CANCER-ASSOCIATED THROMBOSIS: BIOMARKER OF THROMBO-INFLAMMATION

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Conflict Of Interest

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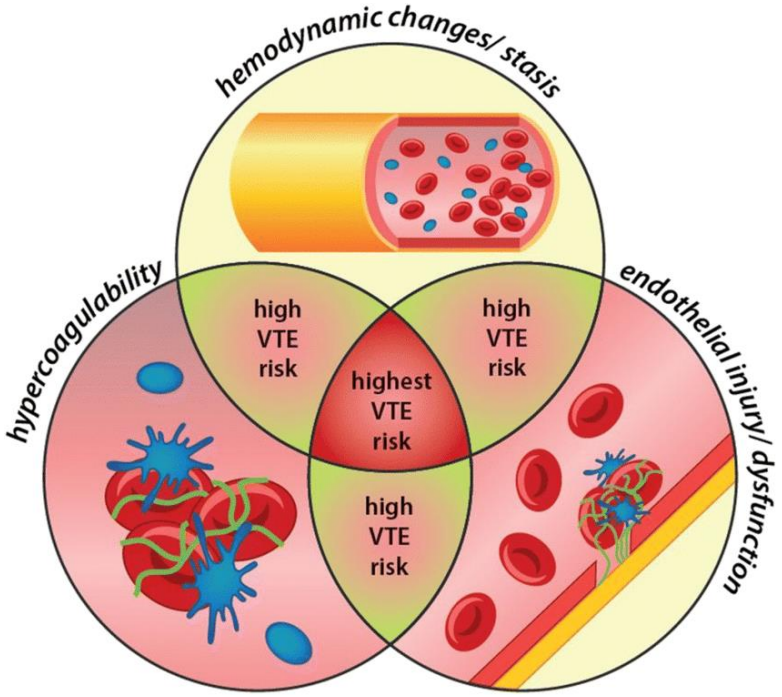
INTRODUCTION

- ≈4-20% of all VTE cases are associated with cancer[1]
- VTE is a leading cause of death in cancer patients[2]
  -- 1 in 5 cancer patients will die with VTE
- Higher mortality in cancer patients with VTE than those without[3]
- Mortality rate 2.2-3.7% in CAT patients[3]
- Effective prevention and treatment reduces morbidity and may decrease mortality

1. Khorana, A.A., et al., *Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy*. J Thromb Haemost, 2007. **5**(3): p. 632-4.
2. Institute, N.C. *Cancer Statistics*. Available from: https://www.cancer.gov/about-cancer/understanding/statistics.
3. Walker, A.J., et al., *Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases*. Eur J Cancer, 2013. **49**(6): p. 1404-13.
4. Chan, T.S., et al., *Increasing incidence of venous thromboembolism due to cancer-associated thrombosis in Hong Kong Chinese*. Thromb Res, 2014. **134**(5): p. 1157-9.

Direct Mechanisms Involved In Cancer-Associated Thrombosis



Virchow's Triad

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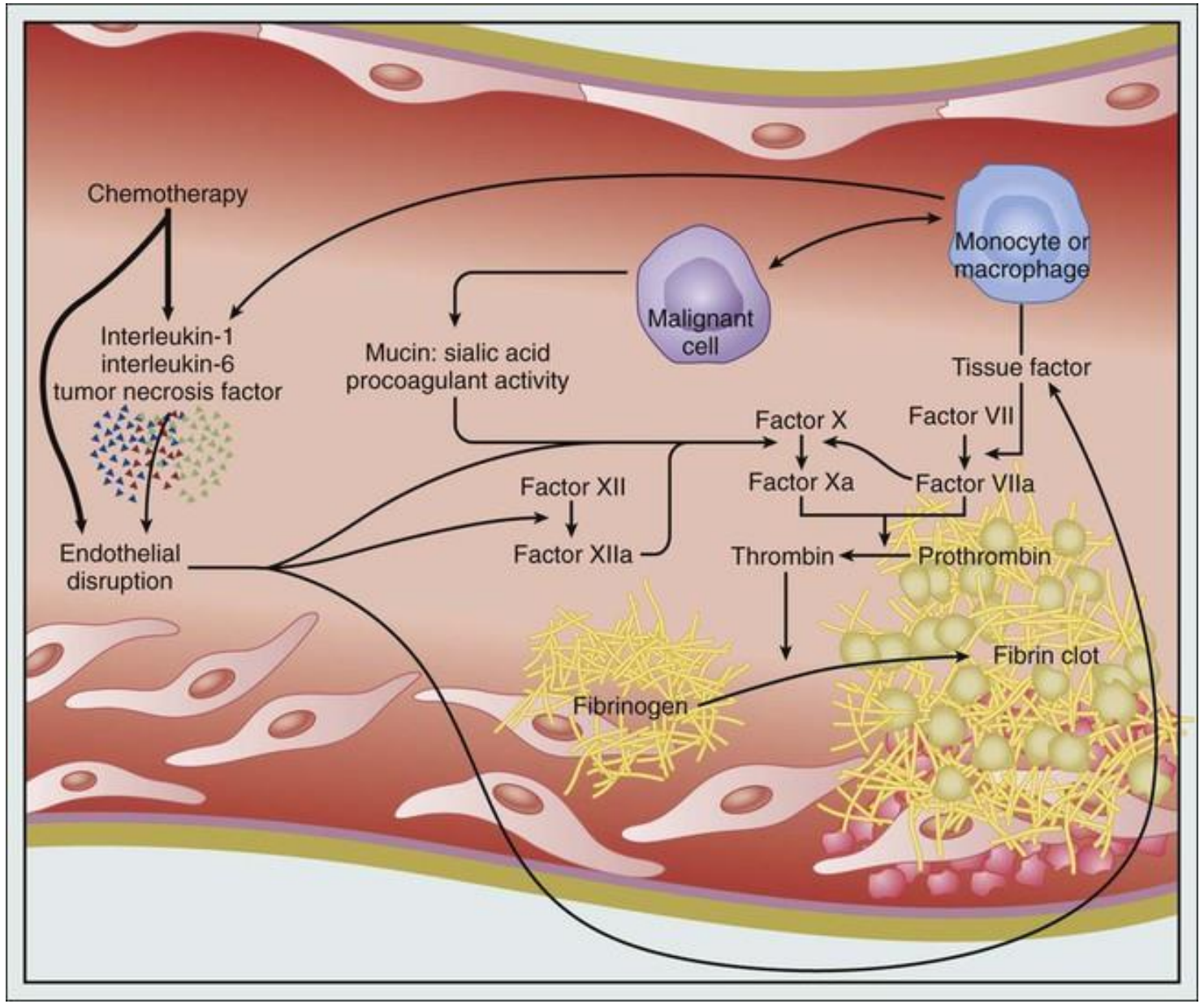


https://www.nejm.org/doi/full/10.1056/NEJMp030086

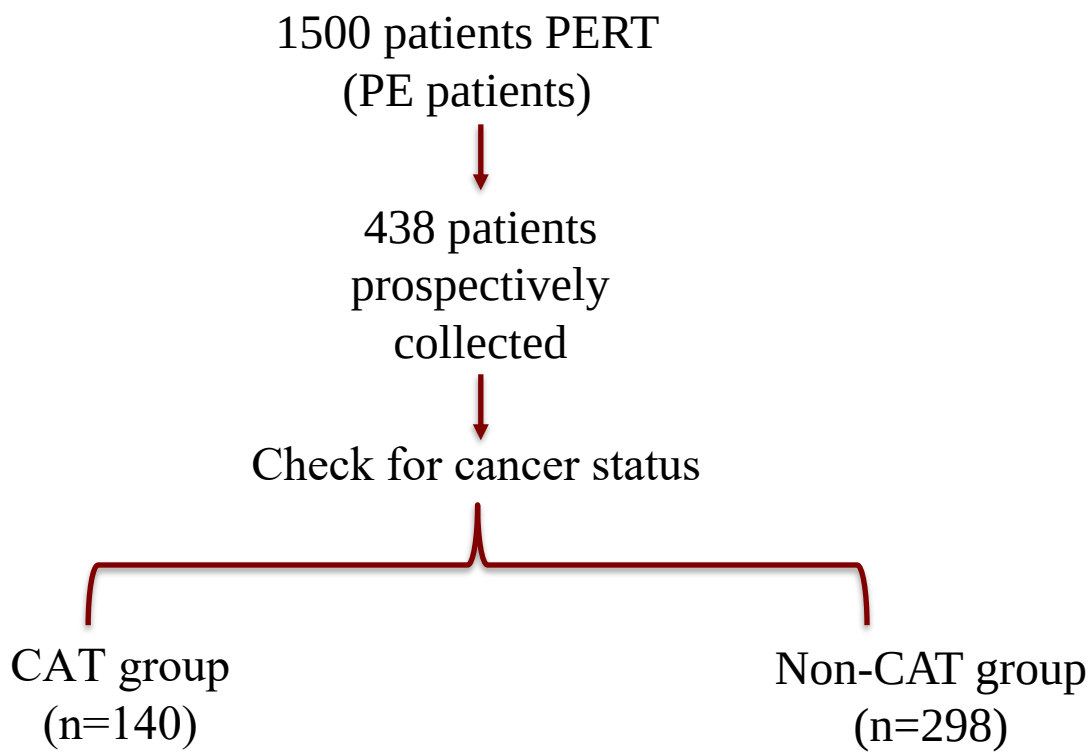
HYPOTHESIS

- **The pathogenesis of thrombo-inflammatory responses may be amplified in cancer-associated thrombosis**

Materials And Methods

- Patient Population: Ongoing Loyola PERT Program
- Sample Collection:
  - PE samples (n= 438) collected with in 24-72 hours
  - Control samples (n=50) from commercial vendor
- Biomarker Profiling: Sandwich ELISA;
  - Thrombo-inflammatory markers: D-Dimer, PAI-1, tPA, TAFIa, vWF, CRP, IL6, TNFa, FVIIa, FIX, FX, and FXIIIa
  - Endothelial dysregulation markers: P-selectin, E-selectin
- Statistical Analysis: IBM® SPSS and GraphPad Prism Software
  - Kolmogorov-Smirnov Test, Student's t Test, Mann-Whitney U Test, and Spearman Correlation Analysis

CONSORT DIAGRAM

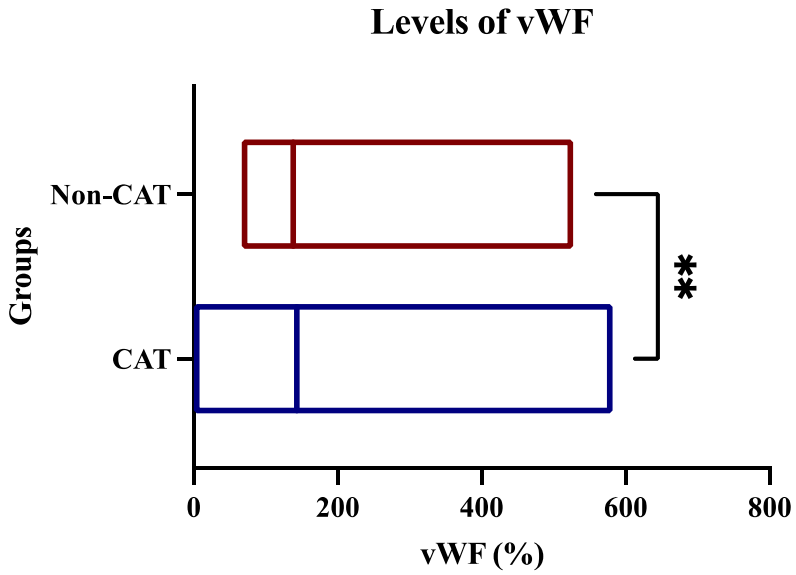


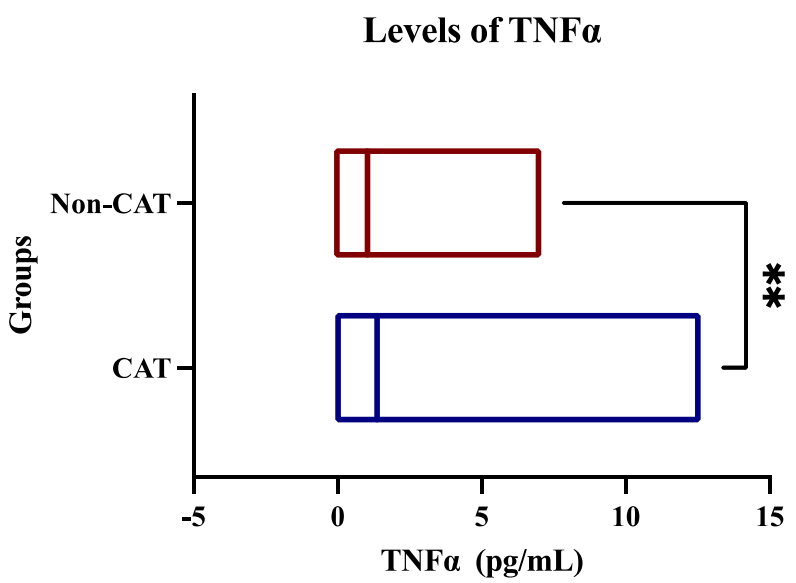
RESULTS

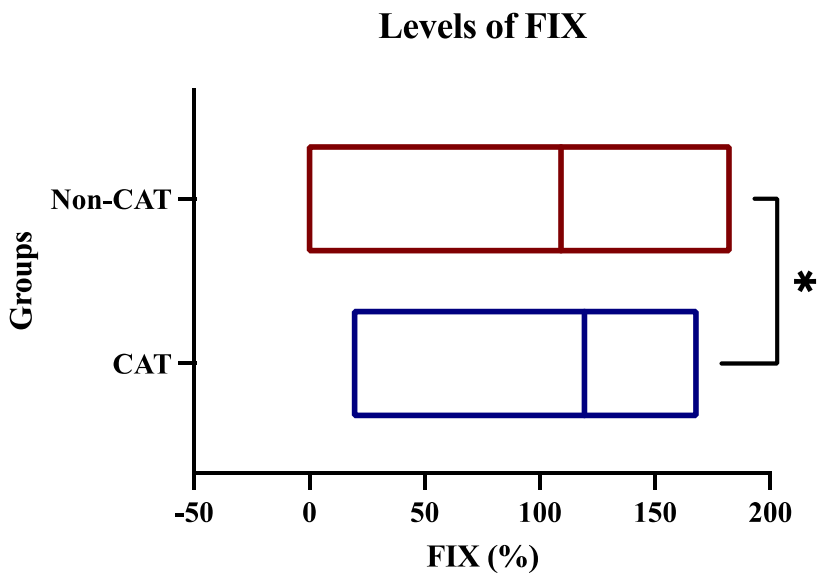
Baseline Characteristics Of Patients

Variables		CAT Group	Non-CAT Group	P Value
Demographics	Patients	140 (32.0%)	298 (68.0%)	ns
	Age	67.5 (60.3-74.8)	61.5 (51.0-72.0)	ns
	Sex • Male • Female	 61 (43.6%) 67 (47.9%)	 132 (44.3%) 132 (44.3%)	ns
	BMI	29.6 (24.2-34.6)	30.1 (24.9-36.8)	ns
PE Severity	PESI Score	125.0 (103.0-166.8)	102.0 (71.0-143.0)	<0.0
	Low Risk	40 (28.6%)	88 (29.5%)	ns
	High Risk	88 (62.9%)	176 (59.1%)	ns
	Troponin	0.035 (0.01-0.35)	0.6 (0.01-0.26)	ns
	BNP	98.0 (44.0-287.7)	124.0 (41.5-349.0)	ns
	Lactate	1.7 (1.1-2.5)	1.6 (1.1-2.4)	ns

Comparison of Various Thrombo-inflammatory and Endothelial Biomarkers in Patients With CAT and Non-CAT Groups







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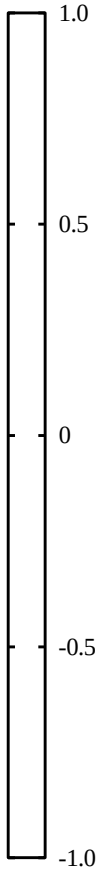
Correlation Analysis (Heat Map) For CAT and Non-CAT Patients

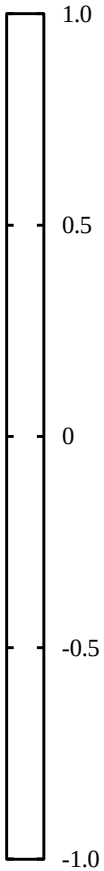
CAT Patients

	D-Dimer (ng/mL)	PAI-1 A (ng/mL)	tPA (ng/mL)	TAFIa (%)	vWF (%)	CRP (ug/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)	E-Selectin (ng/mL)	P-Selectin (ng/mL)	FVII (%)	FIX (%)	FX (%)	FXIIIa (%)
D-Dimer (ng/mL)	1.00	0.13	0.11	0.01	0.06	0.12	0.07	0.05	0.06	0.39	-0.09	0.07	0.08	-0.24
PAI-1 A (ng/mL)	0.13	1.00	0.26	0.01	0.25	0.22	0.41	0.27	0.10	0.27	-0.19	0.19	0.02	0.04
tPA (ng/mL)	0.11	0.26	1.00	-0.19	0.23	0.15	0.25	0.28	0.01	0.20	-0.04	0.02	0.11	0.02
TAFIa (%)	0.01	0.01	-0.19	1.00	0.11		-0.09	0.05	-0.15	-0.08	0.22	0.26	0.10	0.03
vWF (%)	0.06	0.25	0.23	0.11	1.00	0.39	0.06	0.30	0.29	0.34	0.17	0.05	-0.20	-0.08
CRP (ug/mL)	0.12	0.22	0.15		0.39	1.00	0.41	0.30	0.21	0.22	0.26	0.29	-0.05	0.09
IL-6 (pg/mL)	0.07	0.41	0.25	-0.09	0.06	0.41	1.00	0.44	0.34	0.22	-0.15	0.14	0.09	0.15
TNF-α (pg/mL)	0.05	0.27	0.28	0.05	0.30	0.30	0.44	1.00	0.30	0.32	-0.11	0.07	-0.04	0.16
E-Selectin (ng/mL)	0.06	0.10	0.01	-0.15	0.29	0.21	0.34	0.30	1.00	0.22	0.07	0.18	0.17	-0.29
P-Selectin (ng/mL)	0.39	0.27	0.20	-0.08	0.34	0.22	0.22	0.32	0.22	1.00	-0.11	0.06	-0.02	-0.09
FVII (%)	-0.09	-0.19	-0.04	0.22	0.17	0.26	-0.15	-0.11	0.07	-0.11	1.00	-0.11	0.19	0.48
FIX (%)	0.07	0.19	0.02	0.26	0.05	0.29	0.14	0.07	0.18	0.06	-0.11	1.00	0.43	0.10
FX (%)	0.08	0.02	0.11	0.10	-0.20	-0.05	0.09	-0.04	0.17	-0.02	0.19	0.43	1.00	0.15
FXIIIa (%)	-0.24	0.04	0.02	0.03	-0.08	0.09	0.15	0.16	-0.29	-0.09	0.48	0.10	0.15	1.00

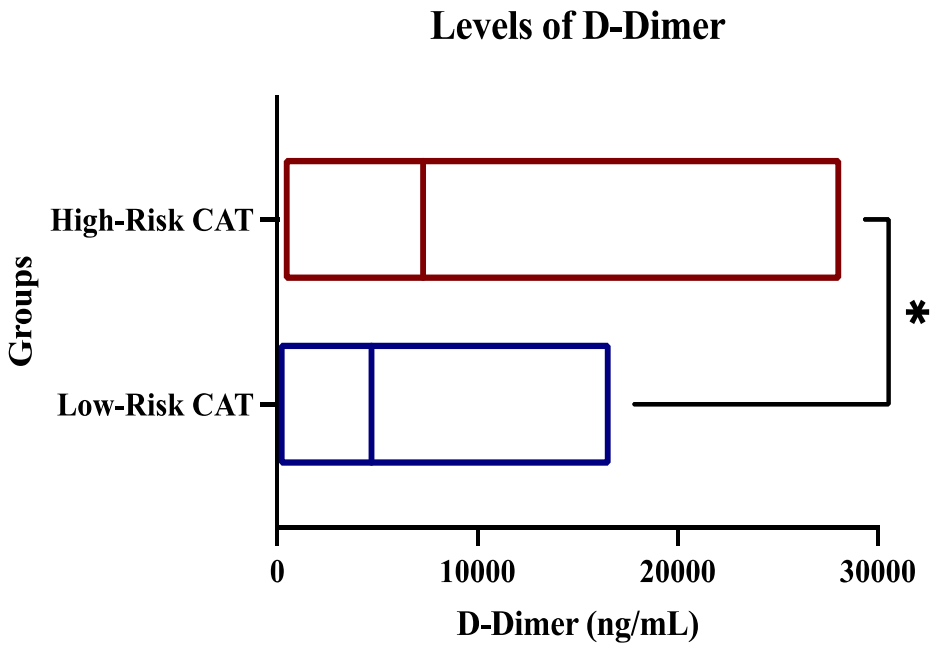


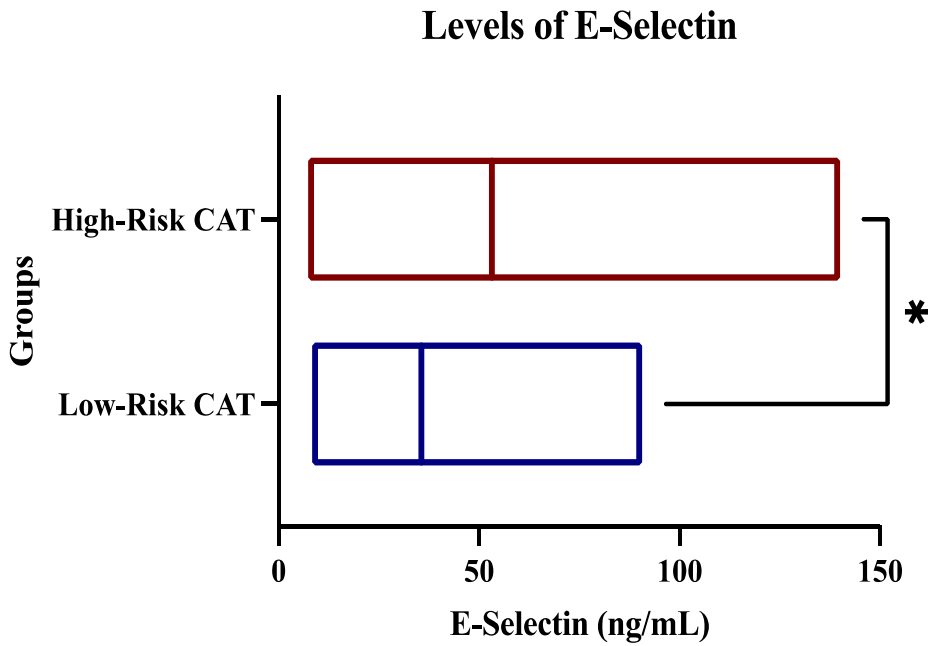
Non-CAT Patients

	D-Dimer (ng/mL)	PAI-1 A (ng/mL)	tPA (ng/mL)	TAFIa (%)	vWF (%)	CRP (ug/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)	E-Selectin (ng/mL)	P-Selectin (ng/mL)	FVII (%)	FIX (%)	FX (%)	FXIIIa (%)
D-Dimer (ng/mL)	1.00	0.06	0.13	0.01	0.20	0.28	0.32	0.12	-0.11	0.30	0.02	0.03	-0.02	-0.13
PAI-1 A (ng/mL)	0.06	1.00	0.26	-0.10	0.10	0.02	0.16	0.10	0.13	0.39	-0.02	0.17	0.09	0.07
tPA (ng/mL)	0.13	0.26	1.00	-0.22	0.21	-0.05	-0.01	0.15	0.02	0.05	-0.17	0.08	-0.08	0.06
TAFIa (%)	0.01	-0.10	-0.22	1.00	-0.02	0.15	-0.13	-0.18	-0.14	0.20	0.37	0.08	0.16	0.20
vWF (%)	0.20	0.10	0.21	-0.02	1.00	0.31	0.23	0.05	0.13	0.08	-0.03	0.19	-0.07	-0.12
CRP (ug/mL)	0.28	0.02	-0.05	0.15	0.31	1.00	0.42	0.10	-0.17	0.20	0.22	0.09	-0.09	0.07
IL-6 (pg/mL)	0.32	0.16	-0.01	-0.13	0.23	0.42	1.00	0.25	0.06	0.08	-0.04	0.04	-0.14	-0.09
TNF-α (pg/mL)	0.12	0.10	0.15	-0.18	0.05	0.10	0.25	1.00	0.29	-0.06	-0.01	0.22	0.02	0.13
E-Selectin (ng/mL)	-0.11	0.13	0.02	-0.14	0.13	-0.17	0.06	0.29	1.00	0.03	-0.02	0.42	0.20	-0.14
P-Selectin (ng/mL)	0.30	0.39	0.05	0.20	0.08	0.20	0.08	-0.06	0.03	1.00	-0.01	-0.02	0.06	0.09
FVII (%)	0.02	-0.02	-0.17	0.37	-0.03	0.22	-0.04	-0.01	-0.02	-0.01	1.00	-0.10	0.19	0.51
FIX (%)	0.03	0.17	0.08	0.08	0.19	0.09	0.04	0.22	0.42	-0.02	-0.10	1.00	0.38	0.04
FX (%)	-0.02	0.09	-0.08	0.16	-0.07	-0.09	-0.14	0.02	0.20	0.06	0.19	0.38	1.00	0.24
FXIIIa (%)	-0.13	0.07	0.06	0.20	-0.12	0.07	-0.09	0.13	-0.14	0.09	0.51	0.04	0.24	1.00



Comparison of Biomarkers Based on PE Severity





CONCLUSIONS

- CAT patients exhibit amplified levels of biomarkers particularly vWF, TNFα, and FIX
- PE severity: higher risk patients had elevated D-Dimer (p=0.027), and E-Selectin (p=0.030).
- These observations may be suggestive of the role of thrombo-inflammatory markers in enhancing the severity of pulmonary embolism in cancer patients
- Furthermore, the pathobiology will help un in developing newer agents.

Clinical Implications

- Cancer patients with PE have an added burden in their health care need
- The implications include hemostatic snags with thrombo-inflammatory complications
- Anticoagulant and anti-inflammatory agents may be of value in the management of PE patients with cancer

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