25%, 75%), seconds	27.30 (25.58,28.90)	24.80 (22.95, 26.35)	< 0.001
Thrombin time, Median (25%, 75%), Seconds	17.00 (16.50,17.40)	17.20 (16.60, 17.65)	0.097
International standardized ratio, Median (25%, 75%), %	0.92 (0.88, 0.96)	0.93 (0.90, 0.95)	0.208
D-dimer, Median (25%, 75%), mg/L FEU	0.20 (0.14, 0.31)	0.45 (0.21, 1.09)	< 0.001

High-density lipoprotein cholesterol, Median (25%, 75%), mmol/L	1.42 (1.20, 1.61)	1.28 (1.10, 1.46)	0.005
Low-density lipoprotein cholesterol, Median (25%, 75%), mmol/L	3.07 (2.67, 3.58)	2.88 (2.48, 3.91)	0.302
Apolipoprotein A1, Median (25%, 75%), g/L	1.16 (1.04, 1.27)	1.10 (1.02, 1.21)	0.033
Apolipoprotein B, Median (25%, 75%), g/L	0.83 (0.73, 0.96)	0.85 (0.76, 1.07)	0.153
Triglyceride, Median (25%, 75%), mmol/L	1.21 (0.88, 1.77)	1.17 (0.86, 1.59)	0.582
CA125, Median (25%, 75%), U/ml	15.6 (9.78, 24.4)	25.9 (13.39, 55.45)	< 0.001
CA199, Median (25%, 75%), U/ml	8.01 (4.06, 15.69)	7.36 (3.53, 29.16)	0.989
CA153, Median (25%, 75%), U/ml	8.40 (6.18, 12.25)	7.5 (5.1, 13.00)	0.495
CEA, Median (25%, 75%), ng/ml	1.35 (0.89, 1.80)	1.60 (1.05, 2.46)	0.057
AFP, Median (25%, 75%), ng/ml	2.50 (1.77, 3.51)	2.19 (1.57, 3.32)	0.363
SCCA, Median (25%, 75%), ng/ml	0.80 (0.60, 1.10)	0.70 (0.58, 1.00)	0.298
HE4, Median (25%, 75%), pmol/L	33.16 (24.86, 45.62)	45.70 (34.80, 66.08)	< 0.001

2 Abbreviations: APTT, activated partial thromboplastin time; CA125, carbohydrate antigen 125;
3 CA199, carbohydrate antigen 199; CA153, carbohydrate antigen 153; CEA, carcinoembryonic

antigen; AFP, alpha-fetoprotein; SCCA, squamous cell carcinoma antigen; HE4, epididymis protein 4.

Table 2(on next page)

Multivariate analyses of risk factors for LEDVT by binary logistic regression models

Table 2 Multivariate analyses of risk factors for LEDVT by binary logistic regression models

Characteristic	aOR	95% Cl	P
Age	1.085	1.034-1.138	0.001
Weight	1.02	0.929-1.119	0.680
BMI	0.945	0.720-1.240	0.683
Operation duration	1.014	1.009-1.020	< 0.001
APTT	0.749	0.635-0.884	0.001
D-dimer	4.929	2.369-10.255	< 0.001
High-density lipoprotein cholesterol	2.202	0.216-22.463	0.505
Apolipoprotein A1	0.095	0.001-8.170	0.300
CA125	1.001	0.999-1.003	0.431
HE4	1.007	1.001-1.012	0.021
Hypertension	3.732	1.405-9.915	0.008
Diabetes	1.1	0.202-5.993	0.912
History of varicose vein	3.823	0.191-76.529	0.380

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index. APTT, activated partial thromboplastin time; CA125, carbohydrate antigen 125; HE4, epididymis protein 4. All listed covariates in the model were not found to have multicollinearity.

Table 3(on next page)

Performance of the nomogram model, Caprini score and biochemical indicators

Table 3. Performance of the nomogram model, Caprini score and biochemical indicators

Characteristics	AUC, 95% CI	Sensitivity, %	Specificity, %
Model	0.927 (0.893-0.961)	96.1	79.5
Caprini	0.684 (0.605-0.763)	63.5	73.3
Biochemical indicators	0.780 (0.716-0.843)	78.8	64.1

AUC, area under the receiver operating characteristic curve. CI, confidence interval.