

Postoperative Venous Thromboembolism Risk After Neoadjuvant Immunotherapy for Advanced Melanoma

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Introduction

- Immunotherapy with immune checkpoint inhibitors (ICI) has revolutionized the management of cutaneous melanoma
- Clinical trials demonstrate improved event-free survival with neoadjuvant ICI
- Recent data suggests ICI may increase venous thromboembolism (VTE) risk, yet this risk remains poorly understood
- Our aim:** evaluate the association between neoadjuvant ICI and postoperative VTE in patients with melanoma

Methods

- Retrospective cohort study using TriNetX
- Patients with cutaneous melanoma undergoing surgery from 2010-2025 stratified by receipt of neoadjuvant ICI
- Primary outcome: 90-day postoperative VTE rate
- Propensity score matched for demographics, BMI, hypercoagulable state, preoperative anticoagulation, disease stage, and comorbidities
- Relative risks (RR), absolute risk differences (ARDs), and number needed to harm (NNH) calculated

Results

Table 1. Clinicodemographic Variables prior to Propensity Matching

	Neoadjuvant ICI (n = 2,331)	No Neoadjuvant ICI (n = 104,767)	p-Value
Sex			
Male	1,504 (65%)	57,034 (57%)	<0.0001
Female	804 (35%)	42,807 (43%)	
Age at Index	62.3 ± 14	63.4 ± 15.1	0.001
Body Mass Index	29.7 ± 6.28	28.8 ± 6.03	<0.0001
Nicotine Dependence	151 (7%)	4,781 (5%)	0.0001
Hypertensive Disorders	683 (30%)	29,668 (30%)	0.90
Ischemic Heart Disease	225 (10%)	10,877 (11%)	0.08
Diabetes Mellitus	240 (10%)	10,080 (10%)	0.63
Liver Disease	122 (5%)	4,523 (5%)	0.08
Chronic Kidney Disease	125 (5%)	5,531 (6%)	0.80
History of Prior VTE	122 (5%)	4,242 (4%)	0.01
Thrombophilia	27 (1%)	1,351 (1%)	0.45
Antiplatelet therapy	373 (16%)	18,594 (19%)	0.003
Anticoagulation	388 (17%)	15,512 (16%)	0.09
Immunosuppressants	46 (2%)	2,325 (2%)	0.29
Estrogens	44 (2%)	3,607 (4%)	<0.0001

Table 2. Clinicodemographic Variables after Propensity Matching

	Neoadjuvant ICI (n = 2,326)	No Neoadjuvant ICI (n = 2,326)	p-Value
Sex			
Male	1,504 (65%)	1,502 (65%)	0.95
Female	804 (35%)	806 (35%)	
Age at Index	62.3 ± 14	62.1 ± 14.3	0.65
Body Mass Index	29.7 ± 6.28	28.7 ± 5.88	0.0004
Nicotine Dependence	151 (7%)	151 (7%)	1.0
Hypertensive Disorders	683 (30%)	661 (29%)	0.48
Ischemic Heart Disease	225 (10%)	203 (9%)	0.26
Diabetes Mellitus	240 (10%)	222 (10%)	0.38
Liver Disease	122 (5%)	97 (4%)	0.08
Chronic Kidney Disease	125 (5%)	115 (5%)	0.51
History of Prior VTE	122 (5%)	102 (4%)	0.17
Thrombophilia	27 (1%)	23 (1%)	0.57
Antiplatelet therapy	373 (16%)	330 (14%)	0.08
Anticoagulation	388 (17%)	362 (16%)	0.30
Immunosuppressants	46 (2%)	39 (2%)	0.44
Estrogens	44 (2%)	51 (2%)	0.47

Table 3. 90-day VTE Risk with Neoadjuvant ICI

Cohort	Patients in Cohort	Patients with VTE	Risk	Risk Difference [95% CI]	p-value	Relative Risk [95% CI]	NNH [95% CI]
ICI	2,326	58	2.5%	0.99% [0.19%, 1.80%]	0.02	1.66 [1.09, 2.51]	101 [59, 3125]
No ICI	2,326	35	1.5%				

Table 4. Singlet versus Doublet ICI Therapy*

	Patients in Cohort	Patients with VTE	Risk	Risk Difference [95% CI]	p-value	Relative Risk [95% CI]
Pembrolizumab only	1,116	42	3.8%	1.75% [0.08%, 3.41%]	0.07	1.85 [0.94, 3.69]
Ipilimumab-Nivolumab	496	≤10	2.0%			

*This analysis was not propensity matched due to sample size

Table 5. Regional Lymphadenectomy

	Patients in Cohort	Patients with VTE	Risk	Risk Difference [95% CI]	p-value	Relative Risk [95% CI]
Regional Lymphadenectomy	616	27	4.38%	1.5% [-0.63%, 3.56%]	0.17	1.5 [0.84, 2.70]
No Regional Lymphadenectomy	616	18	2.92%			

Conclusions

- Neoadjuvant ICI was associated with a **statistically significant 66% increased 90-day risk** of VTE, suggesting possible immune-mediated endothelial activation and synergistic prothrombotic effects of ICI plus surgery
- Combination ICI regimens did not confer significantly higher risk than single-agent therapy in the 90-day postoperative period
- Highlights the possible need for perioperative prophylaxis and risk stratification