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Incidence of postoperative thrombotic events in ovarian cancer patients with a de-escalated prophylactic strategy: A retrospective cohort study

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HIGHLIGHTS

- The incidence of thrombotic events within 6 months of surgery was low in our cohort.
- Pre-operative identifiable risk factors such as age < 57 years and body mass index <21 may help define a low-risk group.
- These findings help personalize thromboprophylaxis in postoperative ovarian cancer patients.

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ABSTRACT

Objective. This study aimed to determine the incidence of thrombotic events in ovarian cancer patients following a de-escalated prophylactic strategy and to stratify risk groups.

Methods. We reviewed the records of patients who underwent debulking surgery for ovarian cancer at a single institution between January 2007 and May 2019. We identified clinically diagnosed and radiologically confirmed cases of thrombotic events—classified as pulmonary thromboembolism (PE), deep vein thrombosis (DVT), and other thrombotic events—within 6 months of debulking surgery.

Results. After excluding 13 patients diagnosed with thromboembolism at the baseline or during neoadjuvant chemotherapy, 799 were analyzed. Since the introduction of medical prophylaxis at our institution in 2009, 482 patients (60%) received medical prophylaxis with subcutaneous injection of low molecular weight heparin for 5 days with mechanical prophylaxis, whereas 317 (40%) received mechanical prophylaxis only. After debulking surgery, thrombotic events occurred in 28 patients (3.5%) including PE ($n = 11$), DVT ($n = 10$), and other thrombotic events ($n = 7$). Multivariable analysis identified age, body mass index (BMI), and operative duration as independent risk factors associated with thrombotic events. A thrombotic event was an independent prognostic factor for overall survival (HR 2.17, 95% CI 1.16–4.1). A cut-off analysis for pre-operative identifiable risk factors showed age < 57 years and BMI < 21 could help define low-risk groups. One patient from 172 low-risk patients (0.58%) experienced a thrombotic event.

Conclusions. The thrombotic event incidence was low in our cohort. A de-escalated prophylaxis strategy may be considered in young (age < 57 years) and lean (BMI < 21) patients.

1. Introduction

Ovarian cancer patients undergoing radical surgery are at high risk of developing deep vein thrombosis (DVT) and pulmonary thromboembolism (PE), which are serious complications leading to increased morbidity and mortality [1,2]. The risk of venous thrombosis is present prior to surgery with or without use of neoadjuvant therapy [3,4], during the peri-operative period [5], and extends well into the post-operative period [6]. While the reported incidence of DVT and PE varies widely from 3.5% to 40.8%, depending on the demographics of the study population and mode of prophylaxis [7–9], the incidence of such events is markedly low in Asian compared to Western populations [10].

Despite the wide variability in the prevalence and the clinical heterogeneity of ovarian cancer, current guidelines such as those from the American Society of Clinical Oncology (ASCO) [11], National Comprehensive Cancer Network (NCCN), and International Initiative on Thrombosis and Cancer (ITAC) [12] all recommend extended thromboprophylaxis of 28 days using a combined regimen of pharmacological prophylaxis with low molecular weight heparin (LMWH) and mechanical prophylaxis (e.g., graduated compression stockings and sequential

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compression devices) [13]. The duration of 28 days was proposed as early as 2002 based on a randomized trial [14], but a recent study by Wagner et al. [6] suggests that 28 days of thromboprophylaxis may be inadequate in reducing the risk of thrombotic events in postoperative ovarian cancer patients.

However, clinical practice often diverges from guidelines. Based on a survey of gynecologic oncologists in 2007, nearly 50% of the respondents did not use LMWH following major surgery [15]. Since then, through quality improvement efforts, the use of LMWH for thromboprophylaxis has increased [16]. However, problems still exist in many hospitals worldwide, where subcutaneous injection of LMWH for 4 weeks or longer after discharge is impractical. Also, the subcutaneous mode of injection frequently results in low patient compliance. Recent studies have shown the possibility of using direct oral regimens such as rivaroxaban [17] or apixaban [18], yet these agents have a potential bleeding risk and are costly for patients. Therefore, especially in a setting of low baseline prevalence of thrombotic events, the risks and benefits of extended prophylaxis should be assessed carefully taking into consideration the demographic and clinical contexts.

The aim of this study was to identify a subgroup of patients at low risk for postoperative thrombotic events to propose a de-escalation strategy. A retrospective analysis was performed for patients who either received less than 28 days of subcutaneous injection of LMWH with mechanical prophylaxis or were managed exclusively with mechanical thromboprophylaxis. The incidence of and risk factors for thrombotic events were analyzed to provide practical insights to guide treatment.

2. Materials and methods

2.1. Patient enrollment

We retrospectively reviewed all the clinical records of ovarian cancer patients who underwent primary debulking surgery (PDS) or neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS), from January 2007 to May 2019 at a single tertiary hospital. The study was approved by the hospital's institutional review board (IRB No #4–2021-1037). The need for informed consent was waived owing to the retrospective nature of the study. All surgical procedures were performed by one of five gynecologic oncology surgeons at our institution. NAC was administered if at least one of the following three criteria was met: 1) pulmonary or hepatic parenchymal metastases were observed on preoperative imaging, 2) the cancer was inoperable or the operative risk was too high due to comorbidities, or 3) an optimal debulking operation (with residual of 1 cm or less) was unlikely due to a high tumor burden (Fagotti score 8 or higher) [19]. The surgical complexity score (SCS) was calculated based on a previously published protocol [20], and was classified as low (1–3), intermediate (4–7), or high (≥8). Surgical procedures with a score of 1 included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy, paraaortic lymphadenectomy, abdominal peritoneum stripping, and small bowel resection. Surgical procedures with a score of 2 included large bowel resection, diaphragm stripping or resection, splenectomy, and liver resection. A score of 3 was given to rectosigmoidectomy with anastomosis.

2.2. Mode of thromboprophylaxis

The mode of thromboprophylaxis was either mechanical prophylaxis, such as the use of graduated compression stockings (GCS) and sequential compression devices (SCD), with or without the addition of a subcutaneous injection of LMWH. Mechanical prophylaxis was placed before the initiation of surgery, and patients were on prophylaxis until complete mobilization was achieved which was approximately 3–5 days post-operatively. In cases of LMWH use, subcutaneous injection of dalteparin (2500 IU) was administered immediately prior to operation and was continued daily for 5 days postoperatively. The duration was based on the timing of ambulation and was a convention at our hospital. At each surgeon's discretion, the duration of LMWH could be shortened in the presence of potential bleeding risks or lengthened in cases with a high-perceived risk of a thrombotic event.

2.3. Collection of clinical variables

Chart review was performed to extract demographic information, treatment-related parameters, and post-operative outcomes. Demographic information included age, body mass index (BMI), past medical history, list of medications prior to surgery, and the American Society of Anesthesiologists (ASA) score. Treatment-related parameters included whether or not the patient received NAC, date of surgery, surgical complications, disease stage, histological results, presence of residual disease (0 cm, 0–0.5 cm, 0.5–1 cm, 1–2 cm, >2 cm), blood loss during surgery (ml), operative duration (min), and length of hospitalization (days). In addition to checking for a thrombotic event, medication lists were reviewed for newly introduced anti-platelet or anti-coagulant agents administered within six months of surgery. Only radiologically confirmed PE, DVT, and other thrombotic events within 6 months were included. For the analysis of clinical outcomes, recurrence and survival data were acquired.

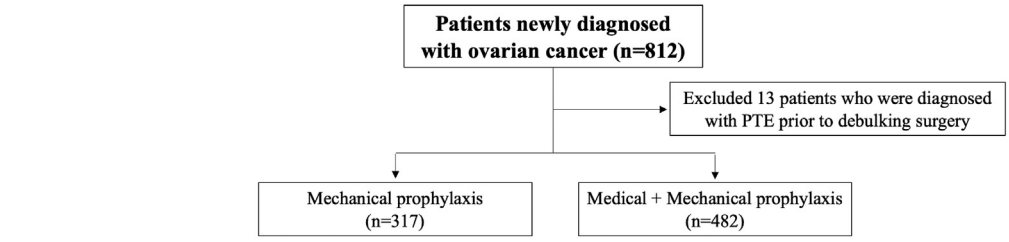
2.4. Statistical analysis

Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was calculated using the Fisher's exact test or chi-squared test for categorical variables and the Student's *t*-test for continuous variables. Receiver operating characteristic (ROC) curves were used to identify the optimal cut-off point for each variable, which was defined as the point at which the sum of the sensitivity and specificity was maximal. Clinical outcomes were determined by progression-free survival (PFS) and overall survival (OS). The outcomes, PFS and OS, were defined as the time since primary surgery (PDS or IDS) to the time of first progression or death, respectively and were analyzed using the Kaplan-Meier method and the log-rank test. A Cox proportional hazards regression model was used to evaluate the impact of thrombotic events and other potential prognostic variables on recurrence and survival. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

After excluding 13 patients diagnosed with thromboembolism at baseline or in association with NAC, a total of 799 patients were included in the analysis (Fig. 1). Since the introduction of medical prophylaxis in 2009, the proportion of patients receiving a subcutaneous injection of LMWH increased rapidly from 10% in 2009, to 45% in 2010, and to 76% in 2011 (data not shown). Altogether, 482 patients (60%) received subcutaneous injections of LMWH for 5 days in addition to mechanical prophylaxis, whereas 317 patients (40%) received mechanical prophylaxis only (GCS in 128 patients and SCD in 189 patients). The choice and duration of thromboprophylaxis was based on the individual physician's discretion, and this led to differences in the characteristics of patients receiving mechanical prophylaxis only versus those receiving both medical and mechanical prophylaxis (Table S1).

Overall, 528 patients (66%) received PDS, and 271 patients (34%) received NAC followed by IDS (Fig. 2). Based on the past medical history, only one patient had a history of DVT, and 53 patients had been on anti-platelet agents and five patients on anti-coagulants prior to surgery, for medical indications other than DVT or PE. During the baseline evaluation of ovarian cancer patients using abdominal, pelvic, and chest computerized tomography (CT), nine patients were found to have asymptomatic thromboembolism. Three additional patients were diagnosed with thromboembolism based on repeated imaging after three cycles of NAC. After the primary operation, thrombotic events



Thrombotic events within 6 months	7 patients (2.2%)	21 patients (4.4%)
Pulmonary embolism (PE)	1	10
Deep vein thrombosis (DVT)	4	6
Other events*	2	5

* Other events:
- STEMI/angina receiving cardiac procedure (n=2)
- Renal vein thrombosis or infarction (n=2)
- Arm phlebitis and thrombus (n=1)
- IJV thrombus (n=1)
- Total arterial occlusion (n=1)

Fig. 1. Incidence of thrombotic events within 6 months of surgery based on the mode of thromboprophylaxis.
Abbreviations: IJV, internal jugular vein; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction.

occurred in 28 patients after a median of 27.5 (1–151) days, which included 11 patients with PE, 10 patients with DVT, and seven patients with other thrombotic events. Among the 21 patients with PE or DVT, 11 patients (52%) had symptoms of dyspnea, leg swelling, or leg pain; the rest of the patients were incidentally diagnosed based on 3-monthly radiological assessments during adjuvant chemotherapy. Among the ten patients with a DVT, thrombosis was complicated by postoperative lymphocele formation in two patients (20%). Other thrombotic events included ST-elevation myocardial infarction/angina necessitating a cardiac procedure ($n = 3$), renal vein thrombosis or infarction ($n = 2$), arm phlebitis and thrombosis ($n = 1$), internal jugular vein thrombosis (n = 1), and total arterial occlusion (n = 1).

A comparison of the characteristics of patients with and without thrombotic events is shown in Table 1. With respect to pre-operative characteristics, patients with thrombotic events were more likely to be older, have a higher BMI, and have an ASA grade of 3–4. A total of 58 patients had been on anti-platelet or anti-coagulation therapies due to their underlying medical condition prior to the primary operation, and none of these patients experienced thrombotic events postoperatively. With respect to the treatment-related parameters, operative duration was significantly longer in patients with thrombotic events. Multivariable logistic regression showed that age, BMI, and operative duration were independent factors affecting the occurrence of thrombotic events (Table 2).

In our patient cohort, thrombotic events were associated with a significantly worse OS (Fig. S1) but not recurrence (Fig. S2). Median PFS was not significantly different in between patients without (1.8 years, range: 0.0–14.5) and with thrombotic events (1.0 years, range: 0.1–4.8) ($p = 0.21$); however, median OS was significantly longer in patients without thrombotic events (3.5 years, range: 0.0–14.5) compared to those with thrombotic events (2.4 years, range: 0.2–4.8) ($p = 0.002$). Cox proportional hazards regression analysis incorporating all pertinent variables showed that thrombotic events were associated with survival (HR = 2.35, 95% CI 1.26–4.4; Fig. 3), but not with recurrence (HR = 1.32, 95% CI 0.79–2.21; Fig. S3).

A risk-stratifying strategy was explored using ROC curve analysis of significant pre-operative parameters identified from the multivariate analysis. An age of 57 years and BMI of 21 were the optimal cut-off

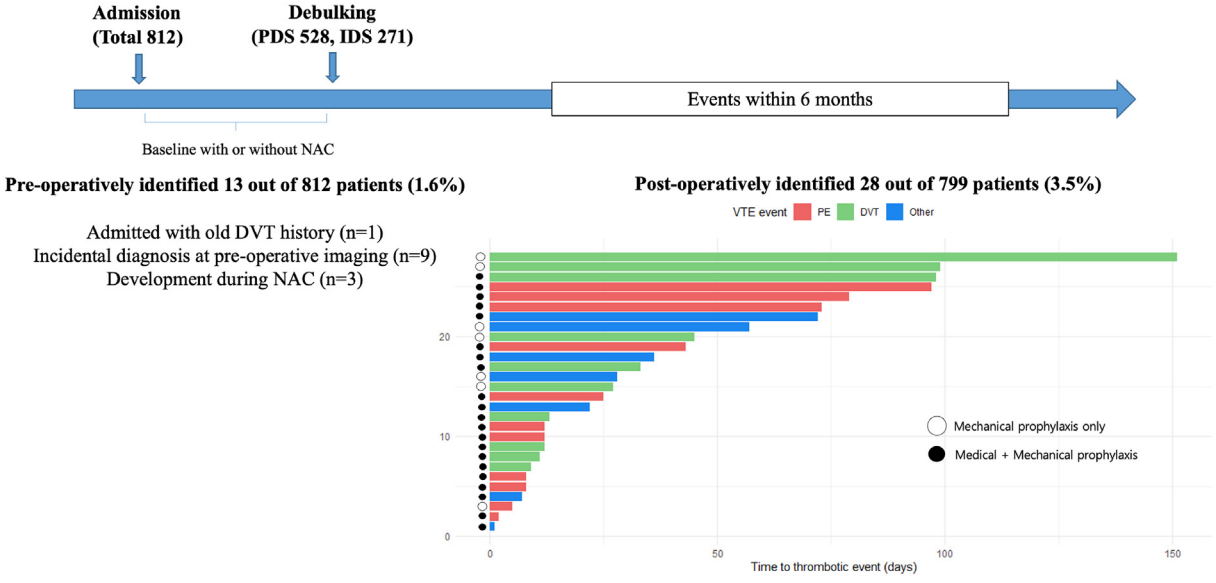


Fig. 2. Therapy timeline showing 13 patients diagnosed with pulmonary embolism preoperatively and 28 patients with thrombotic events within 6 months postoperatively. For the post-operatively diagnosed, days to thrombotic events are shown based on the type of thrombotic event and the mode and duration of thromboprophylaxis.
Abbreviations: DVT, deep vein thrombosis; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 1
Comparison of demographic and treatment-related factors in patients with thrombotic events versus those without.

Variable	Thrombotic event ($n = 28$)	No event ($n = 771$)	p-value
Pre-operative characteristics			
Age, median (range)	62 (41–81)	54 (21–83)	0.003
Body mass index, mean (IQR)	24.8 (22.1–27.9)	23.1 (20.9–24.9)	0.022
ASA			0.003
1	2 (8)	209 (27)	
2	13 (46)	396 (51)	
3–4	13 (46)	166 (22)	
Previous history			0.081
None	13 (47)	491 (64)	
HTN or DM	11 (39)	147 (19)	
RA, SLE, or CKD	0 (0)	7 (1)	
Cancer	2 (7)	59 (8)	
CAOD or CVD	0 (0)	42 (5)	
Other	2 (7)	25 (3)	
Treatment-related factors			
Stage			0.315
1	2 (7)	102 (13)	
2	1 (3)	49 (6)	
3	10 (36)	348 (45)	
4	15 (54)	272 (36)	
Histology			0.725
Serous	23 (82)	548 (71)	
Mucinous	0 (0)	35 (4)	
Endometrioid	1 (4)	59 (8)	
Clear cell	3 (10)	70 (9)	
Mixed adenocarcinoma	0 (0)	13 (2)	
Carcinosarcoma	1 (4)	14 (2)	
Other	0 (0)	32 (4)	
Residual			0.822
none	13 (46)	344 (45)	
<0.5	10 (35)	207 (27)	
<1	3 (11)	83 (11)	
<2	0 (0)	25 (3)	
≥2	1 (4)	32 (4)	
NA	1 (4)	80 (10)	
Complexity			0.822
Low	0 (0)	11 (1)	
Intermediate	21 (75)	594 (77)	
High	7 (25)	161 (21)	
NA	0 (0)	5 (1)	
NAC			0.999
No (PDS)	18 (64)	510 (65)	
Yes (IDS)	10 (36)	261 (35)	
Type of thromboprophylaxis			0.156
Mechanical	7 (25)	310 (40)	
Medical	21 (75)	461 (60)	
Surgery duration, mean (IQR)	444 (235–567)	334 (191–446)	0.015
Blood loss, mean (IQR)	1181 (500–1238)	875.1 (250–1100)	0.222

Abbreviations: ASA, American Society of Anesthesiologists; HTN, hypertension; DM, diabetes mellitus; RA, rheumatoid arthritis; SLE, systemic Lupus Erythematosus; CKD, chronic kidney disease; CAOD, coronary artery obstructive disease; CVD, cerebrovascular disease; PDS, primary debulking surgery; IDS, interval debulking surgery; IQR, inter-quartile range.

limits, based on when the outcome of thrombotic events diverged (Fig. S4). The prevalence of thrombotic events for the subgroups defined by the cut-off points are shown in Fig. 4. When the risk group was defined based on the combination of the two significant factors—low risk if aged <57 years and BMI < 21; high risk if aged ≥ 57 years and BMI ≥ 21; intermediate risk in all other scenarios—the prevalence of thrombotic events was 0.58%, 2.64%, and 6.85%, respectively. Only one patient in the low-risk group experienced a thrombotic event. This patient had a past medical history of gastric cancer, a BMI of 19.1, and was operated on for 9.1 h. One month after surgery, prior to a chemotherapy port insertion, an internal jugular vein thrombosis was identified. Following a cardiology consultation, this patient was treated with warfarin followed by a novel oral anti-coagulant.

Table 2
Multivariable logistic regression analysis for factors associated with thrombotic events.

Characteristic	Odds ratio (OR)	95% CI	p-value
Age	1.042	1.002–1.084	0.037
BMI	1.133	1.018–1.262	0.023
ASA			
1	–		
2	2.547	0.557–11.65	0.228
3–4	3.597	0.735–17.59	0.114
Duration of surgery (hour)	1.002	1.000–1.004	0.018

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval.

4. Discussion

The current guidelines of using extended prophylaxis for 28 days were developed using predominantly Western populations. However, the optimal duration of prophylaxis is questionable for two reasons. First, as suggested by Wagner et al., a subgroup of high-risk patients may need thromboprophylaxis for longer than 28 days. Second, in the setting of low baseline incidence of thrombotic events, such as in Asian patients with a low BMI who are hospitalized for a relatively short duration, de-escalation of thromboprophylaxis duration may be considered. Due to the wide variability in the reported incidence of postoperative thrombotic events in ovarian cancer patients, which ranges from 3% to 40% [7–9], the incorporation of thromboprophylaxis guidelines into practice requires a careful assessment of the baseline demographics as well as treatment-related characteristics, such as the type and complexity of surgical practice at the respective hospital.

In our cohort, the incidence of thrombotic events within 6 months of operation was 3.4%. This number is at the lower end of the reported incidence, especially considering that 39% of patients either received GCS or SCD only. When compared to the cohort in Wagner et al.'s study [6], the clinical aspects of our cohort are comparable, yet the demographic baseline characteristics varied considerably. For instance, our cohort was younger (mean age of 54.7 years vs. 63.4 years), had a lower BMI (23.1 vs. 28.3), and had better physical performance based on the ASA score (22% vs. 42% having ASA > 2). These demographic aspects were significantly associated with the incidence of venous thromboembolism in a recent meta-analysis [21], with high BMI (>30) associated with an odds ratio (OR) of 1.58 and per 10-years increase in age with an OR of 1.22. Thus, our cohort is demographically predisposed to having a relatively low incidence of thrombotic events compared to cohorts in Western populations.

In addition to the demographic characteristics, an important contributor to the low incidence of thrombotic events, was a sizable subgroup of patients (12 patients, 1.6%) who were incidentally diagnosed with DVT or PE either during baseline evaluation or during NAC. Our number of preoperatively diagnosed patients was much lower compared to the previously reported 27% for pre-treatment thrombotic events [22] and 28% for the newly diagnosed thrombotic events during NAC [23]. Nevertheless, considering that thrombotic events were identified in 28 patients post operatively, the 12 patients without a history of DVT or PE, who were asymptomatic and were preoperatively diagnosed, represent an important subgroup who should receive active prophylaxis and postoperative anticoagulation. Including the patient with a previous history of DVT, the 13 patients who were diagnosed with DVT or PE preoperatively were actively managed with either warfarin ($n = 3$) or novel oral anticoagulants ($n = 10$), and none of these patients developed thrombotic events after debulking surgery. Therefore, clinicians should actively look for signs of DVT or PE prior to debulking surgery in ovarian cancer patients.

An interesting finding regarding the underlying medical history of the 28 patients who experienced thrombotic events was that a substantial majority ($n = 26$) either did not have any significant medical history, or only isolated hypertension not requiring medication; the two remaining patients had a history of breast and gastric cancer, respectively. In other words, patients who were on either anti-platelet ($n =$

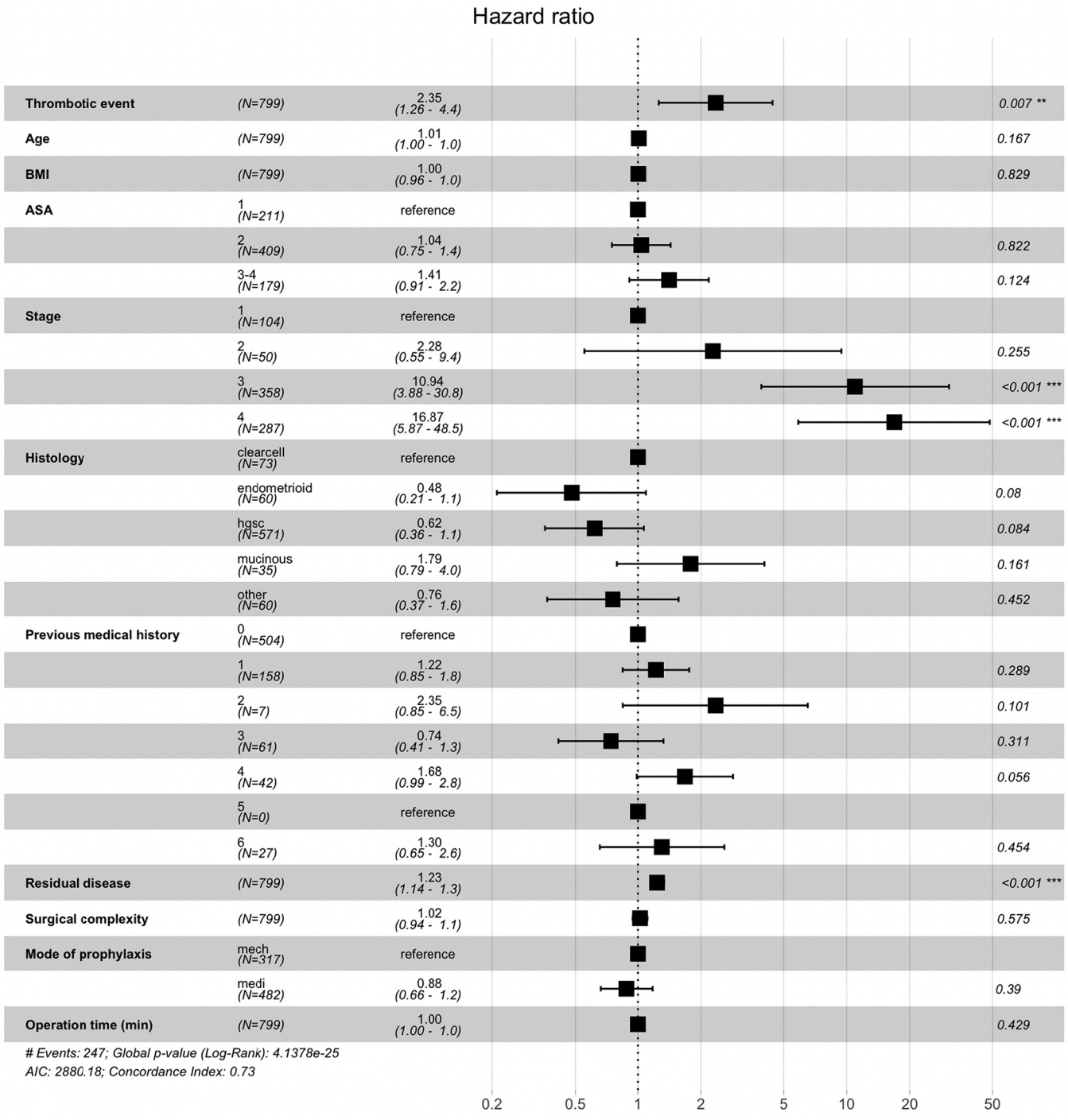


Fig. 3. Cox-regression survival analysis.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

53) or anti-coagulation therapies (n = 5) as indicated by their prior medical history (including coronary arterial obstructive disease, cardiac arrhythmia, cerebral vascular disease, systemic lupus erythematosus, or chronic kidney disease) did not experience thrombotic events postoperatively. Given that a majority of patients on anti-platelet were on simple aspirin (38 out of 53 patients), perhaps not only this medication but the enhanced surveillance postoperatively and increased patient awareness may have contributed to the paradoxical lack of events in these patients.

Recent studies suggest that an enhanced recovery after surgery (ERAS) protocol may help to reduce the incidence of thrombotic events in ovarian cancer patients [24,25]. In our cohort, the duration of hospital admission was relatively long (median of 10 days, range 4–57), and this may have been affected by the nationalized health insurance system which covers hospitalization costs and allows for patients who wish to wait for the final pathological diagnosis prior to discharge. Thus, clinicians should actively encourage early ambulation and educate patients that early discharge is for their benefit. Moreover, a quality improvement activity [16] and tailored exercise or dietary interventions [26] may help ovarian cancer patients during the postoperative and beyond.

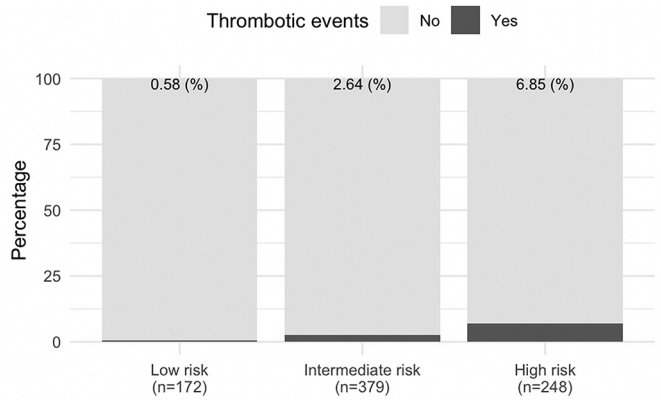


Fig. 4. Risk-group classification based on optimized cut-offs for age and BMI.
* Risk group was based on the combination of the two significant factors: low risk if having age < 57 and BMI < 21; high risk if having age ≥ 57 and BMI ≥ 21; intermediate risk in all other scenarios. Abbreviation: BMI, body mass index.

Our study represents a sizable cohort from a predominantly Asian population in a single hospital. This setting enabled a detailed clinical chart review, including pre-operative past medical history and medications, clinical findings during the operation, and the diagnosis and management of thrombotic events. However, our study is limited in its retrospective design. While general guideline was present, specific decisions surrounding the postoperative type and duration of thromboprophylaxis were in part made by individual clinicians. Moreover, since the rate of thrombotic events varies significantly based on demographics, our finding may not be generalizable in other demographical settings such as in America or Europe (i.e., countries with multicultural ethnic groups) where the cohort is much more heterogeneous or have higher average BMI. Thus, further evaluation with a prospective study design is recommended.

Clinicians should focus their efforts on preventing thrombotic events because the survival of ovarian cancer patients is significantly adversely affected by their occurrence. However, in ovarian cancer patients undergoing debulking surgery, the duration of prophylaxis may not be a "one-size-fits-all" strategy. Our data suggests that in a clinical setting of low-baseline incidence of events, shortened duration of thromboprophylaxis may not necessarily result in an increased rate of thrombotic events.

A subgroup of patients who are young and have low BMI, may be candidates for careful de-escalation from current guidelines. However, patients without underlying medical illness or with no history of antiplatelet or anti-coagulation therapies may be considered at increased risk of a thromboembolic event if they are old and have a high BMI.

Conflict of interest statement

The authors report no conflicts of interest.

Role of the funding source

None.

Authors' contributions

Conceptualization: YK JL; Data curation: YK, JCK, YSC, JP, YJL; Formal analysis: YK, JL; Investigation: YK, JP, YJL, JL, EJN, SWK, SK, YTK; Methodology: YK, JL; Supervision: JP, YJL, JL, EJN, SWK, SK, YTK; Validation: JL, JP, YJL; Visualization: YK, JL; Writing – original draft: YK; Writing – review &editing: JP, YJL, JL, EJN, SWK, SK, YTK. All authors have reviewed and approved the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.02.007.

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