

RISK PREDICTION IN CAT: APPRAISING THE FIRST DECADE AND DEVELOPING THE FUTURE

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TAUSSIG CANCER INSTITUTE



Cleveland Clinic



DISCLOSURES

- Janssen
 - Sanofi
 - Halozyme
 - Bayer
 - Pfizer
 - AngioDynamics
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Initial Development And Validation

Modified and New Risk Scores

Applications of Risk Assessment

Improving Future Approaches



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BACKGROUND: RISK FACTORS EARLY 2000s

- Studies at the time focused primarily on
 - primary cancer site (pancreas, stomach, brain tumors, myeloma), or
 - settings (surgery, central catheters, hospitalization)
- Study reports had heterogeneous populations (mix of inpatients/outpatients/surgical patients)
- No formal risk tools were available
- Impact of simple biomarkers such as platelet/leukocyte counts had not been considered

BACKGROUND: RISK FACTORS

EARLY 2000s

- We decided to focus on cancer outpatients receiving systemic therapy
 - Majority of the patients at risk
 - Poorly represented in current studies
- Access to ANC Study Group cohort data was invaluable
 - Gary Lyman, PI
- Initial report identified multiple risk predictors of VTE in cancer¹
- Subsequent NCI funding allowed for development and validation of formal risk tool²

¹Khorana et al, Cancer 2005

²NCI K23CA120587

RISK SCORE: DEVELOPMENT AND VALIDATION

CLINICAL TRIALS AND OBSERVATIONS

Development and validation of a predictive model for chemotherapy-associated thrombosis

Alok A. Khorana,¹ Nicole M. Kuderer,² Eva Culakova,² Gary H. Lyman,² and Charles W. Francis¹

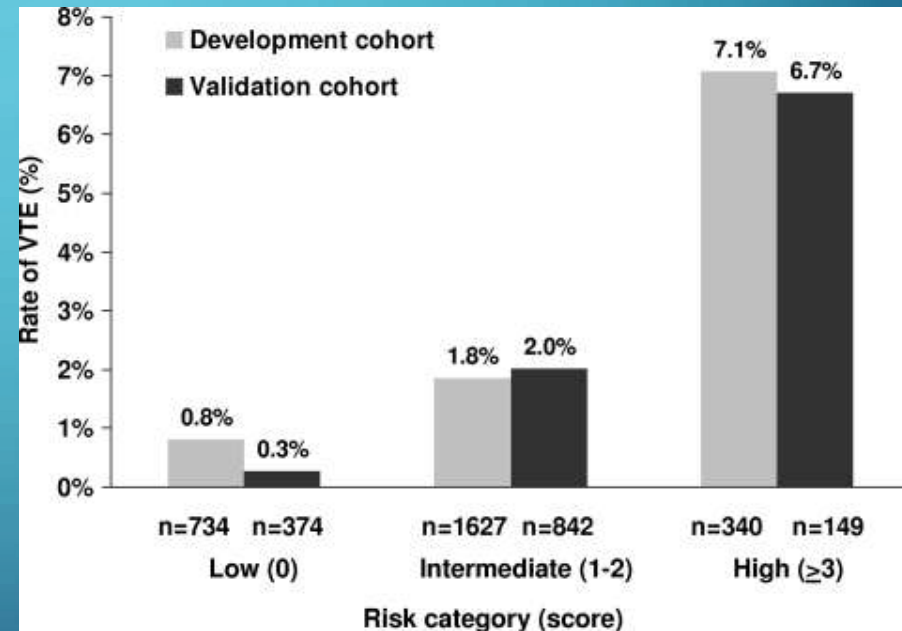
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BLOOD, 15 MAY 2008 • VOLUME 111, NUMBER 10



RISK SCORE DEVELOPMENT AND VALIDATION

Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq 350,000/\text{mm}^3$	1
Hb $< 10\text{g/dL}$ or use of ESA	1
Leukocyte count $> 11,000/\text{mm}^3$	1
BMI $\geq 35 \text{ kg/m}^2$	1



VALIDATION OF RISK SCORE

N>15,000

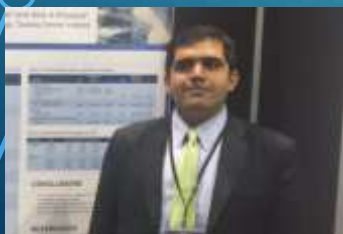


Table 2 Selected external validation studies of the Khorana score

Study	Type, specific patient population	Duration	No. of patients Total n = 12,064	Low-risk (score = 0); rate of VTE	Intermediate-risk (score = 1–2); rate of VTE	High-risk (score ≥ 3); rate of VTE
Kearney et al (2009) ⁵⁴	Retrospective	2 y	112	5%	15.9%	41.4%
Price et al (2010) ⁵⁵	Retrospective, pancreatic	NA	108	NA	14%	27%
Ay et al (2010) ⁵⁶	Prospective	643 d	819	1.5% (0.6–3.9%)	Score = 1; 3.8% (1.9–7.4%) Score = 2; 9.6% (6.2–14.7%)	17.7% (95% CI: 11.0–27.8%)
Moore et al (2011) ⁵⁷	Retrospective, tx with cisplatin		932	13%	17.1%	28.2%
Mandala et al (2012) ⁵⁸	Retrospective, phase I	2 mo	1,415	1.5%	4.8%	12.9%
Verso et al (2012) ¹³	Retrospective	113 d	378	3%		11.1%
Sharma et al (2012) ⁵⁹	Retrospective	NA	150	1.9%	3.9%	9.1%
Moinat et al (2014) ⁶⁰	Prospective, CVP	3 mo	1,097	NA	NA	OR: 3.5 (95% CI: 1–12.3)
Khorana et al (2014) ²²	Prospective	3 mo	35	NA	NA	23%
Lustig et al (2015) ⁶¹	Prospective	3 mo	580	4%	NA	11% (score ≥ 2)
Srikanthan et al (2015) ⁶²	Retrospective, disseminated GCT	11 y	254	NA	NA	OR: 11.8; p < 0.001
Santi et al (2015) ⁶³	Pooled analysis, NHL	NA	1,717	2.2% (95% CI, NA)	4.5% (95% CI: 2.3–6.7)	6.6% (95% CI: 2.4–10.8)
Posch et al (2016) ³⁰	Prospective	2 y	1,685		Score = 1; HR: 3.23 (1.53–6.81, p = 0.002) Score = 2; HR: 4.63 (2.20–9.75, p < 0.001)	HR 6.47 (2.99–14.00, p < 0.001)
Patell et al (2016) ⁴⁴	Retrospective	1 y	2,782	NA	Score ≥ 2 OR: 1.71 (1.16–2.59)	OR: 2.54 (1.29–5.03)

Abbreviations: CVP, central venous port; GCT, germ cell tumor; HR, hazard ratio; NA, not available; NHL, non-Hodgkin lymphoma; OR, odds ratio; tx, treatment.



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Modified and New Risk Scores

Applications of Risk Assessment

Improving Future Approaches

MODIFIED AND NEW RISK TOOLS

Select Risk Tools	Innovation/modification	Efficacy
Vienna CATS	D-dimer+ P-selectin	PPV 35% in score 5 or higher, validation pending
PROTECHT	Substitute gemcitabine or cisplatin, remove BMI	AUC/NNT similar in original report
ONKOTEV	Add mets, compression, prior VTE	Improved AUC, validation pending
COMPASS-CAT	Breast, colorectal, lung, ovarian only	Improved AUC 0.85, PPV 13%
“New” Vienna	Add D-dimer, remove other variables except primary site, use nomogram	Improved C =0.67, validated
Tic-ONCO	Includes genetic risk factors	Improved AUC 0.73, PPV 37%

MODIFIED AND NEW RISK TOOLS

- Only one multicenter head-to-head study with major limitations, allowed for enrollment of patients up to several months after starting chemotherapy¹
 - Over two-thirds of patients were months into chemotherapy
 - Platelet/leukocyte counts usually decline soon after initiating chemotherapy
 - Exclude patients already had VTE during first 3 months (most at risk)

¹van Es et al, *Haematologica* 2017



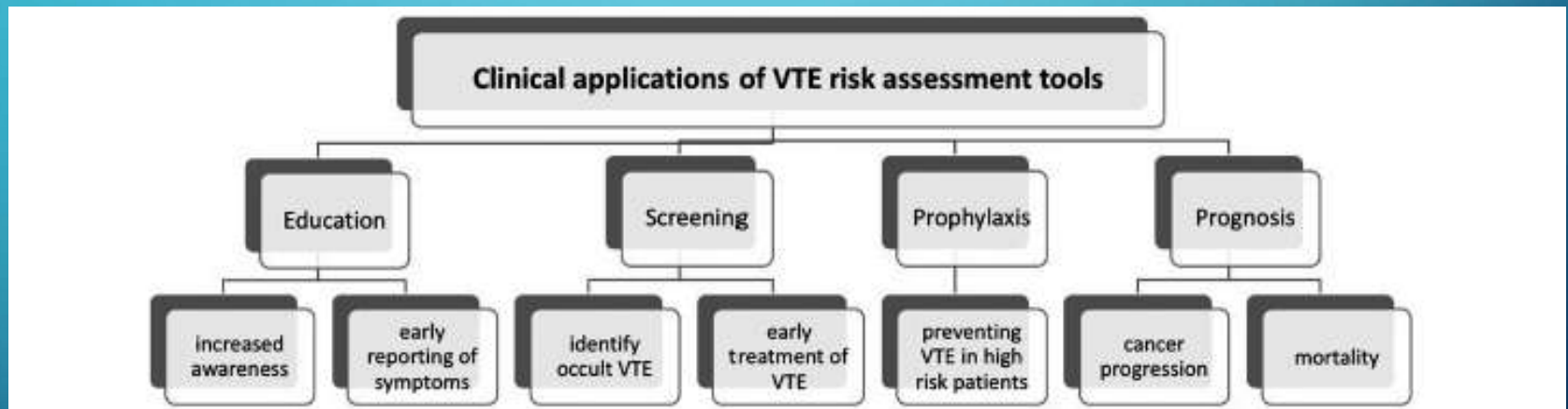
Initial Development And Validation

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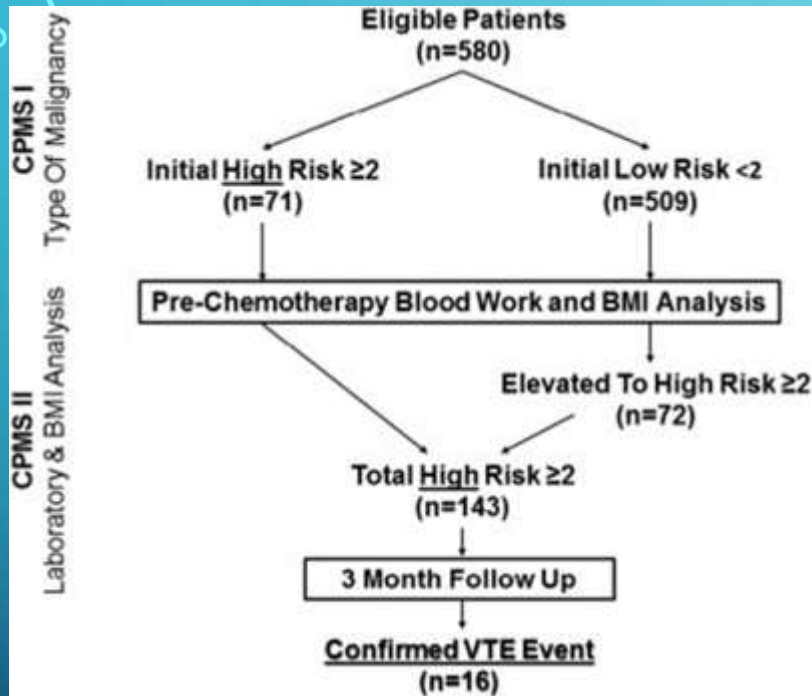
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APPLYING RISK ASSESSMENT

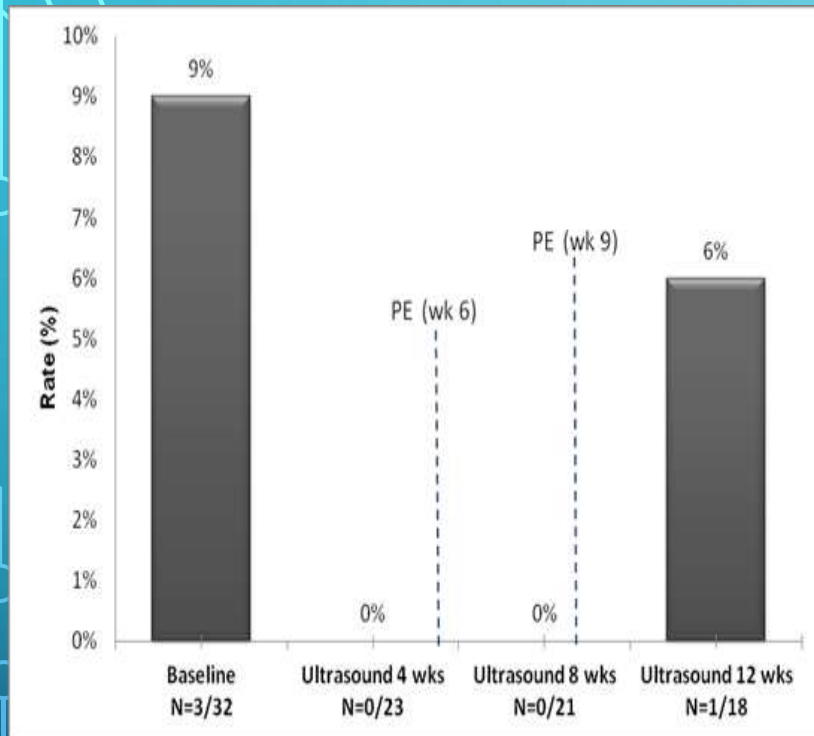


APPLYING RISK ASSESSMENT EDUCATION



- Ottawa Regional Cancer Center – sole provider of cancer care to 1.2 million people
- All new cancer patients were assessed by Risk Score using a computerized algorithm
- Over 3 month period, 25% of patients were found to be high-risk
- High-risk patients' providers were notified and patients were given educational material regarding warning signs/symptoms
- 11% developed VTE further validating Risk Score

APPLYING RISK ASSESSMENT EARLY DETECTION



Baseline characteristics of study population.

	Dalteparin	Observation	Total
Enrolled (n)	-	-	117
Baseline VTE, n (%)	-	-	10 (9%)

UR single institution, $KS \geq 3$

PHACS, multicenter $KS \geq 3$

Khorana AA et al *Throm Res* 2014
Khorana AA et al *Throm Res* 2016

APPLYING RISK ASSESSMENT EMR ALERTS IN EPIC

6/7/2017 visit with Patricia W Testmdonc, MD for Visit (SP) Office

BestPractice Advisory - Zzz Test,Famp L

High (Advisory: 1)

Your patient is at high risk for DVT. We recommend a screening ultrasound of lower extremities. Khorana Score

BestPractice Advisories
Click to view BestPractice Advisory history

Open SmartSet Do Not Open TAUSSIG HIGH RISK VTE ULTRASOUND

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The following actions have been applied:

✓ Sent: This advisory has been sent via In Basket

⚠ Acknowledge Reason

Suspend until later Not applicable. Do not show again

TAUSSIG HIGH RISK VTE ULTRASOUND [9652]

Taussig Ultrasound for VTE

TAUSSIG ULTRASOUND HIGH RISK VTE

<input checked="" type="checkbox"/> Suspected DVT (deep vein thrombosis), bilateral (HCC)	Diagnosis
<input checked="" type="checkbox"/> US LEG VEIN DVT BIL VAS Ordering provider must page CAT Clinic 21662	ONCE, Routine, VASLAB Enter the specific memo account number: Ultrasound tech to page CAT Clinic pager 21662 with positive or negative results.

APPLYING RISK ASSESSMENT PROGNOSIS

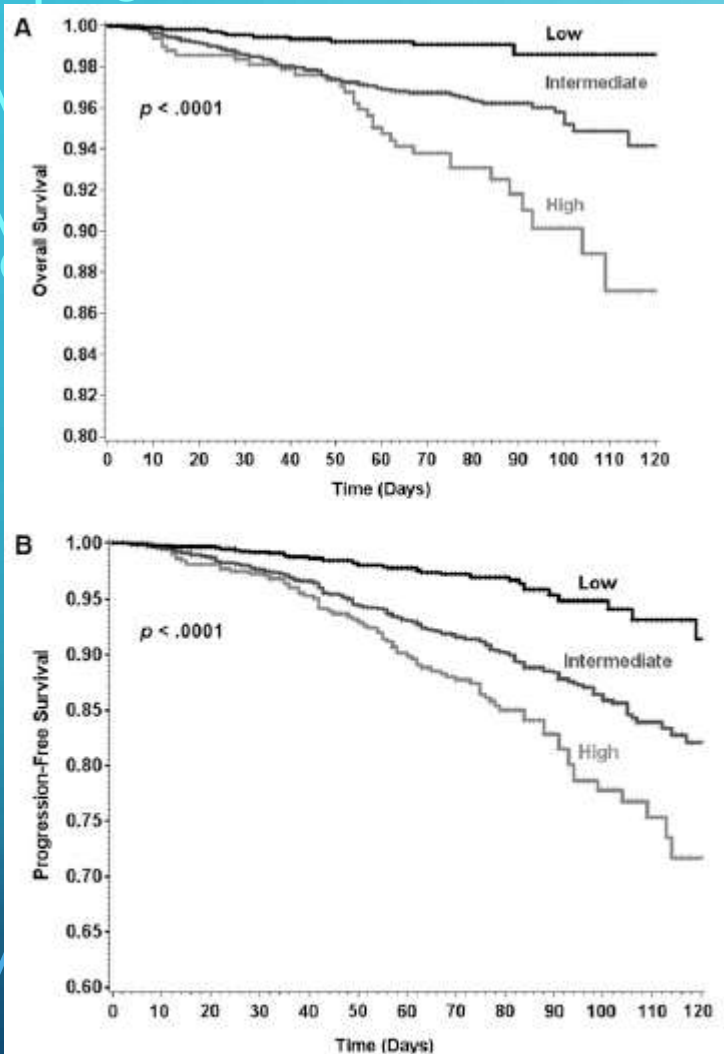
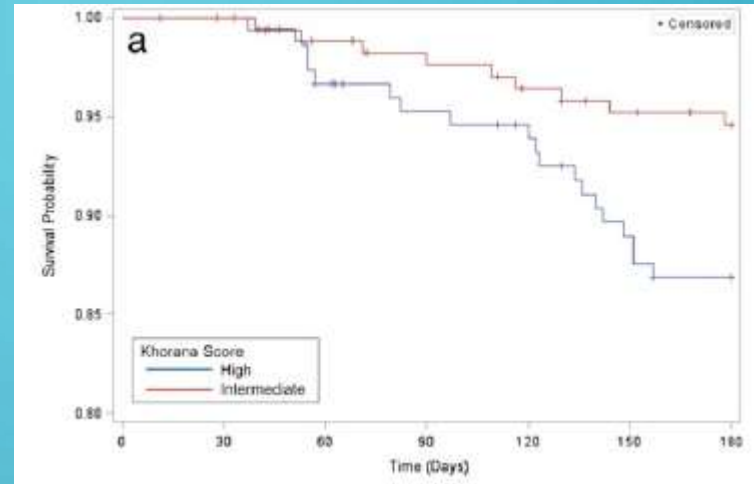
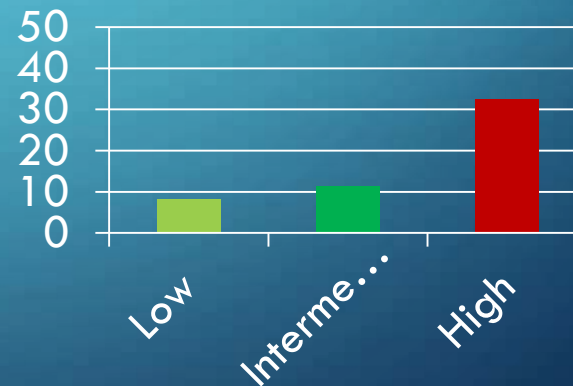


Figure 2. Kaplan-Meier analysis of overall and progression-free survival according to Clinical Risk Score group. **(A):** Overall survival. **(B):** Progression-free survival. Patients with intermediate or high risk based on Clinical Risk Score stratification were found to have worse prognosis than low-risk patients ($p < .0001$ for both).



Pancreas cancer, N= 334



Colorectal cancer, N =1,789

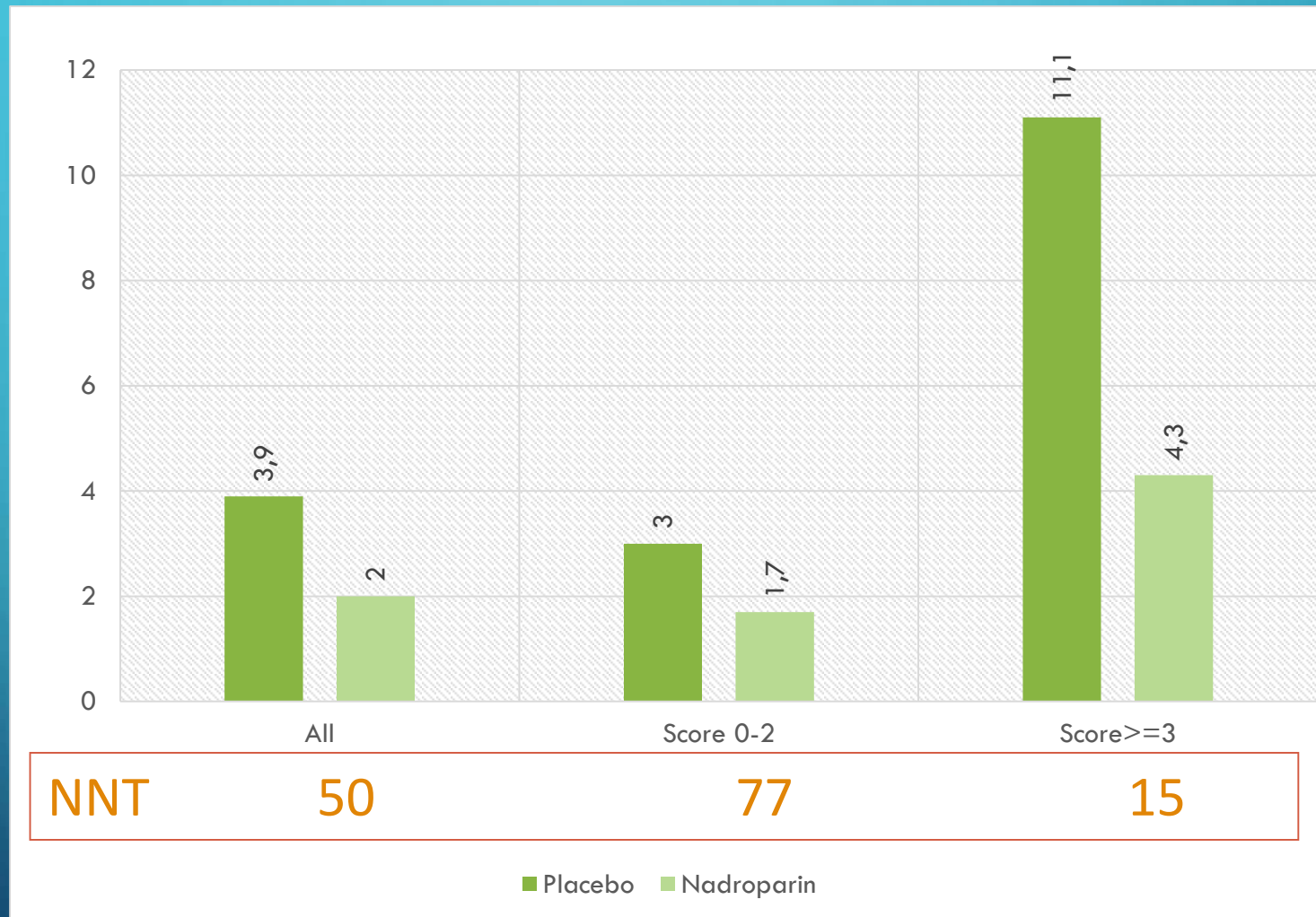
Kuderer et al *Oncologist* 2016

Sohal et al *Cancer* 2015; Sohal et al *ASCO GI* 2016

General cancer population, N= 4,405

APPLYING RISK ASSESSMENT: PROPHYLAXIS

PROTECHT BY RISK SCORE

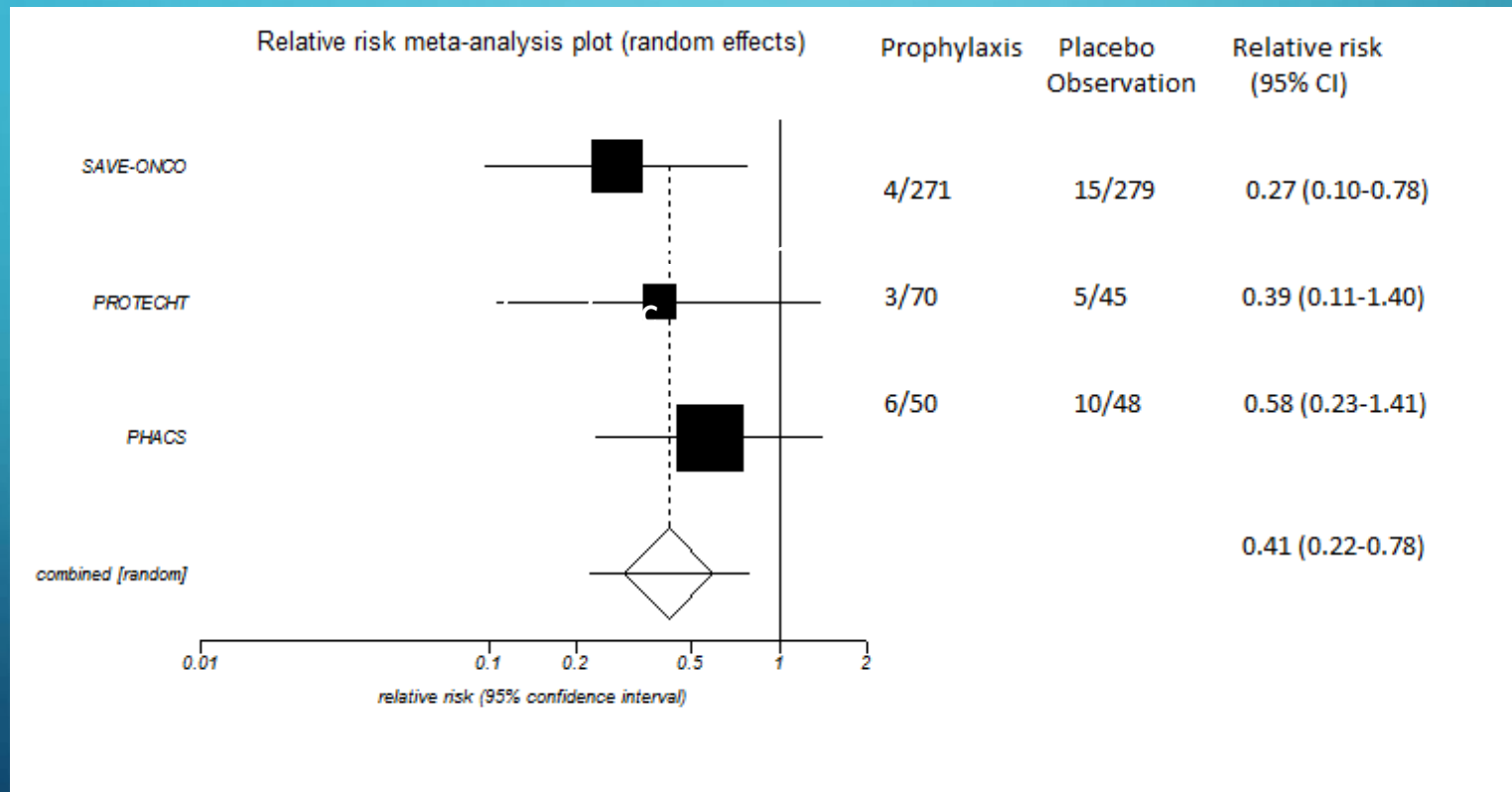


Verso et al, *Int Emerg Med* 2012

APPLYING RISK ASSESSMENT: PROPHYLAXIS

META-ANALYSIS OF STUDY PATIENTS WITH “KHORANA SCORE” ≥ 3 : SAVE-ONCO¹, PROTECHT² AND PHACS³

N=763 patients with score ≥ 3



Pooled RR for VTE with prophylaxis 0.41 (95% CI: 0.22 to 0.78); P = 0.006

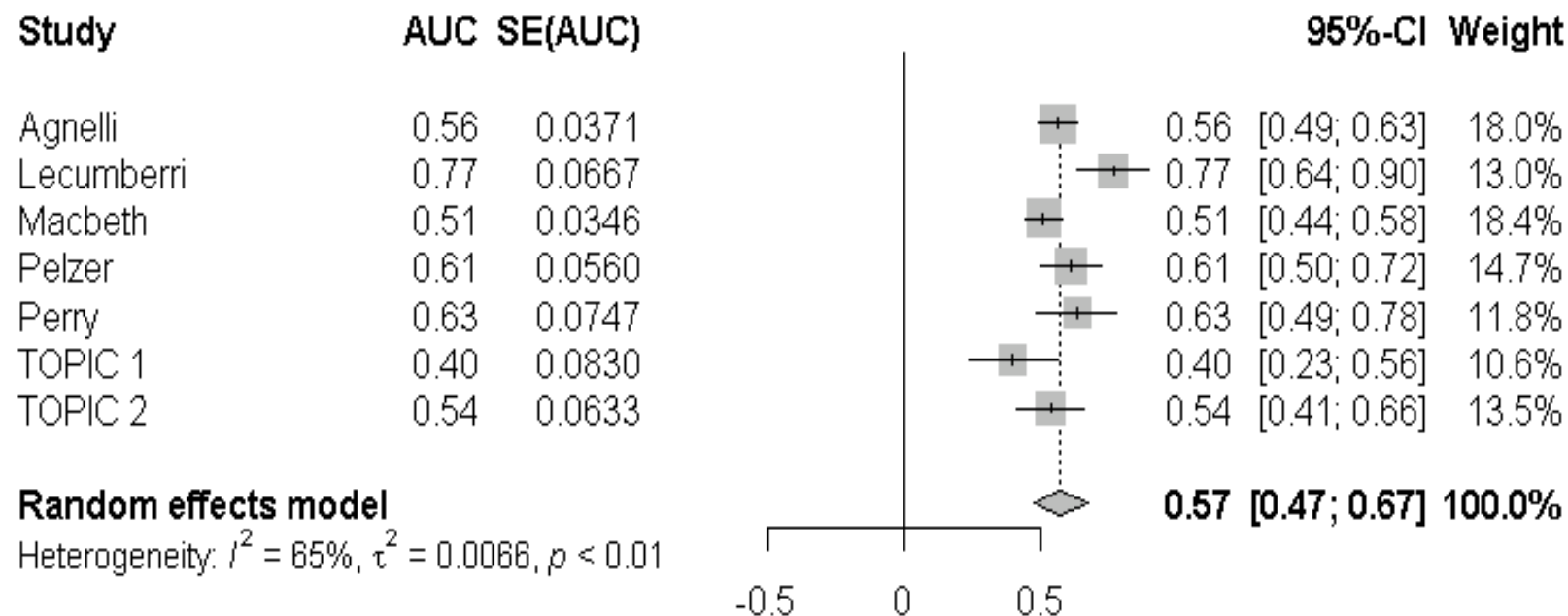
¹George et al 2011; ²Verso et al 2012

³Khorana et al *Throm Res* 2016

APPLYING RISK ASSESSMENT: PROPHYLAXIS

AN INDIVIDUAL PATIENT DATA META-ANALYSIS [N=7]

STUDY N=3403



- 6-month VTE was 9.8% among high-risk Khorana score patients and 6.4% among low-to-intermediate risk patients (OR 1.6; 95%-CI 1.1-2.2)
- In high-risk patients, LMWH decreased VTE by 64% vs placebo or observation (OR 0.36; 95%-CI, 0.22-0.58)

APPLYING RISK ASSESSMENT: EXPANDING INDICATION FOR PROPHYLAXIS

Study	Agent	Study Population	N
AVERT	Apixaban 2.5 mg BID x 6 mos	“Khorana score” ≥ 2	600
CASSINI	Rivaroxaban 10 mg QD x 6 mos	“Khorana score” ≥ 2	841



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STRENGTHS AND LIMITATIONS

Table 3

Strengths and limitations of the risk score.

Strengths	Limitations
Simplicity, utilizes commonly measured variables	Low positive predictive value
High negative predictive value	Majority of patients classified as “intermediate” risk
Multiple external validation studies spanning a decade	Not consistently effective in single sites of cancer e.g., lung
Predictive of benefit from thromboprophylaxis	Need for BMI variable in non-US populations has been questioned
Predictive of screen-detected DVT	
Predictive of mortality	

IMPROVING FUTURE APPROACHES TO RISK ASSESSMENT: EXISTENTIAL CHALLENGES

How can risk scores be improved?

Do we improve by making more complex?

e.g., adding -omic risk factors

Do we improve by making more narrow?

e.g., scores for lung, breast, colon ad infinitum

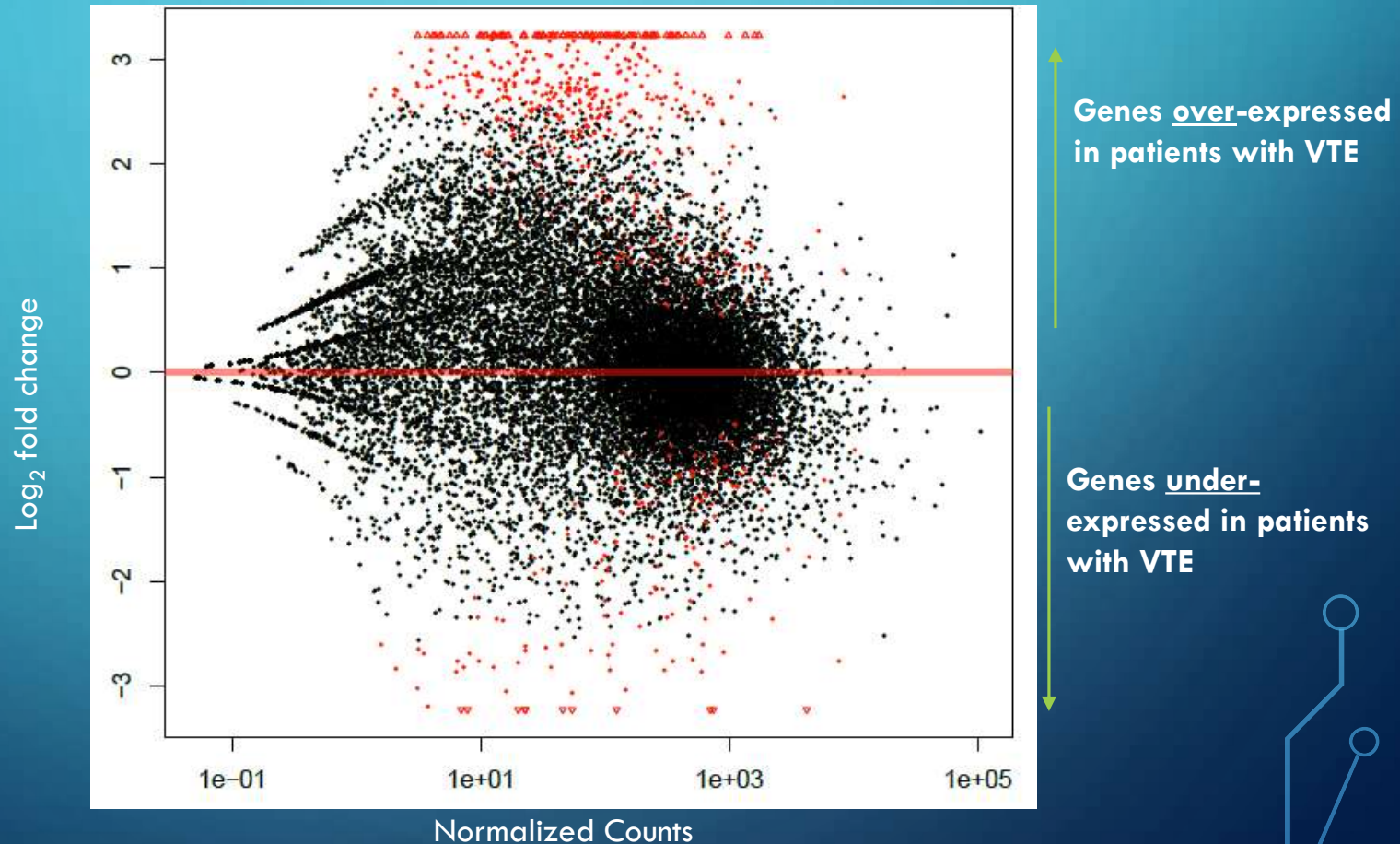
Do we continue to search for the elusive pan-biomarker?

caution: tissue factor saga

IMPROVING FUTURE APPROACHES

- Cancer medicine is in paradigm shift
- Genomics testing of tumor tissue is widely available clinically
- “Liquid biopsies” (circulating tumor DNA) and miRNA profiling approaches are also becoming more common
- Biologically agnostic, overcomes “streetlight effect”

DIFFERENTIAL GENE EXPRESSION IN LUNG CANCER PATIENTS WITH AND WITHOUT VTE



DIFFERENTIAL GENE EXPRESSION IN LUNG CANCER PATIENTS WITH VTE

Genes Over-Expressed in Lung Cancer Patients with VTE

Gene	Log (fold-change)	Q value	Mechanism
MIAT	4.8	0.000003	Myocardial infarction transcript
SHC4	4.6	0.00003	Ras activating pathway
CR1	4.2	0.0004	Complement receptor
NLRP14	3.8	0.0001	Activates and regulates inflammatory response
IL5RA	3.6	0.006	Activates and regulates inflammatory response
CLNK	3.6	0.004	Regulates inflammatory response

DIFFERENTIAL GENE EXPRESSION IN LUNG CANCER PATIENTS WITH AND WITHOUT VTE: GSEA

Associated Gene Set Pathways	Enrichment Score	FDR q Value
IL2-STAT5 Signaling	0.3026	0.4401
Allograft Rejection	0.2752	0.2585
IL6-JAK-STAT3 Signaling	0.2698	0.6826
Interferon-gamma Response	0.2592	0.6489
K-RAS Signaling Up	0.2290	0.6795
Complement	0.2044	0.675
Inflammatory Response	0.2002	0.7792
K-RAS Signaling Down	-0.2279	1
Apoptosis	-0.3061	0.7323

IMPROVING FUTURE APPROACHES (2)

- *Identifying innovative biomarkers, using –omics approaches*
- Setting the bar high
 - If sacrificing simplicity, need risk tools with high PPV (40+% range)
- Identify predictors of bleeding in cancer patients
- Continued spirit of collaboration is vital

CONCLUSIONS

- Risk assessment approaches have undergone considerable evolution in the past decade
 - Formal development and validation
 - Biomarker screening and development
- Emerging applications for risk assessment need to be clinically integrated
- Many challenges remain
 - Improving specificity while maintaining applicability
- Credit for the success goes to the collaborative spirit of the CAT community
 - Key to continued improvements