New drugs, old problems: immune checkpoint inhibitors and cancer-associated thrombosis

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ABSTRACT

A frequent side effect of cancer treatment is venous thromboembolism (VTE), which is made more likely by systemic anticancer medication. Immune checkpoint inhibitors (ICIs) have emerged as a paradigm-shifting treatment for many cancers. Early trials investigating the efficacy of ICIs did not identify thrombosis as a significant adverse event of concern. An initial meta-analysis reported a 1.1% [95% confidence interval (CI) 0.5-2.1] risk of arterial thromboembolism (ATE) and a 2.7% (95% CI 1.8-4.0) rate of vein thrombosis. ICIs have, however, been linked to ATE and VTE in an increasing number of post-marketing investigations. The reported incidence rates of cumulative VTE range from 5-8% at 6 months to 10-12% at 12 months, while the rates of ATE vary from 1-2% at 6 months to 17 months. Furthermore, a number of studies show a correlation between reduced survival and ICI-related thromboembolism. In order to provide a compiled and thorough narrative on the mechanisms, incidence, risk factors, and survival related to ICI-associated VTE and ATE, this narrative review summarizes the literature.

Introduction

Cancer patients have a greater risk of both venous thromboembolism (VTE) and arterial thromboembolism (ATE).[1] Chemotherapy and other anti-cancer therapies increase the risk of VTE, including deep vein thrombosis (DVT), and pulmonary embolism (PE).[2-5] Cancer patients have a four-to-twelve-fold higher incidence of VTE.[6,7] This risk increases 23-fold in chemotherapy or targeted treatment patients.[8] ATE includes myocardial infarction, stroke, and peripheral arterial embolism.

The advent of immune checkpoint inhibitors (ICIs) is a paradigm shift in cancer therapeutics. ICIs target programmed cell death protein 1 (PD-1) or its ligand (PD-L1) or cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) to prevent tumor immune evasion.[1,9] The United States Food and Drug Administration and the European Medicines Agency both granted approval to the first ICI, ipilimumab, in 2011.[10] ICIs are now widely used to treat lung cancer, melanoma, renal cell carcinoma, head and neck cancer, and colorectal cancer subsets.[9,11] A meta-analysis of these randomized controlled trials (RCTs) found a low 1.1% [95% confidence interval (CI) 0.5-2.1] risk of ATE and a moderate 2.7% (95% CI 1.8-4.0) risk of VTE.[12] Similar rates (VTE rates: 1.5% in melanoma and 1.9% in lung cancer) were also revealed by another meta-analysis of RCTs and prospective studies of ICI use in patients with melanoma and lung cancer.[13]

Here we provide a comprehensive review of the existing data about the occurrence of VTE or ATE in association with ICI therapy of various malignancies. We examine the candidate mechanisms of thrombosis in this setting, provide an overview of the

documented incidence in different cohort studies, and analyze risk factors for thromboembolism in patients receiving ICIs.

Immune checkpoint inhibitors as therapeutics in cancer

ICIs target 'immune checkpoints' stimulatory and inhibitory processes that directly affect immune cells. Homeostatic immune checkpoints balance pro- and anti-inflammatory signals.[14] Tumor microenvironment immune cells become anergic due to regulatory T cells recruitment, persistent inflammation, and the production of chemicals such CTLA-4 or PD-L1, which drive immune cell proliferation and evasion. The most researched immunological checkpoints are CTLA-4, PD-1, and PD-L1. T-cell receptors activate T cells.[14] T-lymphocytes express CTLA-4 protein receptors, which compete with CD28 to generate cytokines like interleukin (IL)-1. T cells produce less proinflammatory cytokines and have lower overall survival (OS) when CTLA-4 is activated.[15]

PD-1 is another anti-tumor T-lymphocyte receptor. T-lymphocyte survival, proinflammatory cytokine production, and proliferation are inhibited by PD-1 activation. Tumor cells reduce T-lymphocyte anti-tumor activity by producing PD-L1. ICIs assault cancer cells via CTLA-4 and PD-1/PD-L1 activation.[15] A full list of approved ICI agents to date is shown in Table 1.[14]

Incidence of venous thromboembolism and arterial thromboembolism

ICIs can cause immune-related gastrointestinal, cutaneous, thyroid, or hematological disorders like autoimmune hemolytic anemia or thrombocytopenia collectively known as immune-related adverse events; although initial studies did not recognize VTE or ATE as such.[9] The earlier systematic review and meta-analyses of 68 studies (18 retrospective studies and the remaining clinical trials examining the efficacy of ICIs, N=20,273) found 1.1% (95% CI 0.65-1.45%) and 2.7% (95% CI 1.4-5.4%) of ATE and VTE in cancer patients receiving ICIs.[12] A recent meta-analysis found that ICI users had no higher risk of VTE than non-ICI users [odds ratio (OR) 0.99, 95% CI 0.82-1.19].[16] However, the challenge with relying on RCT data is that RCTs may have underreported thrombosis events.[17]

Multiple post-marketing cohort studies have examined rates of thromboembolism in patients with various malignancies receiving ICIs, ICI plus chemotherapy, or chemotherapy alone. Table 2 lists ICI patients' VTE and/or ATE characteristics and published study results. A large single-institution study evaluated the incidence of VTE; of 1,686 patients, 404 (24%) experienced VTE during immunotherapy (using an expanded definition of VTE to include visceral thrombotic events). In a similar retrospective study by the Vienna group, of 672 patients, 47 VTE events occurred during a median follow-up of 8.5 months [cumulative incidence 12.9% (95% CI, 8.2-18.5)].[1] Another large cohort study of 2854 patients found a VTE rate of 7.4% at 6 months and 13.8% at 1 year.[18] The risk of VTE increased over 4-fold after initiating ICI therapy [hazard ratio (HR) 4.98, 95% CI 3.65-8.59, P<0.001]. DVT risk increased by 5.7-fold (HR 5.70, 95% CI 3.79-8.59, P<0.001) and PE risk increased by 4.75-fold (HR 4.75, 95% CI 3.20-7.10, P<0.001).

Thrombosis in ICI patients was evaluated in three Danish population cohort studies.[8,19,20] Two reported both ATE and VTE,[19,20] whereas one reported only VTE.[8] These studies reported a 2-4% VTE rate at 6 months and a 4-7% rate at 12 months, lower than retrospective studies. The difference in incidence rates may be due to the use of ICD10 codes and/or imaging codes in population research, rather than individual record review.[17]

Table 1. Immune checkpoint inhibitors listed by generic names, their year of approval (Food and drug administration), and cancers for which they are used.[15,53]

Generic name	Approval year	Indications
Anti-CTLA-4 antibody		
Ipilimumab	2011	Melanoma, CRC, RCC
Anti-PD-1 antibodies		
Pembrolizumab	2014	Cervical cancer, RCC, urothelial carcinoma, gastroesophageal adenocarcinoma, esophageal cancer, HCC, HNSCC, NSCLC, Hodgkin's lymphoma, large B-cell lymphoma, melanoma, MCC
Nivolumab	2014	CRC, HCC, HNSCC, Hodgkin's lymphoma, melanoma, NSCLC, SCLC, RCC, urothelial carcinoma
Cemiplimab	2018	Cutaneous SCC
Dostarlimab (with chemo)[54]	2023	Primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high[54]
Anti-PD-L1 antibodies		
Avelumab	2015	MCC, RCC, urothelial carcinoma
Atezolizumab	2016	Breast cancer, NSCLC, SCLC, MCC, urothelial carcinoma, RCC
Durvalumab	2016	NSCLC, urothelial carcinoma

CRC, colorectal cancer; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; MCC, Merkel cell carcinoma; SCLC, small cell lung cancer; SCC, squamous cell carcinoma; PD-L1, programmed cell death protein ligand-1.

However, Mulder *et al*. found that ICI patients had a 6-month cumulative incidence of VTE of 4.1% (95% CI 2.3-6.7%), similar to chemotherapy patients' 3.5%.[8]

These studies show a high frequency or incidence of VTE, although cancer patients in general have high rates of VTE throughout therapy. Since control groups receiving chemotherapy alone were rarely included, the retrospective cohort studies alone cannot definitively prove an increased risk compared to chemotherapy. A US claims-based study examined VTE risk variables and incidence in advanced lung cancer patients under-

Table 2. Summary of incidence rates of venous and arterial thrombosis from select studies of cancer patients receiving immune checkpoint inhibitors.[17]

Study	Country	Study design	N (cohort size)	Type of cancer	Follow-up [Median (IQR)]	VTE incidence % (95% CI)	ATE incidence % (95% CI)
Hegde *et al.*, 2017[39]	USA	Retrospective	76	Lung	10.8 mo	18.4	2.6
Ibrahimi *et al.*, 2017[55]	USA	Retrospective	154	Lung 20.8% Melanoma 20.1% Ovarian 12.3%	7 mo (198 days)	10.4	0
Hsu *et al.*, 2018[56]	Taiwan	Retrospective	50	Non-small cell lung cancer (n=24, 48%) Hepatocellular carcinoma (n=4, 8%)	N/A	2	N/A
Bar *et al.*, 2019[28]	Israel	Retrospective	1215	All cancers Melanoma 40.5% Lung 28.7%	12 mo	AVE (including MI, stroke, PE, multisite DVT): 6 mo: 2.6 12 mo: 3.0 AVE plus single site DVT:6 mo: 4.9 12 mo: 5.8	
Nichetti *et al.*, 2019[47]	Italy	Retrospective analysisfrom prospective APOLLO cohort	217	NSCLC	37.8 mo	7.4	6.5
Ando *et al.*, 2020[41]	Japan	Retrospective	122	Lung, kidney, stomach, urothelial, melanoma	N/A Time to thrombosis 90 days (range 6-178)	4.1 Likely 6 mo rate	4.9
Drobni *et al.*, 2020[29]	USA	Retrospective	2842	All cancers NSCLC 28.8% Melanoma 27.9%	2 years	N/A	Composite: 5.35/100 person-years MI: 2.49 Stroke: 2.08
Deschênes-Simard *et al.*, 2021[46]	Canada	Retrospective	593	NSCLC	12.7 (4.9-22.7) mo	9.9 (7.5-12.3) 76.5 (59.9-97.8) per 1000 person-years	1.3
Gong *et al.*, 2021[18]	USA	Retrospective	2854	All cancers NSCLC 28.4% Melanoma 28.2%	194 days (IQR 65-412)	6 mo: 7.4 12 mo: 13.8	N/A
Gutierrez-Sainz *et al.*, 2021[40]	Spain	Retrospective	229	Lung 48% Melanoma 23.6% RCC 11.8%	9.8 mo	7 (4-10)	N/A
Guven *et al.*, 2021[48]	Turkey	Retrospective	133	RCC 26.3% Melanoma 24.1% NSCLC 18.8%	10.1 (5.8-18.5) mo	11.3	N/A
Haist *et al.*, 2021[57]	Germany	Retrospective	280	Melanoma	28 mo (95% CI 23.4-32.6)	12.5	4.3
Hill *et al.*, 2021[26]	USA	Retrospective	435 (a) ICI: 171 (b) ICI+chemo: 157 (c) chemo then durvalumab: 107	NSCLC	N/A	6 mo: (a) 7.6 (4.3-12.2) (b) 9.9 (5.8-15.3) (c) 9.4 (4.8-15.8) 12 mo: (a) 9.0 (5.3-14.0) (b) 12.8 (7.8-19.0) (c) 12.2 (6.8-19.2)	N/A
Icht *et al.*, 2021[51]	Israel	Retrospective	176	NSCLC	6 mo (187 days)	4.5 (2.1-8.3)	N/A

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going first-line ICI-, chemotherapy-, or ICI + chemotherapy regimens.[21] Among 2299 eligible patients (ICI-based, n=605; chemo-based, n=1092; ICI + chemotherapy, n=602) with a median follow-up of 9.1 months, the VTE incidence rates (95% CI) per 100 person-years were 17.8 (95% CI 16.0 to 19.5) overall, 13.5 (95% CI 10.6 to 16.5) for ICI-based, 18.0 (95% CI 15.5 to 20.5) for chemo-based, and 22.4 (95% CI 20.2 to 24.5) for ICI + chemotherapy.[21] Due to the wide diversity of underlying malignancies, accompanying cancer therapies such as chemotherapy, and variable follow-up periods, thrombosis rates varied quite widely between studies. Overall, VTE incidence was 5-8% at 6 months and 10-15% at 12 months.

In general, retrospective cohort studies showed higher rates than RCTs (1-2% in meta-analysis),[12,13,17] but not substantially higher when considering the 9-10% 6-month VTE risk in ambulatory cancer patients with a Khorana score of ≥2 undergo-

Table 2. Continued from previous page.

Study	Country	Study design	N (cohort size)	Type of cancer	Follow-up [Median (IQR)]	VTE incidence % (95% CI)	ATE incidence % (95% CI)
Kewan *et al.*, 2021[50]	USA	Retrospective	552	All cancers NSCLC 47.3%	12.1 mo	12.1	1.3
Madison *et al.*, 2021[58]*	USA	Retrospective	6127	Lung	6 mo	6.3	2.6
Moik *et al.*, 2021[1]	Austria	Retrospective	672	Melanoma 30.4% NSCLC 24.1% RCC 11%	8.5 mo	6 mo: 5.0 (3.4-6.9) 12mo: 7.0 (5.1-9.3) Overall: 12.9 (8.2-18.5)	6 mo: 1.0 (0.4-2.0) 12 mo: 1.8 (0.7-3.6) Overall 1.8 (0.7-3.6)
Mulder *et al.*, 2021[8]**	Denmark	Population cohort	370	All cancers	6 12	4.1 (2.3-6.7) 7.1 (4.2-11.1)	N/A
Roopkumar *et al.*, 2021[25]	USA	Retrospective	1686	Lung 49.6% Melanoma 13.2%	438 days (range 7-1971)	6 mo: 7.1 12 mo: 10.9 Overall: 24	N/A
Sheng *et al.*, 2021[24]	USA	Retrospective	351	RCC	12.8 mo	11 Total thromboembolism: 6 mo: 4.4 (2.6-6.9) 12 mo: 9.8 (6.8-13.4)	2
Sussman *et al.*, 2021[45]	USA	Retrospective	228	Melanoma	27.3 mo	6 mo: 8.0 (4.9-12.0) 12 mo: 12.9 (8.9-17.7)	6 mo: 2.2 (0.8-4.8) 12 mo: 4.5 (2.3-7.8)
Alma *et al.*, 2022[49]	France	Retrospective	481	Lung	9.8 mo	9.8	N/A
Bjornhart *et al.*, 2023[42]	Denmark	Retrospective	146 prospective (A) * 426 retrospective (B)	NSCLC	16.5 mo	6 mo: 13.0 12 mo: 14.4 Overall: 14 6 mo: 4.9 12 mo: 5.6 Overall: 6	N/A
Canovas *et al.* 2022[43]	Spain	Retrospective	665 291	Lung Melanoma	14 mo 17 mo	6.9 All thrombosis: 8.4 (6.23-10.6) 4.8 All thrombosis: 5.8 (3.34-9.18)	1.5 1
Endo *et al.* 2022[44]	Japan	Retrospective	120	Lung	Within 6 mo	2.5	4.2
Khorana *et al.* 2023[21]*	USA	Retrospective	(a) ICI: 605 (b) ICI+chemo: 602	N SCLC	9.1 mo	6 mo: (a) 8.1 (b) 12.8 12 mo: (a) 13.5 (10.6-16.5) (b) 22.4 (20.2-24.5)	N/A
May *et al.* 2022[59]*	USA	Retrospective	1823	All cancers	6 mo	7.3	N/A
Sanfilippo *et al.* 2022[27]*	USA	Retrospective	1754	All cancers	6 mo	4.1	N/A
Sheng *et al.* 2022[23]	USA	Retrospective	279	Urothelial	5.6 mo	13 Total thromboembolism: 6 mo: 9.1 (6.0-13.0) 12 mo: 13.6 (9.6-18.4)	2
Moik *et al.* 2021[19]**	Denmark	Population cohort	3259	All cancers	6 12 24	3.9 (3.3-4.7) 5.7 (4.9-6.6) 7.3 (6.2-8.4)	1.3 (0.9-1.8) 2.2 (1.7-2.8) 3.1 (2.4-3.8)
Overvad *et al.* 2022[20]**	Denmark	Population cohort	3946	All cancers	6 12	2.6 3.8	1.3 1.9

*Outcomes identified by ICD codes; **Outcomes were identified by ICD10 codes +/− imaging codes. CI, confidence interval; MI, myocardial infarction; mo, months; N/A, not available; USA, United States of America. IQR, interquartile range; VTE, venous thromboembolism; ATE, arterial thromboembolism; AVE, acute vascular event; PE, pulmonary embolism; DVT, deep vein thrombosis; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; ICI, immune checkpoint inhibitor.

ing chemotherapy.[17,22] Since ICIs can substantially prolong survival, their use in cancer therapy may increase the risk of thrombosis as a function of exposure time.[17] A study found that metastatic renal cell carcinoma and urothelial carcinoma patients' thrombosis rates plateaued after 30 and 36 months, respectively.[23,24] This shows that thrombosis risk increases with ICIs therapy duration.

Further, a recent meta-analysis found that combination ICIs increased the incidence of myocardial infarction and VTE in non-small cell lung cancer patients.[13] A different study found that combined-ICIs did not enhance risk.[25] Other trials found similar risk of ICI-chemotherapy combination compared to chemotherapy alone,[26,27] and comparable thrombosis rates.[17,28] Given the frequent significant baseline differences in these patients, comparing the risks of thrombosis linked with chemotherapy plus ICIs to ICI alone or chemotherapy alone may be problematic.

Arterial thromboembolism incidence

ATE incidence data are scarce. Some studies suggest rates within 1-2% over 6-17 months (Table 2). In a study of various malignancies, ATE incidence at 6 months, 12 months, and 24 months was 1.3 (95% CI 0.9-1.8), 2.2 (95% CI 1.7-2.8), 3.1 (95% CI 2.4-3.8), respectively.[19] In contrast, in a Vienna cohort study, 9 ATE events occurred in 672 patients [cumulative incidence 1.8% (95% CI, 0.7-3.6)].[1] ICIs were associated with threefold more cardiovascular (CV) events than other anticancer therapies in a matched cohort analysis of 2842 patients by Drobni *et al*. In the same matched cohort study, the comparison of risk increases in before and after ICI use were also similar.[29] A recent meta-analysis of 61 studies found that ICI regimens increased ATE risk [odds ratio (OR) 1.58, 95% CI 1.21-2.06].[16] More research is needed to evaluate if reducing and managing CV risk factors can help this population.

Candidate mechanisms and biomarkers

The exact mechanisms of ICI-related thrombosis are not fully understood. ICIs' principal immune-related toxicity mechanisms involve T-cell-mediated autoimmune-like reactions.[12] Impaired immunological checkpoints are connected to pro-inflammatory conditions and elevated cytokine levels.[9] By boosting pro-inflammatory T cells and macrophages in atherosclerotic plaques, PD-1 blockade accelerates atherogenesis, vascular inflammation, and atherosclerosis.[30,31] Pre-clinical animal models demonstrate that ICI use promotes atherosclerotic disease, which may increase arterial thrombotic events.[9] Activated T cells can also increase tissue factor production by macrophages and monocytes, increasing hypercoagulability.[9,32,33] In a pilot translational study, blood samples from 25 patients (15 of whom developed VTE after starting ICIs, and 10 of whom did not) at the time of starting the treatment (ICIs) were analyzed. Results showed pretreatment levels of myeloid-derived suppressor cells (5.382±0.873 *vs*. 3.341±0.3402, mean±SEM; P=0.0045), IL-8 (221.2±37.53 *vs*. 111.6±25.36, mean±SEM; P=0.016), and soluble vascular cell adhesion molecule 1 (1210±120.6 *vs*. 895.5±53.34, mean±SEM; P=0.0385) were significantly higher in patients that developed VTE. These indicators suggest a role for immune-mediated inflammation and shed light on thrombus development in ICI patients.[17,25]

To maximize patient benefit, limit toxicity, and direct combination therapy, predictive biomarkers are needed. An important study evaluated whether early C-reactive protein (CRP) dynamics could predict ICI-associated VTE.[34] In 405 patients, CRP was measured at baseline and every 4 weeks for the first 3 months of ICI therapy. A 2.5-fold spike in CRP indicated a flare, whereas a 50% decline was defined as a response. In a multivariable analysis that included death, an early CRP flare was associated with VTE [HR 3.58 (95% CI 1.07-11.94)]. Patients with CRP response had the lowest VTE risk. In a follow-up study, early CRP kinetics were also found to serve as a tumor-agnostic predictor of treatment response, progression risk, and mortality.[35]

A small study of 30 patients receiving ICIs found that a baseline high sensitivity (hs)-troponin T (TnT) ≥14 ng/L was associated with a higher risk of CV outcomes/primary endpoints, including death, stroke, transient ischemic attack (TIA), PE, and/or heart failure (HF).[17,36] Therefore, only individuals with hs-TnT ≥14 ng/L before the first cycle died from stroke/TIA or new-onset HF. Additionally, nine out of thirteen patients with progression of cardiac disease exhibited hs-TnT ≥14 ng/L before the first cycle (P=.012).[36] In another retrospective study of 135 patients receiving first-line pembrolizumab for metastatic cancer, hs-troponin I (TnI) >50 ng/L before the first and second doses was an independent predictor of major adverse cardiac events, such as myocarditis, acute coronary syndrome, HF, VTE, CV hospitalization, and/or mortality (HR 8.1, 95% CI 1.67-37.4) after a mean follow-up of 490 days.[37] Before the first pembrolizumab dose, hs-TnI >50 nl/L increased all-cause death risk. In view of these findings, the European Society of Cardiology 2022 cardio-oncology guidelines recommend monitoring cardiac troponin before each ICI cycle.[17, 38] Table 3 lists candidate biomarkers with their rationales.

Risk factors

Understanding ICI cancer patients' thrombosis risk variables may help identify high-risk patients and target thromboprophylaxis. Multiple cohort studies have attempted to identify risk factors associated with ICI-related VTE (Table 4). In the Vienna

Table 3. Candidate biomarkers of immune checkpoint inhibitor-associated venous thromboembolism or arterial thromboembolism.

Biomarker	Outcome
MDSC[25]	VTE development after ICI initiation
IL-8[25]	VTE development after ICI initiation
sVCAM-1[25]	VTE development after ICI initiation
Early CRP flare*[34]	Risk of ICI-associated VTE
CRP response**[34]	Lower risk of ICI-associated VTE
hs-TnT ≥14 ng/L***[36]	Higher risk of CV outcomes
hs-TnI >50 ng/L[37]	Independent predictor of major cardiac events^

MDSCs, myeloid-derived suppressor cells; VTE, venous thromboembolism; ICI, immune checkpoint inhibitor; IL-8, interleukin-8; sVCAM-1, soluble vascular cell adhesion molecule-1; CRP, C-reactive protein; hs-TnT, high sensitivity troponin T; hs-TnI, high sensitivity troponin I. *CRP flare is when it increases 2.5 times; **CRP response is when it is decreased by 50%; ***baseline hs-TnT ≥14 ng/L; ^major cardiac events including myocarditis, acute coronary syndrome, heart failure, VTE, cardiovascular hospitalizations and cardiac death.

cohort study, a prior VTE history predicted future VTE [sub-distribution HR (SHR), 3.69; 95% CI, 2.00-6.81]. Patient-related factors like: female gender,[39,40] history of thromboembolism,[1,18,28,41-45] younger age,[18,25,46] smoking,[46,47] and poor Eastern cooperative oncology group status,[44,48] history of hypertension) were among the potential risk factors identified.[18] Cancer-related factors like lung cancer,[28,29] metastasis,[25,42,49] were also identified. Interestingly, history of melanoma showed a decreased chance of VTE.[18] For treatment-related factors: combined ICI use (16.7% *vs*. 5.0% at 6 months and 21.3% *vs*. 9.5% at 12 months, respectively; P=0.02),[45] combined chemotherapy-ICI use have been identified as risk factors for VTE.[17,26,27] However, it is still an area of discussion whether ICI combination regimens or ICI chemotherapy regimens increase VTE risk compared to any one medication alone.[17] Also, Sheng *et al*. concluded that in a cohort of urothelial cancer patients on ICIs are associated with a higher risk of thromboembolism.[23] Drobni *et al*. studied the use of steroids or statins and found that statins or corticosteroids can attenuate ICI-induced total aortic plaque volume growth by more than threefold.[17,29] Although arterial thrombosis data are scarce, studies showed risk variables such as age, diabetes, hypertension, smoking, and a history of CV illness like traditional athrosclerosis.

The Khorana score (KS) has previously been validated to predict risk in heterogenous cancer population receiving systemic therapy. Its value in prediction in an immunotherapy-only cohort has not been fully evaluated. Some studies found KS to predict for risk of VTE[18,20,45] whereas others did not.[1,24,26,42,47-51]

Immune checkpoint inhibitors-related thromboembolism and survival

While some studies have found no correlation between thrombosis and poor survival in patients receiving ICIs,[40,46,48]

Table 4. Select risk factors for thrombosis identified in cancer patients receiving immune checkpoint inhibitors.

Study	Risk factors for thrombosis (multivariable)[17]	Result highlights
Hegde *et al.*, 2017[39]	Female	In the multivariate analysis, gender was the only covariate that significantly correlated with thromboembolic events (Female *vs.* Male HR 3.1, 95% CI 1.02-9.5, P=0.045)
Bar *et al.*, 2019[28]	NSCLC	Whether using chemotherapy or ICIs, the AVE rate for patients with adenocarcinoma of NSCLC was comparable
	H/o AVE	Two percent (2.6%) of patients experienced AVEs within six months of the start of their ICIs (95% CI 1.8-3.6).
	Hypertension Dyslipidemia	Lung adenocarcinoma, prior AVE, hypertension and dyslipidemia were correlated with AVEs
Nichetti *et al.*, 2019[47]	Current smoker PD-L1 >50%	Smokers (42.9% *vs.* 23.3%, p = 0.05) [compared to no TE event group] PD-L1 expression >50% (43.3 *vs.* 18.8%, P=0.01) [compared to no TE event group]
Ando *et al.*, 2020[41]	h/o thromboembolism	One risk factor for the incidence of CAT was a history of arterial or venous thromboembolism (ATE or VTE) (odds ratio: 6.36, P=0.039)
Drobni *et al.*, 2020[29]	Overall study: ICIs, age, h/o stroke, diabetes, hypertension, NSCLC, male, h/o radiation	A matched cohort analysis showed a three-fold increase in CV events after ICI beginning (hazard ratio, 3.3 [95% CI, 2.0-5.5]; P<0.001). At 2 years, CV events increased from 1.37 to 6.55 per 100 person-years in the case-crossover (adjusted hazard ratio, 4.8 [95% CI, 3.5-6.5]; P<0.001). ICIs increased overall aortic plaque volume progression >3-fold (from 2.1%/y before to 6.7%/y after) in the imaging research
Deschênes-Simard *et al.*, 2021[46]	Age <65 Higher PD-L1 level Smoking <12 mo from diagnosis to ICIs	Patients aged <65 (HR =2.00; 95% CI =1.11-3.59) Tumors with PD-L1 between 1-49% (HR =3.36; 95% CI = 1.19-9.50) or >50% (HR =3.22; 95% CI =1.21-8.57) Active smoking (HR =2.00; 95% CI =1.12-3.58) A time lag of less than 12 months between diagnosis and first ICI treatment (HR =2.06; 95% CI =1.09-3.89)
Gong *et al.*, 2021[18]	Age ≤65 Khorana score ≥2 h/o hypertension Strong trend: h/o VTE (HR 1.42, 95% CI 0.99-2.06) (melanoma is associated with decreased risks)	After initiating an ICI, the risk of VTE was 7.4% at six months and 13.8% at a year After initiating an ICI, the rate of VTE increased by a factor of four (HR 4.98, 95% CI 3.65-8.59, P<0.001) Deep vein thrombosis (HR 5.70, 95% CI 3.79-8.59, P<0.001) and pulmonary embolism (HR 4.75, 95% CI 3.20-7.10, P<0.001) were associated with 5.7- and 4.75-fold greater risks, respectively A history of melanoma and advanced age predicted a decreased risk of VTE, but a higher Khorana risk score, a history of hypertension, and a history of VTE suggested a higher risk when comparing individuals with and without a VTE incident

To be continued on next page

others have.[1,25,28,45,47] In a large study, Roopkumar *et al*. found that patients on ICIs who developed VTE had decreased OS [HR=1.22 (95% CI 1.06-1.41), P<0.008].[25] In the Vienna cohort study, VTE was associated with shorter OS as well (transition HR for death, 3.09; 95% CI, 2.07-4.60).[1] Similarly, another retrospective study showed that VTE was linked to a shorter OS in 219 immunotherapy-treated melanoma patients without brain metastases (median OS 1.3 years *vs*. not reached;P<0.001; HR 3.47 [95% CI, 1.66-7.24]).[52] Bar J. *et al*. observed a significant link between VTE and shorter survival.[28] On the other hand, a study found no correlation between VTE and poor OS [HR 1.33 (95% CI 0.63-2.80), P=0.44],[40] and another found no correlation between VTE and OS in thrombosis patients [HR 1.18 (95% CI 0.83-1.70), P=0.335.[46] In a cohort specifically studying urothelial cancer patients on ICIs, showed that the thromboembolism was associated with lower OS (HR 2.296, P=0.0004) with Bajorin score 1 or 2 (HR 1.490, P=0.0315), and Bajorin score 2 (HR 3.50, P<0.0001).[23] It is unclear whether this association with OS represents a biologic correlation (*i.e.*, VTE is a surrogate for aggressive tumor biology or tumor immune escape mechanisms) or simply an association with higher tumor burden.

Conclusions

ICIs represent a paradigm shift in treatment of malignancy, and their use is only expected to grow in the near future. Results

Table 4. Continued from previous page.

Study	Risk factors for thrombosis (multivariable)[17]	Result highlights
Gutierrez-Sainz *et al.*, 2021[40]	Female Melanoma	Melanoma and female sex were found to be independently l inked to a higher incidence of VTE Melanoma was also independently associated with [HR 2.42 (1.20-4.86), P=0.01] shorter OS
Guven *et al.*, 2021[48]	ECOG ≥1	A higher incidence of venous thrombosis was observed in patients (29.3% of patients) with a baseline ECOG performance level of 1 or higher (ECOG ≥1 *vs.* 0, HR: 3.023, 95% CI: 1.011-9.039, P=0.048)
Hill *et al.*, 2021[26]	Cancer treatment types (ICI-chemotherapy, targeted therapies) Smoking	Treatment type (P=0.034) Nicotine dependency (P=0.048)
Kewan *et al.*, 2021[50]	Anticoagulation at the time of ICI (univariate)	Incidence rate ratio: 2.23a
Moik *et al.*, 202[11]	h/o VTE	SHR, 3.69; 95% CI, 2.00-6.81
Roopkumar *et al.*, 2021[25]	Younger age Metastasis Biomarkers	Pretreatment levels of myeloid-derived suppressor cells (5.382 G 0.873 *vs.* 3.341 G 0.3402, mean G SEM, P=0.0045), interleukin 8 (221.2 G 37.53 *vs.* 111.6 G 25.36, mean G SEM, P=0.016), and soluble vascular cell adhesion protein 1 (1,210 G 120.6 *vs.* 895.5 G 53.34, mean G SEM, P=0.0385) were significantly higher in those who developed venous thromboembolism
Sussman *et al.*, 2021[45]	Combination ICI Khorana score ≥1 h/o CAD Anticoagulation at treatment start	Combination ICI (HR 2.70; 95%CI: 1.28 to 5.70; P=0.009) Khorana score ≥1 (HR 2.24; 95%CI: 1.06 to 4.74; P=0.03) History of coronary artery disease HR 2.71; 95%CI: 1.16 to 6.29; P=0.02) Anticoagulation at treatment start (HR 4.14; 95% CI: 1.60 to 10.7; p=0.003)
Alma *et al.*, 2022[49]	Metastasis BMI	Metastatic patients (11.1% *vs.* 1.5%, P=0.015) [univariate analysis] BMI (OR 1.07; 1.01-1.14, P=0.028) [logistic regression]
Bjornhart *et al.*, 2022[42]	h/o VTE ICI as first-line treatment Other mets (non-brain, liver, bone)	VTE was substantially linked to a lower OS in a multivariate analysis (HR 2.12 CI 95% [1.49-3.03], P<0.0001)
Canovas *et al.*, 2022[43] Lung cancer cohort	Hgb <10.9 g/dL at the start of ICI NLR <4.55 h/o thrombosis	HR 2.05; 95% CI: 1.14 to 3.69; P=0.008 [multivariate analysis] HR 2.14; 95% CI: 1.24 to 3.67; P=0.010 [multivariate analysis] HR 2.45; 95% CI: 1.2 to 5.01; P=0.010 [multivariate analysis]
Canovas *et al.*, 2022[43] Melanoma cohort	LDH >198 U/L NLR >3.01	HR 4.51; 95% CI: 1.01 to 20.24; P=0.049 [multivariate analysis] HR 3.65; 95% CI: 1.25 to 10.62; P=0.018 [multivariate analysis]
Endo *et al.*, 2022[44]	ECOG ≥2 h/o of thromboembolism	OR 3.84; 95% CI: 1.34 to 11.00; P=0.01 OR 6.03; 95% CI: 2.09 to 17.40; P<0.001
Khorana *et al.*, 2023[21]	History of radiation BMI ≥40 kg/m^2	Baseline radiation: HR, 1.25; P=0.03 Severe obesity (BMI ≥40 kg/m2): HR, 1.77; P=0.06
Sanfilippo *et al.*, 2022[27]	ICI-chemotherapy (*vs.* ICI alone)	ICI-chemotherapy HR =1.75 (95% CI: 1.07-2.83)

HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; AVE, acute vascular event; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand-1; TE, thromboembolism; ATE, arterial thromboembolism; VTE, venous thromboembolism; CV, cardiovascular; OS, overall survival; ECOG, eastern cooperative oncology group; CAD, coronary artery disease; Hgb, hemoglobin; h/o, history of; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; BMI; body mass index; IQR, interquartile range; KS, Khorana score; OR, odds ratio; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio.

of multiple recent cohort and population studies indicate a high incidence and/or prevalence of both VTE and ATE in association with ICI therapy, although it is unclear whether this is higher than observed with chemotherapy and whether it is a function of increased exposure time given substantial prolongation in survival with ICI therapy. Ongoing studies are evaluating mechanisms and candidate biomarkers have been identified. The association of ICI-related VTE/ATE with worsened survival is of particular concern and deserves further investigation as does the benefit of primary thromboprophylaxis.

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