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Development and validation of a risk model for prediction of venous thromboembolism in gynaecological cancer patients

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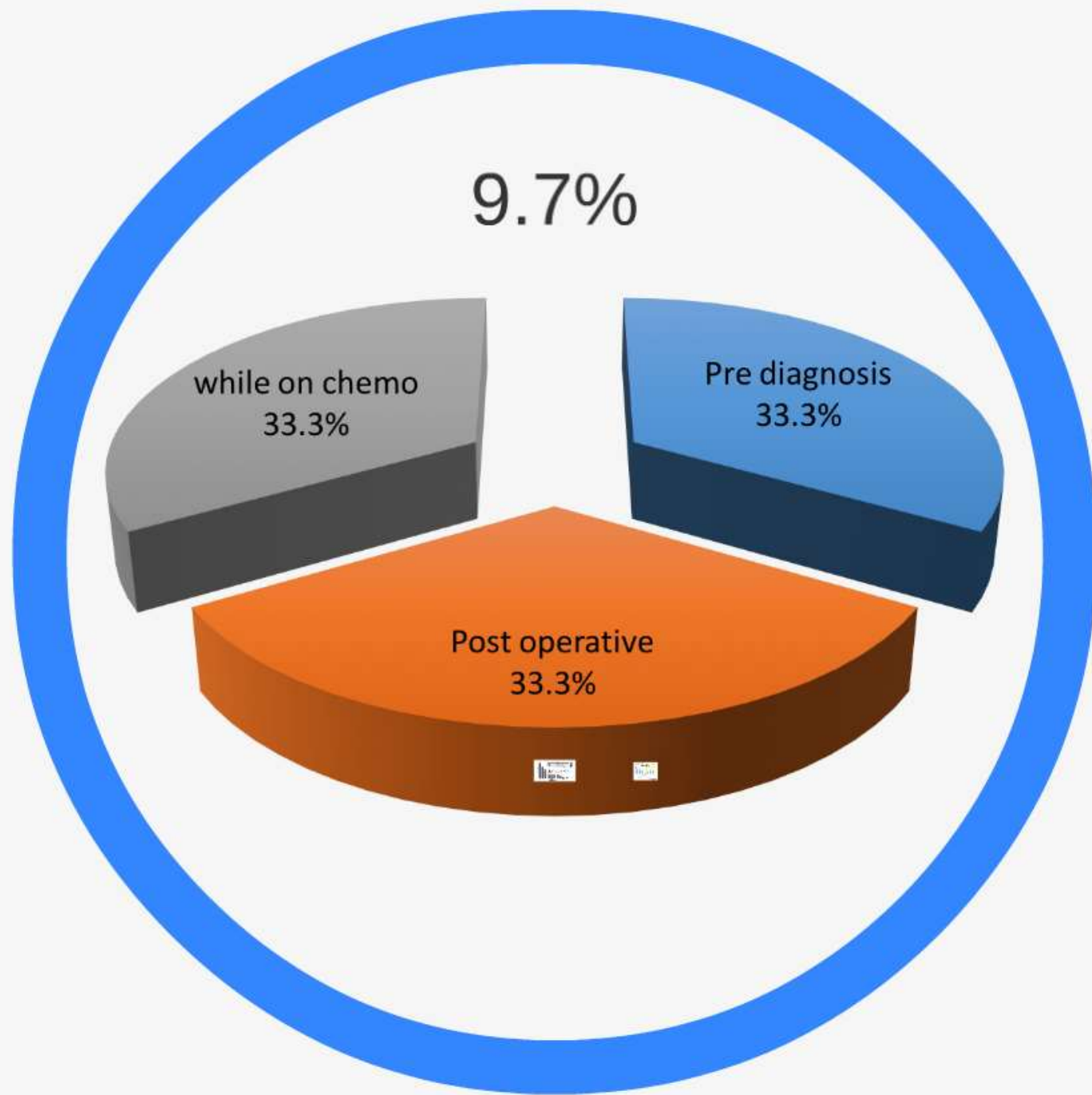
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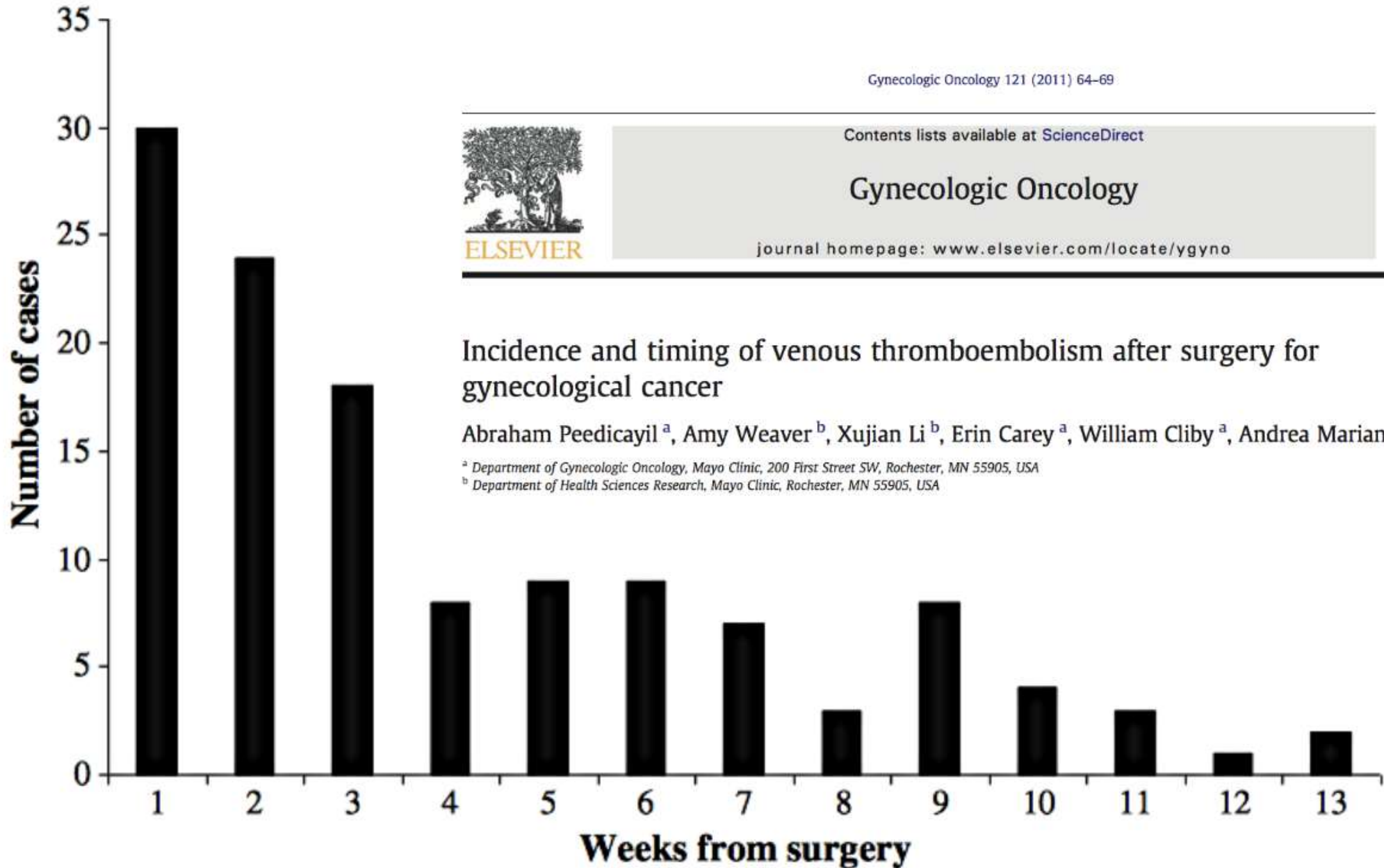


Gynaecological cancer and VTE

- Ovarian cancer: 10% (clear cell cancer 27%)
- Endometrial cancer: 1.5 – 10.5% (advanced disease)
- Cervical cancer: 3 -4%

Risk of VTE – patient, tumour and treatment related





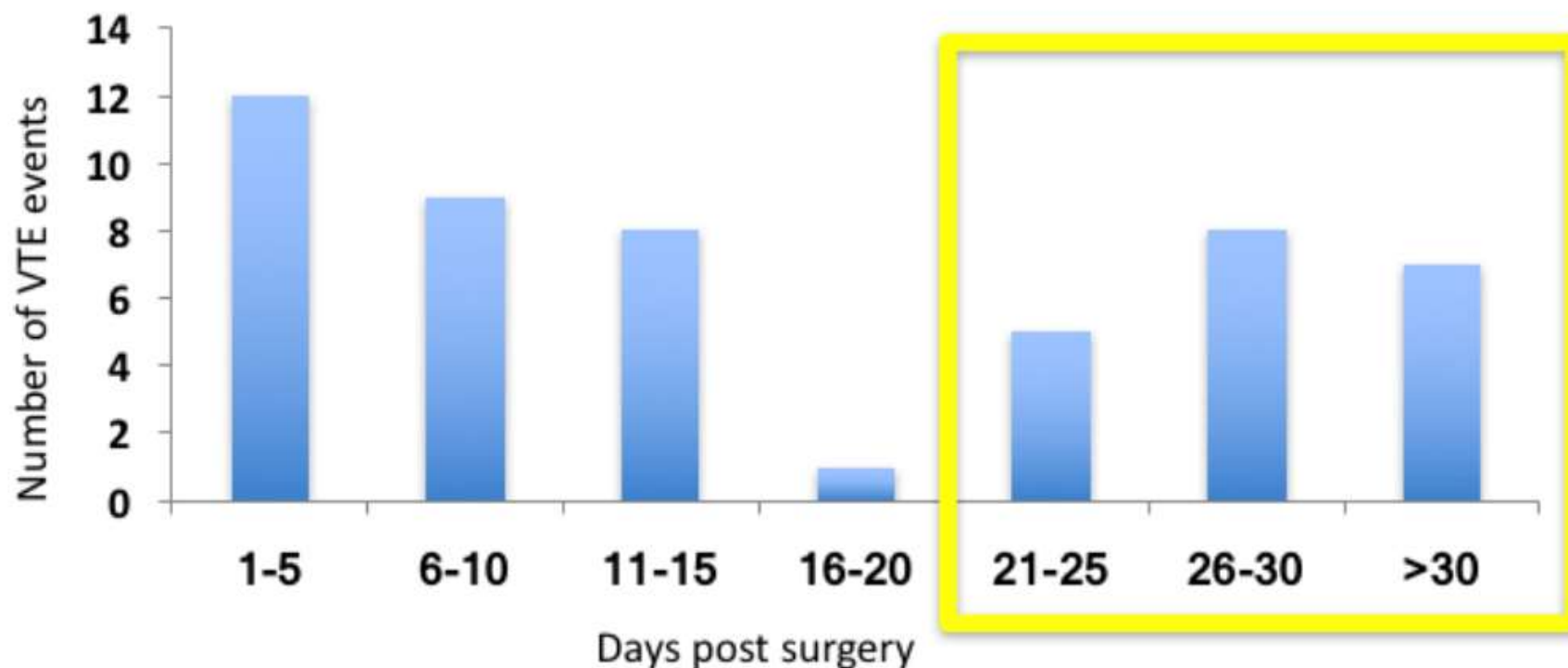
Incidence and timing of venous thromboembolism after surgery for gynecological cancer

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@RISTOS: VTE Risks persist in cancer surgery patients



40% of VTE were observed more than 21 days after cancer surgery

Agnelli G, et al. Ann Surg 2006

International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer



Dominique Farge, Henri Bounameaux, Benjamin Brenner, Francis Caiffinger, Philippe Debourdeau, Alok A Khorana, Ingrid Pabinger, Susan Salymoss, James Douketis, Ajay Kalkar

- VTE still occurs in gynaecological cancer patients post surgery despite LMWH prophylaxis
- Resistance to extended LMWH prophylaxis with increasing use of minimally invasive surgery



Need to identify higher risk and lower risk patients

Prophylaxis of venous thromboembolism (VTE) in surgically treated patients with cancer

International Advisory Panel ranking: 8-60 out of 9-00

- 1 Use of low-molecular-weight heparin (LMWH) once per day or low-dose unfractionated heparin (UFH) three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 12-24 h preoperatively and continued for at least 7-10 days; no data are available to allow conclusions regarding the superiority of one type of LMWH over another (grade 1A). Values and preferences: LMWH once per day is more convenient.
- 2 Evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer is insufficient (grade 2C). Values and preferences: similar.
- 3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A). Values and preferences: equal (no preferences).
- 4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in patients with cancer is indicated in patients with a high VTE risk and low bleeding risk (grade 1B). Values and preferences: longer duration of injections.
- 5 Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in patients with cancer undergoing laparoscopic surgery is recommended in the same way as for laparotomy (grade 2C).



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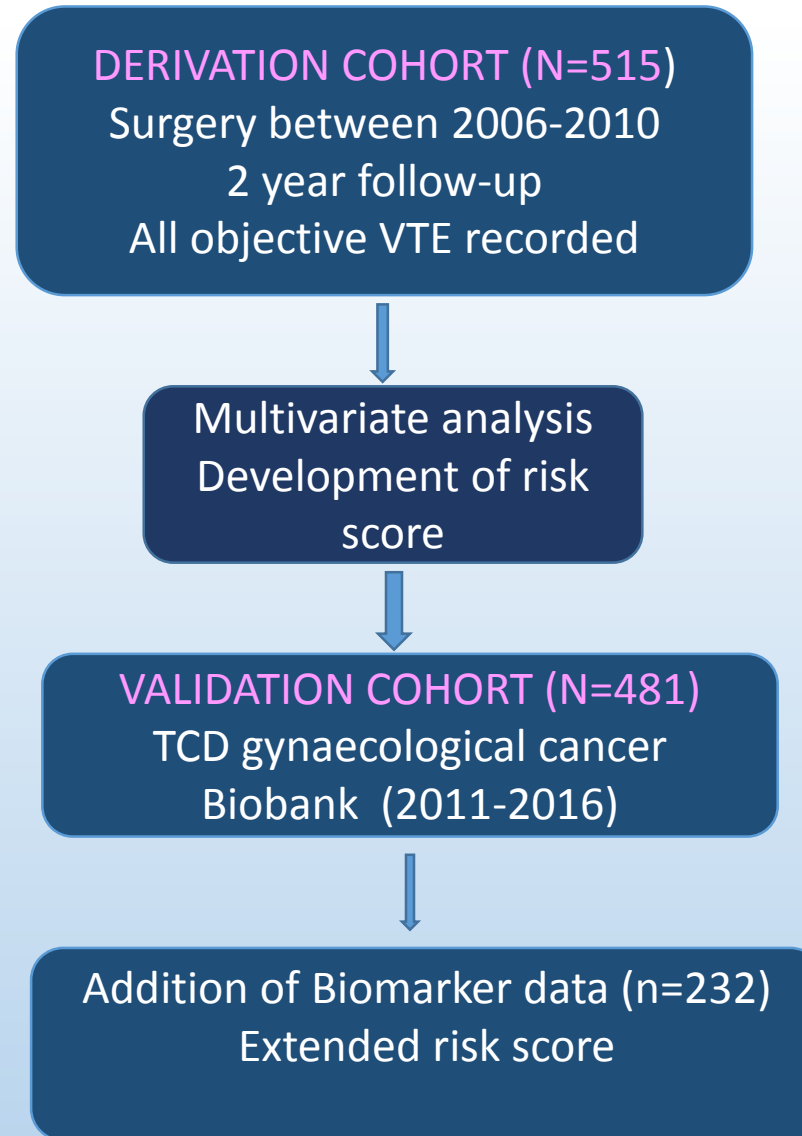


Aim of our study

Develop and validate a risk score for VTE risk in gynaecological cancers patients following surgery

To determine the predictive ability of an extended score following addition of haemostatic biomarker data.

Study Design





Derivation cohort

- Patients who underwent surgery for gynaecological cancer at St. James Hospital Dublin 2006-2010
- Large tertiary referral gynaecological cancer centre
- Patients with a previous VTE were excluded
- Patients on therapeutic or long term anticoagulation were excluded
- Follow up for at least 2 years from surgery
- All objectively diagnosed VTE recorded
- 95% open surgeries
- LMWH prophylaxis for duration of hospital stay

Demographics

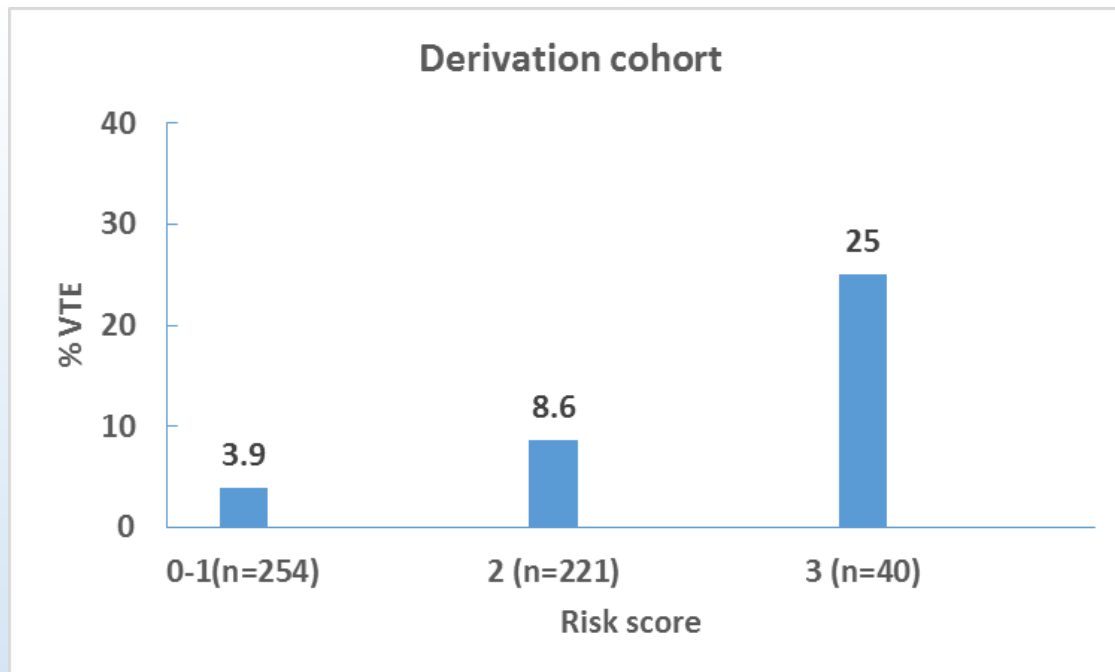
		No VTE (n=476)	VTE (n=39)
Age (yrs)			
Tumour site	Ovarian	265	24
	Endometrial	128	9
	Cervical	58	3
	Other	25	3
Histology	Clear Cell	16	2
	Serous	138	20
	Endometrial adenocarcinoma	96	5
	Squamous	64	5
	Borderline	64	1
	Other	98	6
Stage	I	286	10
	II	30	2
	III or IV	155	25
BMI	>30	140	16
	<30	336	23
Chemotherapy	Yes	211	30
	No	265	9
Radiotherapy	Yes	93	10
	No	383	29
Surgical complexity	Low	168	8
	Intermediate or High	308	31
Alive at follow up	Yes	403	27
	No	70	12



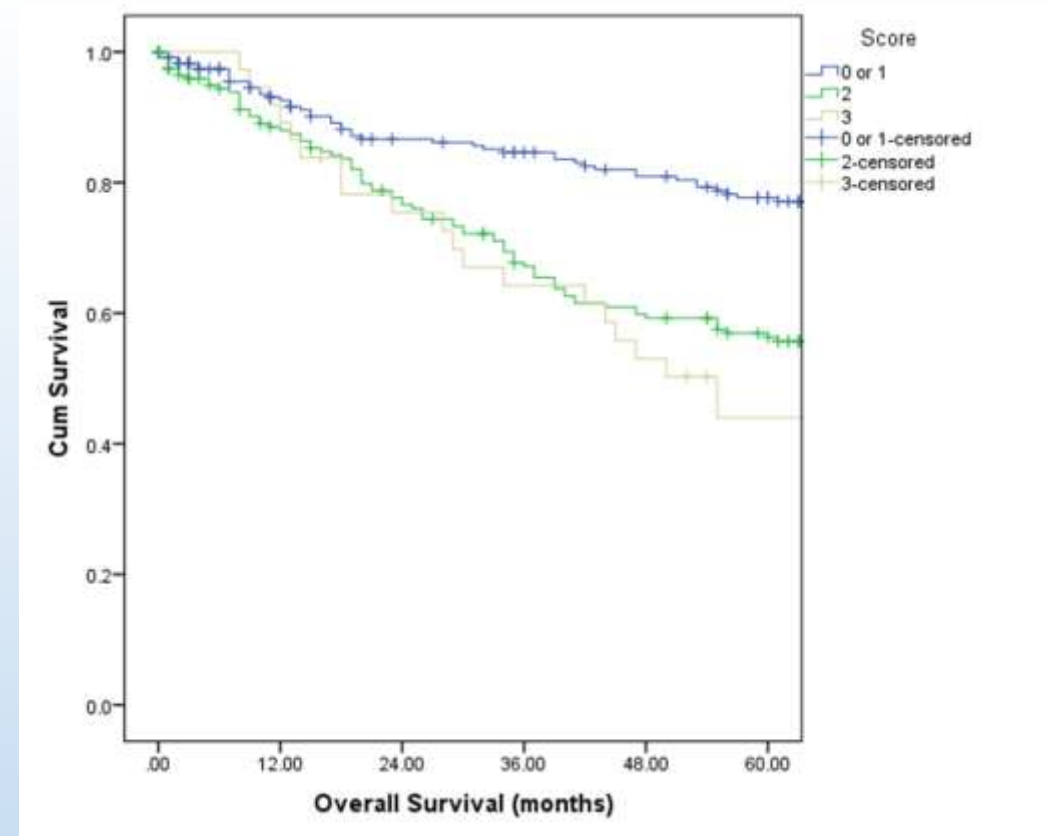
Multivariate analysis- variables

- Age
- Histological subtype
- Tumour origin
- Stage
- Grade
- Chemotherapy
- Radiotherapy
- Surgical complexity
- BMI
- White cell count
- Neutrophils
- Lymphocytes
- Haemoglobin
- Platelet count

Risk factor	Score
BMI >30	1
Chemotherapy treatment (before or after surgery)	1
Surgical complexity (Intermediate or high)	1



Risk Score	OR	(95% CI)
0-1	1	-
2	1.832*	0.766-4.384
3	6.210*	2.163-17.825



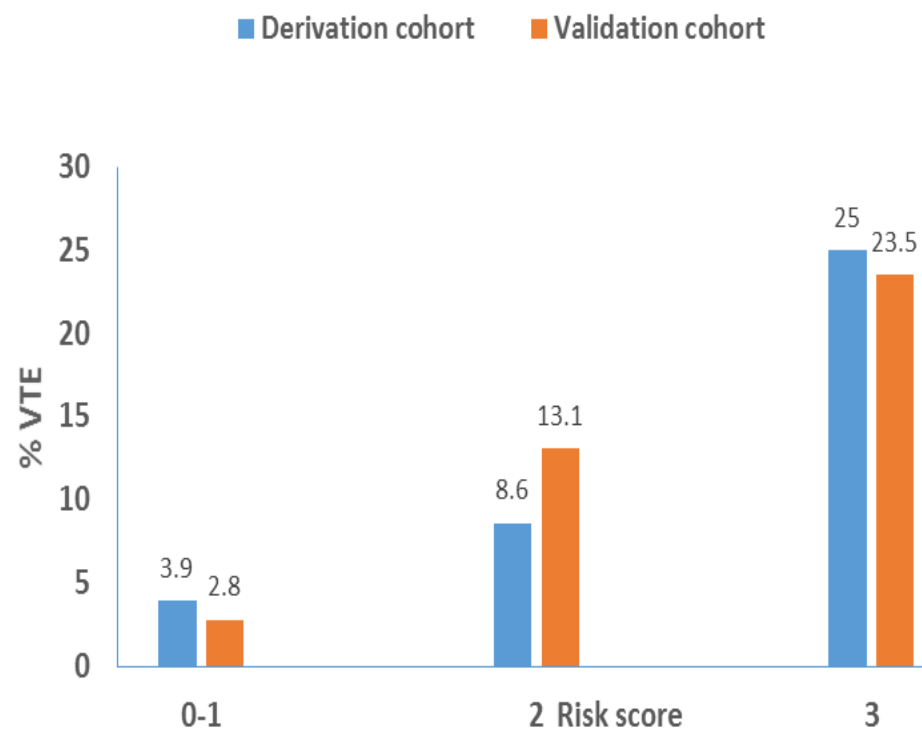
*Adjusted for age, tumour site and cancer stage



Validation cohort

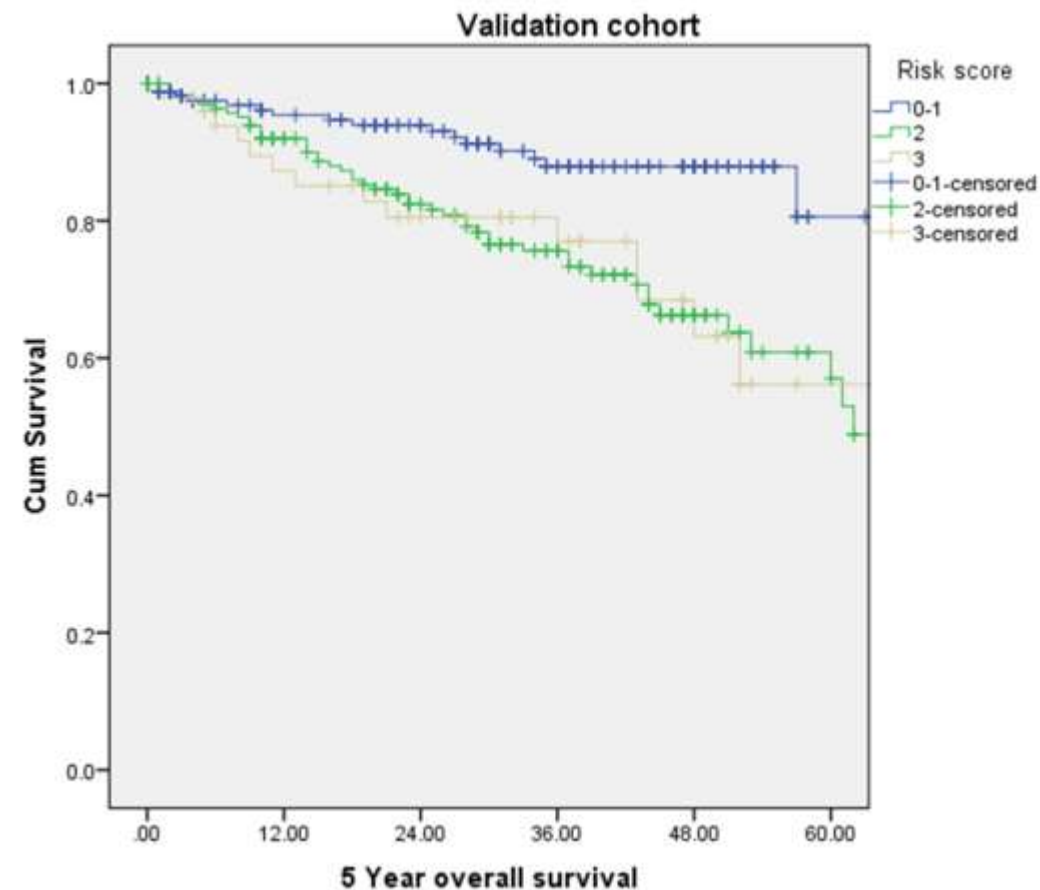
- TCD gynaecological cancer biobank
- Biobank of samples from >1000 gynaecological cancer patients with database of clinical information and follow-up.
- Blood samples taken before surgery
- Patients who underwent surgery from 2011-2016
- Patients were included following the same inclusion/exclusion criteria as the derivation cohort
- Larger number of laparoscopic surgeries
- Introduction of extended prophylaxis in May 2012

Demographics (Validation Cohort)		No VTE (n=440)	VTE (n=40)
Age (yrs)		57.7	60.4
Tumour Origin	Ovarian	164	20
	Endometrial	191	13
	Cervical	66	2
	Other	19	5
Histology	Clear Cell	16	4
	Serous	118	17
	Endometrial adenocarcinoma	157	10
	Squamous	56	1
	Other	99	5
Stage	I	237	10
	II	39	2
	III or IV	146	24
BMI	>30	152	22
	<30	221	18
Chemotherapy	Yes	235	30
	No	204	10
Radiotherapy	Yes	292	29
	No	132	5
Surgical complexity	Low	136	7
	Intermediate or High	303	33
Surgery type	Open	250	33
	Laparoscopic	184	7
Extended prophylaxis	Yes	376	30
	No	64	10
Alive at follow up	Yes	399	27
	No	41	13

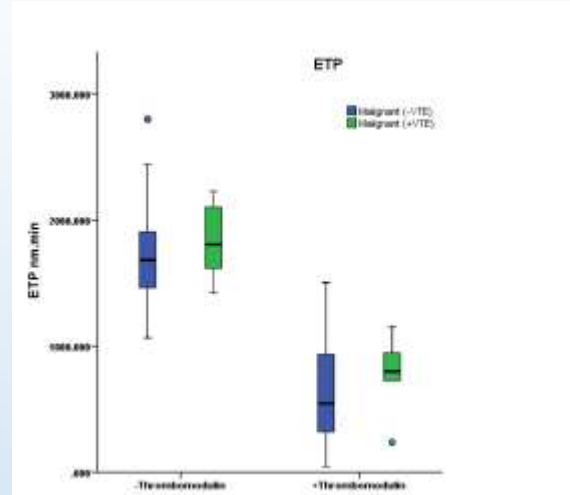
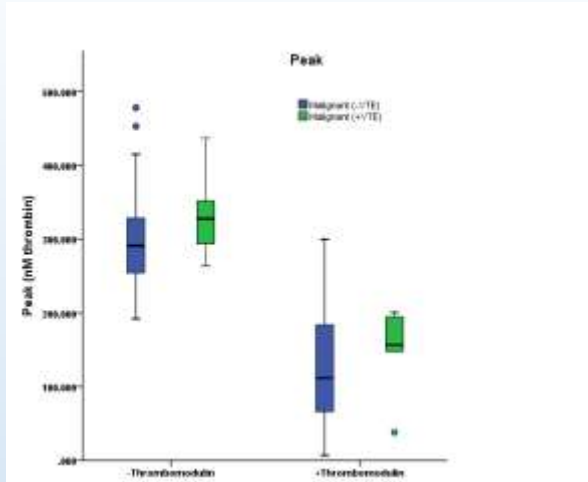


Risk Score	OR	(95% CI)
0-1	1	-
2	3.496*	1.189-10.285
3	6.680*	1.99-22.409

*Adjusted for age, tumour site and stage



Addition of Biomarkers



- Study in ovarian cancer suggested thrombin generation (ETP) was a potential predictor
- Peak or ETP?
- 1pm or 5pm TF?
- Addition of thrombomodulin?

Abu Saadeh et al, 2016

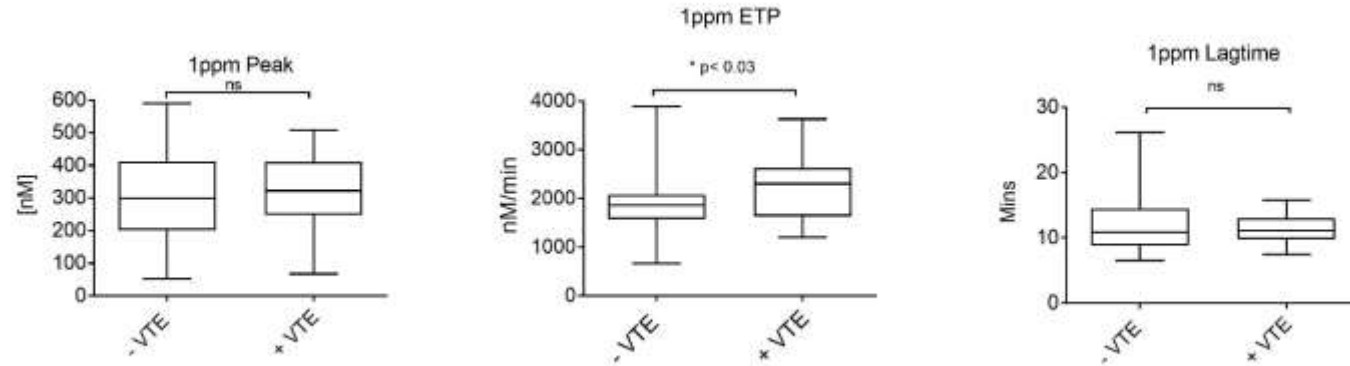
Optimisation study

- 24 VTE compared with 48 non VTE gynae cancer patients from the validation cohort matched for age histology, tumour site, treatment
- Samples taken before surgery
- ETP assay: 1pm , 5pM TF +/- Thrombomodulin

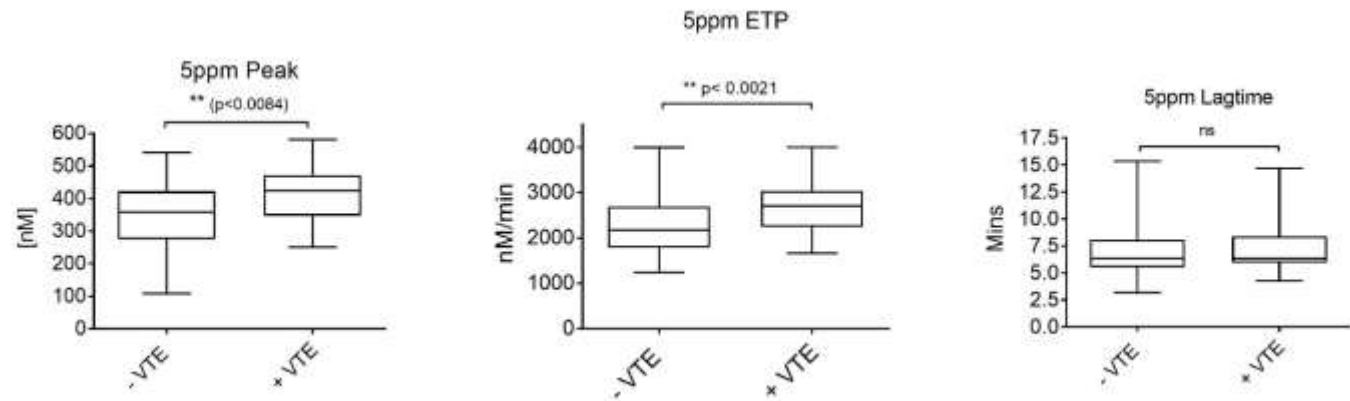


ETP optimisation

1 pM TF



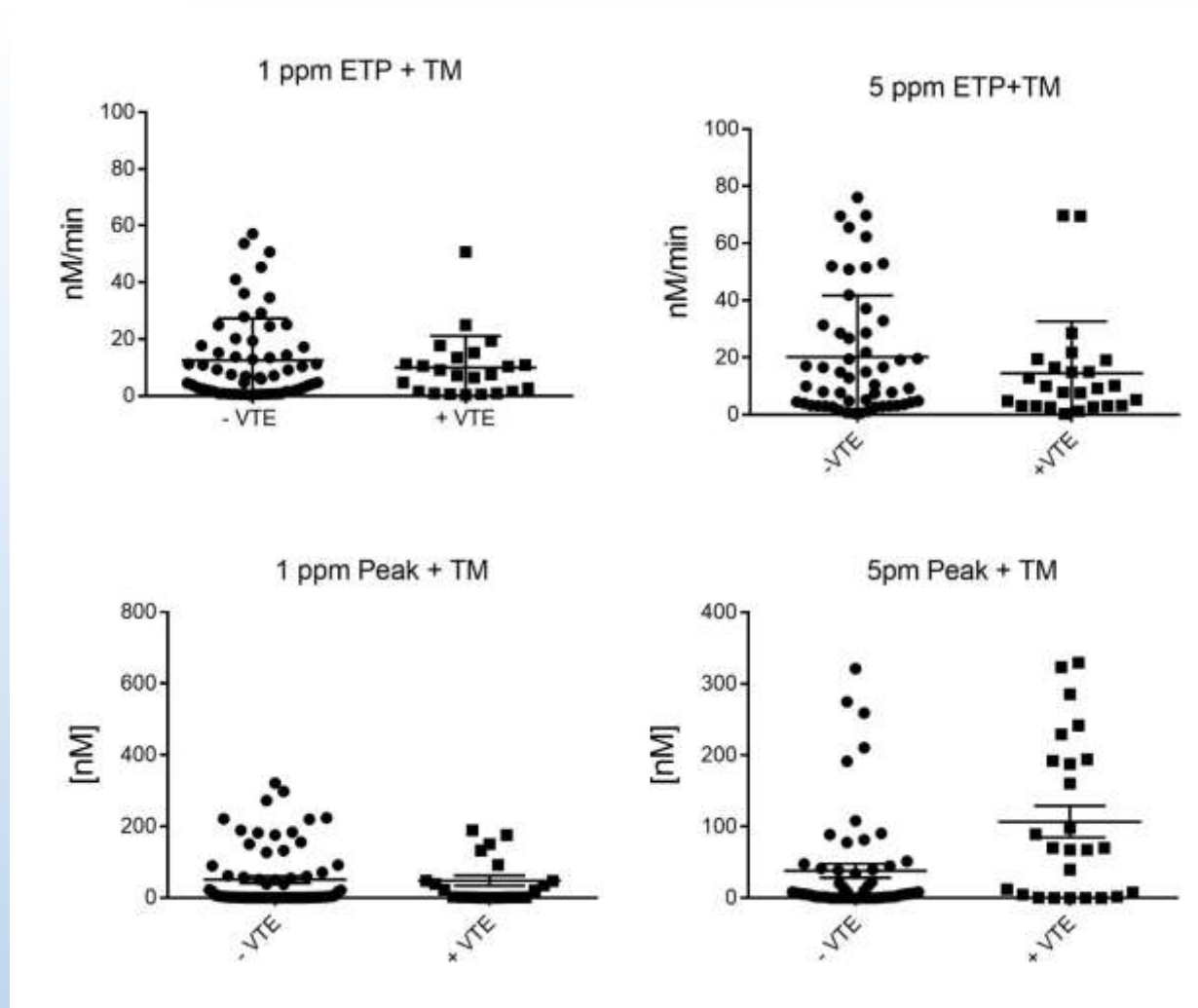
5 pM TF



- 5pm and 1pm TF showed significant increase in ETP in VTE.
- 5pm TF ETP was the most reproducible (CV <10%)



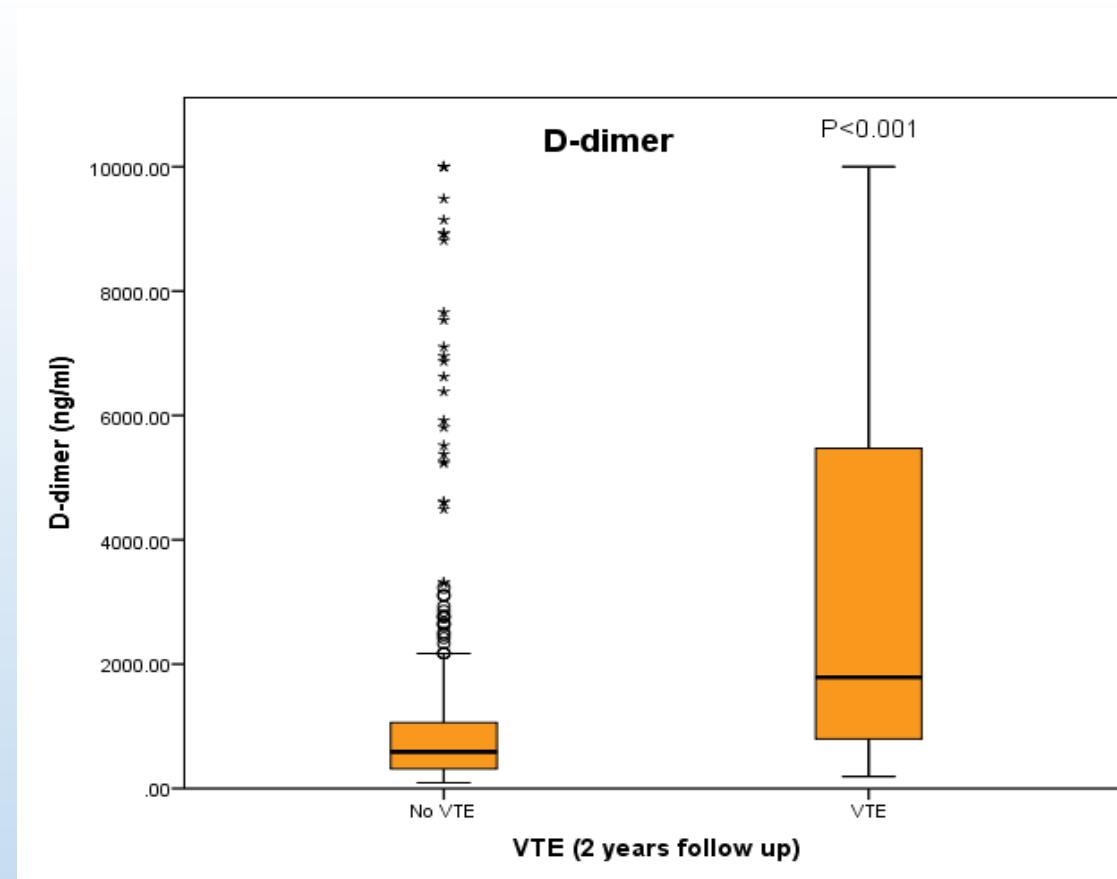
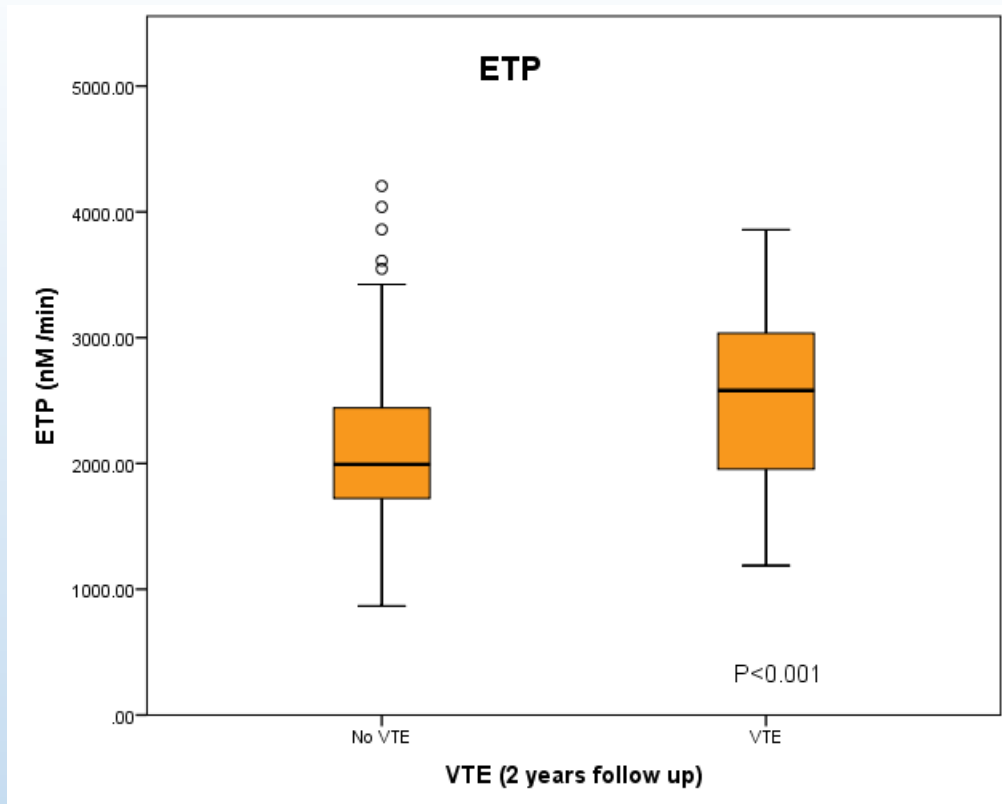
Addition of Thrombomodulin



- 5pm +TM was significant but variability was an issue



Biomarkers in the Validation cohort



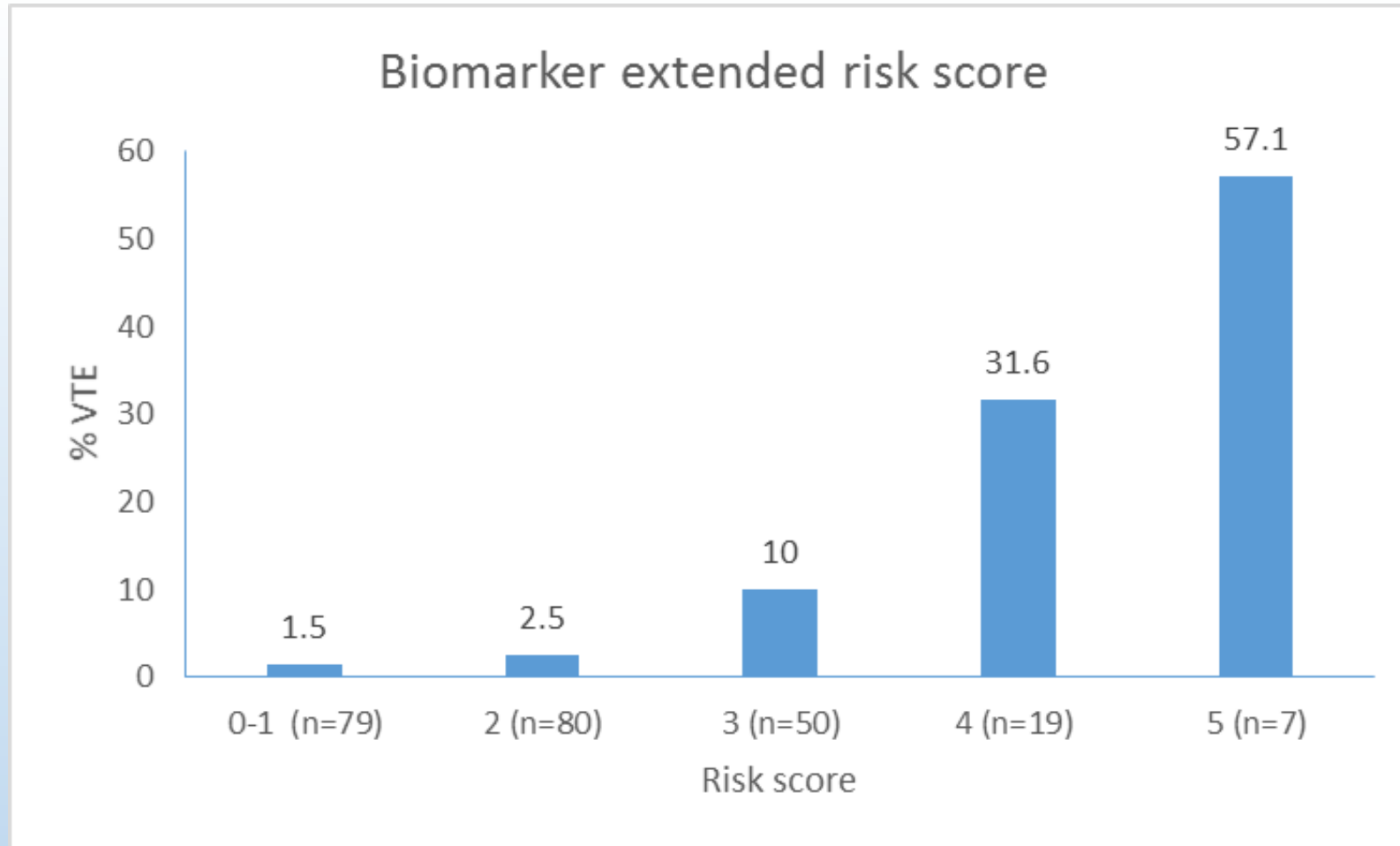
- ETP measured at 5pm
- D-dimer measured in all gynaecological cancer patients in the hospital laboratory

Extension of the score with biomarker data

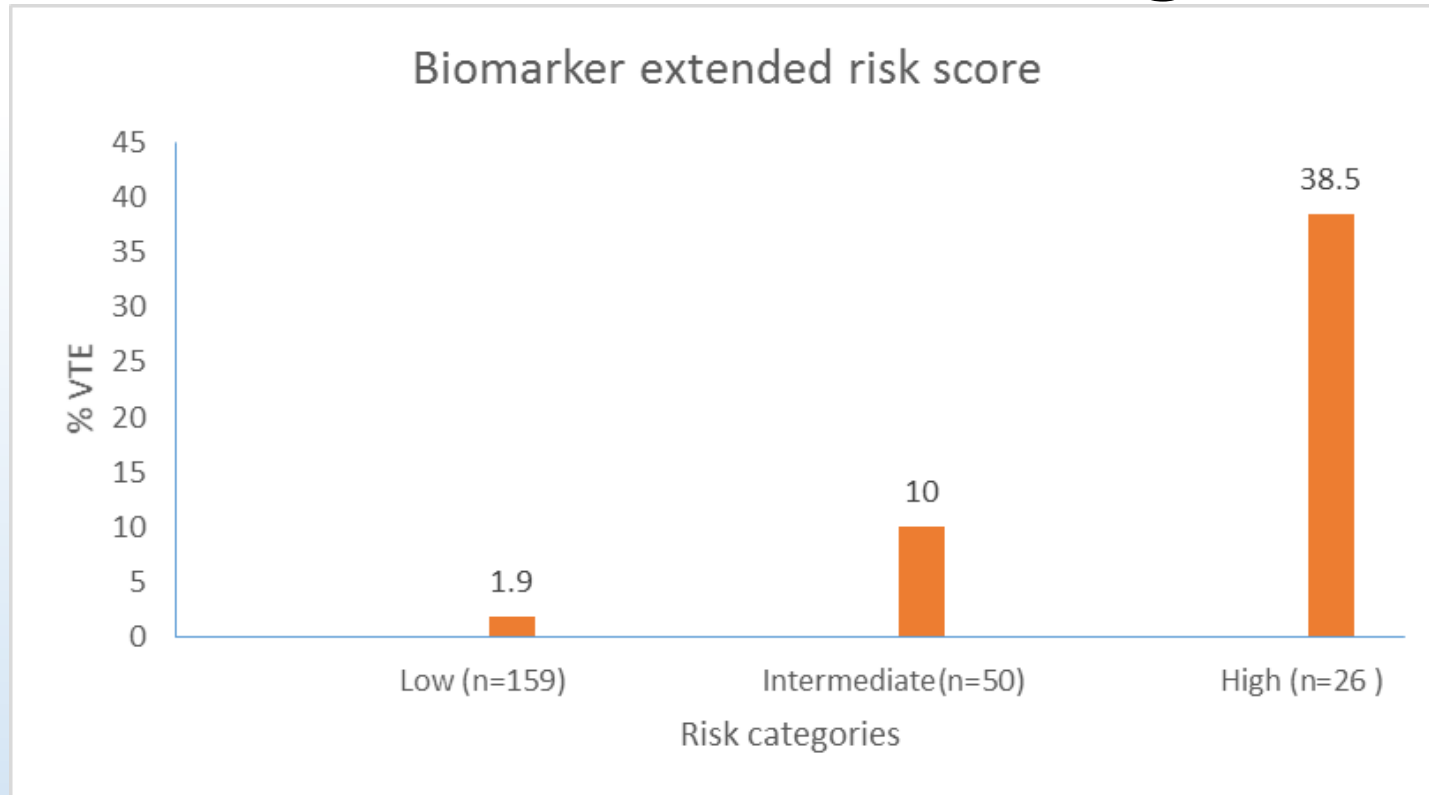
- Data available on both biomarkers for 232 patients(VTE n=18)
- Score of +1 was added for values over the 75th Centile

BMI>30	1
Surgical complexity =Intermediate /high	1
Chemotherapy treatment (before or after surgery)	1
ETP >2460 nm/min	1
D-dimer >1260	1

Biomarker extended risk score- results



Low Intermediate and High risk

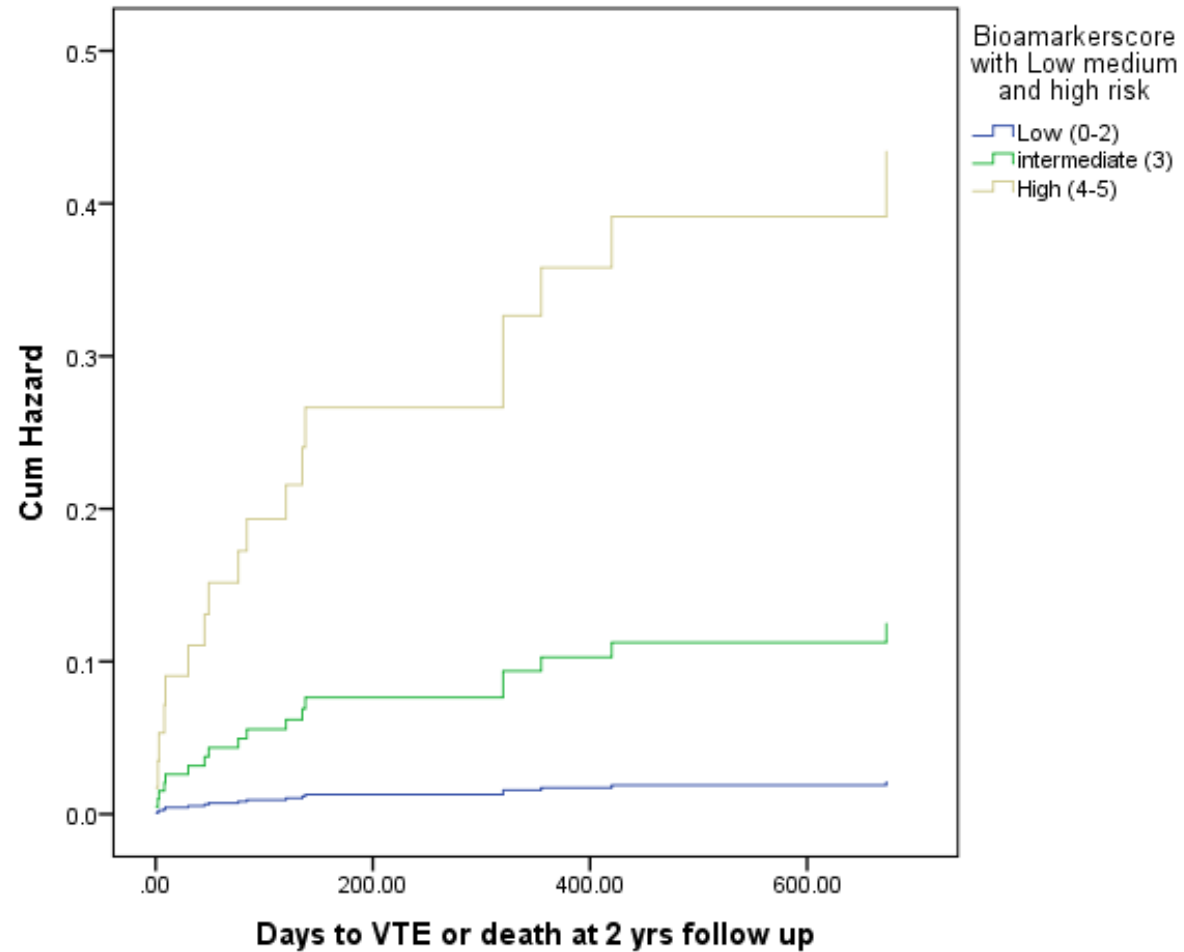


Risk category	OR	(95% CI)
Low	1	-
Intermediate	6.720	1.406-32.11
High	28.549	6.134-132.875

Adjusted for age, tumour site and stage



Biomarker extended risk score



Adjusted for age, tumour site and cancer stage



Sensitivity, specificity, PPV, NPV of the high risk category

	Sensitivity (%)	Specificity (%)	Positive predictive ability (PPV) (%)	Negative predictive ability (NPV) (%)
Derivation cohort-high risk score	25.6	93.7	25	93.8
Validation cohort high risk score	29.2	87.0	29.2	89.4
Validation cohort Biomarker extended high risk score	55.5	92.1	62.5	95.6

Conclusion

- Combining clinical risk factors with coagulation biomarkers in gynaecological cancer patients can identify both high and low risk patients
- This may lead to better strategies for preventing cancer associated VTE particularly following gynaecological cancer surgery



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