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ORIGINAL RESEARCH

Early Change in C-Reactive Protein and Venous Thromboembolism in Patients Treated With Immune Checkpoint Inhibitors

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ABSTRACT

BACKGROUND Patients with cancer treated with immune-checkpoint inhibitors (ICIs) have a substantial risk of venous thromboembolism (VTE). The association between ICI-induced inflammation and hypercoagulability is unclear, and no biomarkers currently exist to stratify VTE risk.

OBJECTIVES The authors sought to determine the association between the early changes in C-reactive protein (CRP) after ICI initiation and the risk of VTE.

METHODS This retrospective cohort study included patients with cancer initiating ICI therapy from 2 academic cancer centers, serving as discovery and external validation cohorts. Patients were stratified based on CRP trajectories during the first 3 months of ICI treatment, with a CRP rise defined as a 2-fold increase from baseline. Patients were followed for VTE for the duration of ICI therapy, and competing risk and time-dependent analyses were used.

RESULTS A total of 822 patients were included. In the discovery cohort (n = 405), the cumulative VTE incidence in patients with a CRP rise (n = 159, 39.3%) was 19.9% (95% CI: 8.4%-34.8%), compared with 8.6% (3.1%-17.6%) in those without a CRP rise. After adjusting for key patient- and cancer-specific confounders, the subdistribution HR for VTE in patients with a CRP rise was 2.64 (95% CI: 1.06-6.62). This was confirmed in the external validation cohort (n = 417; subdistribution HR: 2.25; 95% CI: 1.03-4.94), with VTE incidences of 22.9% (95% CI: 9.7%-39.3%) in patients with a CRP rise and 10.8% (95% CI: 7.4%-15.1%) in those without. The association between CRP rise and VTE risk was confirmed in a time-dependent analysis and was consistent after adjusting for disease progression as a potential time-dependent confounder.

CONCLUSIONS Early CRP changes during ICI therapy are associated with an increased risk of VTE, suggesting a potential association between ICI-induced inflammation and hypercoagulability. CRP trajectories may serve as a biomarker for ICI-associated VTE. (JACC CardioOncol. 2024;6:965-975) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CRP = C-reactive protein

ECOG = Eastern Cooperative Oncology Group

ICI = immune checkpoint inhibitor

sdHR = subdistribution HR

VTE = venous thromboembolism

Patients with cancer have an increased risk of venous thromboembolism (VTE), a well-recognized complication associated with increased morbidity and mortality.[1] In clinical practice, the occurrence of VTE may also lead to delays, interruptions, or even discontinuation of anticancer therapies, adversely affecting the diseases course.[1-3]

Since the introduction of immune checkpoint inhibitors (ICIs), the treatment landscape in medical oncology has dramatically changed. ICIs are increasingly used to treat various cancers[4] by inhibiting tumoral immune-evasive pathways, inducing a strong and often sustained anticancer effect.[5] As a result, ICIs have led to significant advances in the treatment of various cancer types, with a subset of patients achieving ongoing remission despite advanced disease stages.[5]

However, ICI therapy is associated with an array of immune-mediated, inflammatory adverse events, which are well-characterized.[6,7] By contrast, the risk of VTE associated with ICI therapy has been less clear, partly due to the limited information on cardiovascular complications in landmark clinical trials, as these trials often apply frequency and severity thresholds for reporting adverse events.[8-10] Recent observational studies, however, have indicated a substantial risk of VTE associated with ICI therapy, with cumulative incidences ranging from 11% to 24%.[3,10-15]

Currently, it remains unclear whether ICIs exert a causal prothrombotic effect or if the observed VTE risk merely reflects the underlying risk profiles of patients based on disease- and patient-specific risk factors.[11,16] However, established risk factors and prediction models for VTE, derived from the general population of cancer patients, have shown limited predictive utility when applied to cohorts undergoing ICI therapy.[3,17] Notably, these clinical risk models for selecting ambulatory cancer patients for primary thromboprophylaxis (eg, the Khorana score) were developed in the preimmunotherapy era.[18-20] Specific risk factors and biomarkers for predicting VTE in patients treated with ICI are currently lacking. A better understanding of the potential link between ICI-associated inflammation and the risk of VTE, as well as an enhanced ability to predict ICI-associated VTE, may address this unmet need in a steadily growing patient population.

Increasing levels of C-reactive protein (CRP) after treatment initiation have been reported as an early indicator of the ICI-associated inflammatory response.[21] Recently, transient early CRP elevations after ICI initiation have been identified as a favorable prognostic biomarker for treatment response and survival, suggesting a potential role for CRP trajectories in reflecting ICI-associated anticancer immunity and the accompanying systemic inflammatory response.[22-25] However, the role of CRP levels in predicting VTE during ICI therapy has not been evaluated. Therefore, we performed a retrospective cohort study to investigate the associations between early CRP trajectories after ICI initiation and VTE risk. Furthermore, we used a second cohort to externally validate our results.

METHODS

STUDY DESIGN AND PATIENT COHORT. This retrospective cohort study included patients from 2 academic centers. Consecutive adult patients with histologically confirmed cancer treated with an ICI at the Vienna General Hospital of the Medical University of Vienna, Vienna, Austria, between January 2015 and November 2018, were used as the discovery cohort. Details on inclusion and exclusion criteria have been reported previously.[3] In addition, patients from the AUTRICHE registry (AUsTrian Registry for Immune CHEckpoint inhibitors), comprising consecutive adult patients treated with ICI at the Medical University of Graz, Graz, Austria, served as an external validation cohort.

In both cohorts, patients were required to have at least 3 CRP measurements within the first 3 months of ICI therapy initiation (ie, baseline levels and at least 2 longitudinal measurements) to be included in the analysis. Patients with missing baseline CRP values or insufficient longitudinal CRP measurements (fewer than 2 values within the first 3 months after ICI initiation) were excluded. The study was approved by the ethics committees of both institutions (Medical University of Vienna: No. 2213/2019; Medical University of Graz: No. 31-357 ex 18/19).

STUDY PROCEDURES AND VARIABLES. Data on patient demographics, cancer treatment, and ICI

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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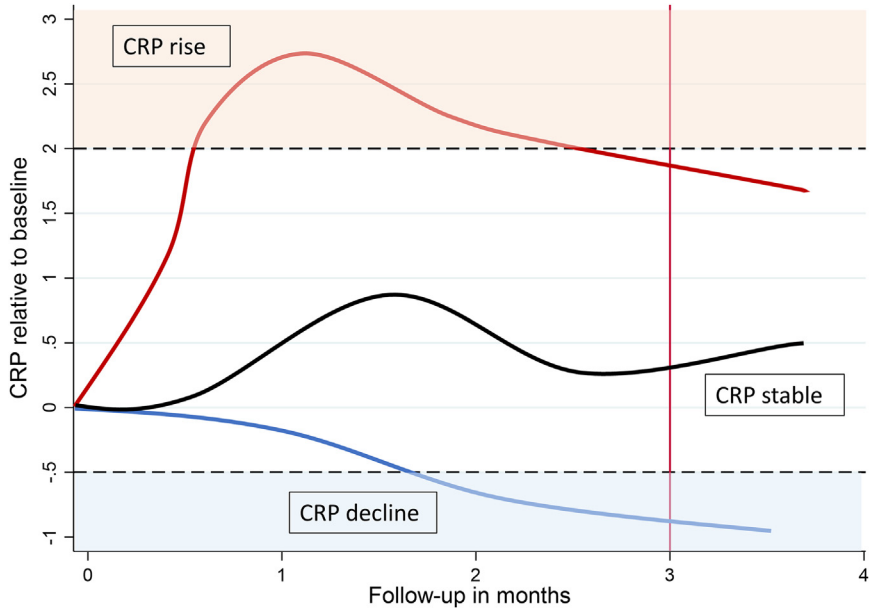
FIGURE 1 Schematic Representation of CRP Change Subgroups



Patients are stratified into groups based on the pattern of longitudinal C-reactive protein (CRP) levels during the first 3 months of immune checkpoint inhibitor therapy: CRP rise (defined as a ≥2-fold increase from baseline), CRP decline (defined as a ≥50% decrease from baseline), and CRP stable (no rise or decline from baseline).

therapy were obtained by electronic chart reviews. CRP measurements were collected from the electronic laboratory files both at study baseline (ie, at the closest pretreatment timepoint within 2 weeks before ICI therapy initiation) and longitudinally over the first 3 months of ICI therapy.

Pretreatment laboratory evaluations, including CRP measurement, represent a local standard of care before each cycle of systemic antineoplastic therapy at both study centers. CRP was routinely measured using particle-enhanced turbidimetric immunoassay, following local standard protocols. Patients were stratified based on individual CRP trajectories within 3 months of ICI therapy. A CRP rise was defined as a 2-fold or greater increase from baseline levels, based on previous classifications of longitudinal CRP trajectories in ICI therapy.[22,23,25] Conversely, a CRP decline was defined as a 50% or greater decrease in levels compared to baseline measurements. All available CRP measurements during the first 3 months of follow-up were used to classify patients, with the highest recorded level defining a CRP rise and the lowest defining a CRP decline. A schematic representation of patient stratification according to longitudinal CRP changes after ICI therapy initiation is visualized in **Figure 1**.

ENDPOINTS. The primary study endpoint was the first occurrence of VTE during ICI therapy, including deep vein thrombosis, pulmonary embolism, splanchnic vein thrombosis, or sinus vein thrombosis. Both symptomatic and incidental VTE events were included as outcome events. The observation period for VTE occurrence began on the first day of ICI therapy and ended upon death, initiation of subsequent systemic anticancer therapy other than ICI, or a maximum of 3 months after the last ICI cycle. Objective diagnostic imaging and confirmation by an independent adjudication committee were required to verify VTE events.

Secondary study endpoints included all-cause mortality and disease progression, which encompassed radiologic progression defined by immunotherapy-specific response evaluation criteria in solid tumors (iRECIST) or death. Data were obtained from the official Austrian death registry and electronic medical files.[26]

STATISTICAL ANALYSIS. Baseline clinicopathologic characteristics and treatment specifics were summarized using absolute frequencies and percentages or median with corresponding 25th-75th percentiles (Q1-Q3), as appropriate. The median follow-up time

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was calculated using the reverse Kaplan-Meier method. Longitudinal CRP trajectories were visualized by plotting the quadratic fit to biomarker data with 95% CIs.

To analyze VTE risk, we used a competing risk framework that accounted for all-cause death as a competing event to avoid overestimating cumulative risks in the setting of substantial underlying mortality.[27] Cumulative VTE incidences were obtained using the competing risk estimator with corresponding standard errors, following Marubini and Valsecci,[28] and Gray's method[29] was applied for between-group comparisons. Further, the association between CRP group allocation and VTE risk was modeled using a proportional subdistribution hazard regression model according to Gray's method, adjusting for potential confounders in multivariable analysis (cancer type, stage, Eastern Cooperative Oncology Group [ECOG] performance status, comorbidity burden as reflected by the Charlson comorbidity index, and concomitant cancer therapies). Results are presented as the subdistribution HR (sdHR) with 95% CIs.[30]

In addition, the effect of time-dependent covariates on VTE risk was analyzed using multistate models.[31] To account for the time-dependent nature of longitudinal CRP trajectories, CRP changes were included as a time-dependent covariate in the time-to-event analysis of VTE risk. Specifically, the analysis timeframe was split at the date of change in CRP group allocation (eg, the date of CRP doubling relative to baseline for the CRP rise group), reporting the transition HR for VTE after the occurrence of CRP rise. For visualization, a landmark analysis was conducted to compare VTE risks based on CRP trajectories within the first 3 months of ICI therapy.

We similarly adjusted the VTE risk analysis for disease progression using a multistate model. The association between CRP group allocation and VTE was adjusted for disease progression during follow-up as a time-dependent covariate. Also, multivariable adjustments were made for baseline CRP levels and included an interaction term between longitudinal CRP group and baseline CRP to account for intraindividual dependencies. A 2-sided P value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata version 16.1 software (StataCorp LP).

RESULTS

STUDY COHORT. Overall, 405 cancer patients treated with ICI at the Medical University of Vienna served as the discovery cohort. The median age was 63 years (Q1-Q3: 53-72 years), and 38.3% were female. Patients had a variety of underlying cancers, with melanoma (n = 135; 33.3%), non-small cell lung cancer (n = 105; 25.9%), renal cell carcinoma (n = 36; 8.9%), and head and neck cancer (n = 31; 7.7%) being the most frequent tumor types. Most patients presented with distant metastatic disease (stage IV) at the initiation of ICI therapy (n = 334; 91.3%) and had a good ECOG performance status (ECOG 0: n = 215; 67.0%).

ICI therapy was initiated with palliative intent in the majority of patients (n = 394; 97.3%), and the median treatment line was second-line systemic therapy (Q1-Q3: 1-2). Patients received a median of 6 ICI therapy cycles (Q1-Q3: 4-16 cycles; range: 1-76 cycles). Overall, 187 deaths occurred (46.2% of the study population), with a median overall survival of 23.7 months (95% CI: 18.5-37.3 months). Further, disease progression occurred in 295 patients (72.8% of the study population), with a median progression-free survival of 4.7 months (95% CI: 3.5-6.7 months). Details on the patient characteristics of the discovery cohort are summarized in **Table 1**.

CRP CHANGES AFTER TREATMENT INITIATION. A total of 2,740 CRP measurements were collected from 405 patients, with a median number of 5 measurements per patient (Q1-Q3: 3-8 measurements). At baseline, before ICI treatment began, the median CRP level was 13.8 mg/L (Q1-Q3: 3.7-44.6 mg/L). In total, 283 patients (69.9%) had baseline CRP levels above the local institutional upper reference limit (>5 mg/L).

Within the first 3 months of ICI therapy, 159 patients (39.3%) experienced a CRP rise, defined as a 2-fold or greater increase from baseline. Supplemental Figure 1 visualizes the fitted CRP trajectories for patients based on the occurrence of an early CRP rise. CRP levels decreased by 50% or more compared with baseline in 126 patients (31.1%), with no prior CRP rise in 108 of these patients (26.7%). A small proportion of patients (n = 18; 3.3%) experienced fluctuating CRP levels, fulfilling the criteria for both a CRP rise and decline. The remaining 138 patients (34.1%) were classified as CRP stable, with no rise or decline from baseline.

CRP CHANGES AND RISK OF VTE. During a median follow-up of 7.9 months after ICI initiation (Q1-Q3: 3.9-16.2 months), 29 VTE events were observed, with a cumulative incidence of 12.7% (95% CI: 6.9%-20.5%). The median time from study inclusion to VTE diagnosis was 4.1 months (Q1-Q3: 2.1-5.4 months). Baseline CRP levels measured before ICI therapy were not associated with VTE risk, with a sdHR of 0.95 (95% CI: 0.44-2.05) per doubling of CRP and a sdHR of 1.05 (95% CI: 0.49-2.26) for levels above 5 mg/L.

In patients with a CRP rise within the first 3 months of ICI therapy, the cumulative incidence of VTE was 19.9% (95% CI: 8.4%-34.8%), with rates of 8.9% (95% CI: 5.0%-14.2%) at 6 months and 11.0% (95% CI: 6.4%-17.1%) at 12 months. Conversely, in patients without a CRP rise, the cumulative incidence of VTE was 8.6% (95% CI: 3.1%-17.6%), with rates of 3.9% (95% CI: 1.9%-7.0%) at 6 months and 5.0% (95% CI: 2.7%-8.6%) at 12 months (Grayś method: $P = 0.028$) (**Figure 2**). The median time to VTE was 4.1 months (Q1-Q3: 2.7-5.3 months) in patients with a CRP rise and 3.7 months (Q1-Q3: 2.0-5.9 months) in those without. The median time from the date of CRP rise to VTE diagnosis was 1.8 months (Q1-Q3: 1.2-2.4 months).

Patients with a CRP decline during the first 3 months had a lower cumulative incidence of VTE, with rates of 2.5% (95% CI: 0.7%-6.4%) at 6 months and 3.4% (95% CI: 1.1%-8.0%) at 12 months. The lowest incidence was observed in the subgroup of patients with a CRP decline and no prior CRP rise, with rates of 1.9% (95% CI: 0.3%-6.1%) at 6 months and 3.0% (95% CI: 0.8%-7.9%) at 12 months. Patients classified as CRP stable (no rise or decline in CRP) had a cumulative incidence of VTE of 5.7% (95% CI: 2.5%-10.8%) at 6 months and 6.9% (95% CI: 3.2%-12.5%) at 12 months (Supplemental Figure 2). Detailed cumulative incidences of VTE for the different CRP trajectory subgroups are provided in **Table 2**.

In competing risk regression, the occurrence of a CRP rise after ICI initiation was associated with an increased risk of VTE (sdHR: 2.34; 95% CI: 1.12-4.91). This association persisted after multivariable adjustment for age, sex, cancer type, stage, ECOG performance status, and comorbidity burden (sdHR: 2.64; 95% CI: 1.06-6.62). The use of concomitant systemic cancer therapies or immunotherapy combinations did not affect the association between CRP rise and VTE risk (Supplemental Table 1). Furthermore, CRP rise was independently associated with an increased risk of VTE after adjusting for disease progression during follow-up, with a sdHR of 2.08 (95% CI: 1.04-4.15) as a time-dependent covariate.

Upon investigating the association between VTE and disease progression, we found that 10 of 29 VTEs (34.5%) occurred within 3 months before or after confirmed disease progression. Importantly, the strength of the association between CRP rise and VTE remained consistent for VTEs occurring within 3 months of disease progression, with a sdHR of 2.12 (95% CI: 0.64-7.00), and for VTEs outside this timeframe, with a sdHR of 2.51 (95% CI: 0.97-6.43). Of note, these analyses are limited by reduced statistical power due to the lower number of outcome events.

TABLE 1 Baseline Characteristics of the Study Cohort

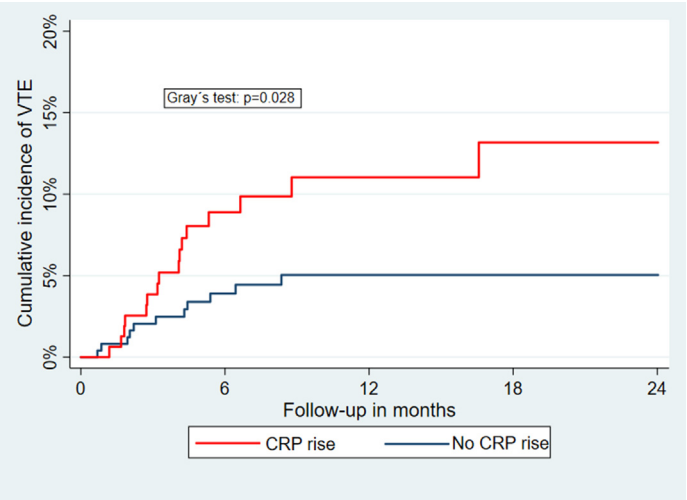
	N	% Missing	Median (Q1-Q3) or n (%)
Demographics and clinical characteristics			
Age, y	405	0	63 (53-72)
Female	405	0	155 (38.3)
BMI, kg/m^2	330	18.5	24.4 (21.0-27.7)
ECOG performance status	321	20.7	
ECOG 0			215 (67.0)
ECOG 1			78 (24.3)
ECOG ≥2			28 (8.7)
Charlson comorbidity index	405	0	8 (6-9)
Cancer characteristics			
Tumor type	405	0	
Melanoma			135 (33.3)
Non–small cell lung cancer			105 (25.9)
Renal cell carcinoma			36 (8.9)
Head and neck squamous cell carcinoma			31 (7.7)
Lymphoma/myeloma			21 (5.2)
Urothelial			19 (4.7)
Hepatocellular cancer			12 (3.0)
Gynecological			12 (3.0)
Sarcoma			9 (2.2)
Colorectal cancer			9 (2.2)
Others[a]			16 (4.0)
Stage	366	9.6	
I-III			32 (8.7)
IV			334 (91.3)
Therapeutic management			
Immune checkpoint inhibitor agent	405	0	
Nivolumab			173 (42.7)
Pembrolizumab			156 (38.5)
Ipilimumab			45 (11.1)
Atezolizumab			7 (1.7)
Avelumab			3 (0.7)
Ipilimumab plus nivolumab			21 (5.2)
Therapy cycles			6 (4-16), range: 1-76
Treatment intent			
Adjuvant			11 (2.7)
Palliative			394 (97.3)
Line of anticancer therapy			2 (1-2), range: 1-6
Prior chemotherapy			234 (58.4)
Concomitant therapy during immune checkpoint inhibitor	405	0	
Chemotherapy			14 (3.5)
Targeted therapy			40 (9.9)
Radiotherapy			77 (19.0)
Medical anticancer therapy after immune checkpoint inhibitor therapy	397	2.0	118 (29.7)

[a]Others comprise Merkel-cell carcinoma (n = 4), malignant pleural mesothelioma (n = 3), gastroesophageal cancer (n = 2), breast cancer (n = 2), small-cell lung cancer (n = 2), penile carcinoma (n = 1), glioma (n = 1), and thyroid carcinoma (n = 1).

BMI = body mass index; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group performance status.

Next, we accounted for the potential confounding effect of intraindividual correlations between CRP changes and baseline CRP values. The association between CRP rise and VTE risk remained significant

FIGURE 2 Cumulative Incidence of VTE Based on Early CRP Rise (≥2-Fold) After ICI Initiation



Cumulative incidence functions were derived from competing risk analysis, accounting for all-cause mortality as a competing outcome event. The figure shows a significantly higher cumulative incidence of venous thromboembolism (VTE) in patients with an early C-reactive protein (CRP) rise after immune checkpoint inhibitor (ICI) initiation compared to those without.

after expanding the multivariable model to include baseline CRP levels, with a sdHR of 2.66 (95% CI: 1.04-6.81), and after adjusting for an interaction term between baseline CRP levels and CRP group assignment, with a sdHR of 3.14 (95% CI: 1.06-9.31). The occurrence of a CRP decline was associated with a nonsignificant decrease in VTE risk, with a sdHR of 0.41 (95% CI: 0.16-1.06). The sdHR upon multivariable adjustment for age, sex, cancer type, stage, ECOG performance status, and comorbidity burden was 0.46 (95% CI: 0.15-1.40).

TABLE 2 Cumulative Incidence of VTE by CRP Subgroups

		Cumulative Incidence of VTE			
CRP Group		**6 mo**	**12 mo**	**24 mo**	**Overall**
Overall	405 (100)	5.8 (3.8-8.5)	7.3 (4.9-10.4)	8.1 (5.8-16.1)	12.7 (6.9-20.5)
CRP rise					
Yes	159 (39.3)	8.9 (5.0-14.2)	11.0 (6.4-17.1)	13.2 (7.4-20.6)	19.9 (8.4-34.8)
No	246 (60.7)	3.9 (1.9-7.0)	5.0 (2.7-8.6)	5.0 (2.7-8.6)	8.6 (3.1-17.6)
CRP decline	126 (31.1)	2.5 (0.7-6.4)	3.4 (1.1-8.0)	3.4 (1.1-8.0)	9.2 (1.8-23.0)
No prior rise[a]	108 (26.7)	1.9 (0.3-6.1)	3.0 (0.8-7.9)	3.0 (0.8-7.9)	9.7 (1.6-26.6)
CRP stable	138 (34.1)	5.7 (2.5-10.8)	6.9 (3.2-12.5)	6.9 (3.2-12.5)	6.9 (3.2-12.5)

Values are n (%) or cumulative incidences in % (95% CI). [a]Indicates patients with a C-reactive protein (CRP) decline and no prior CRP rise. A schematic representation of CRP group allocation is visualized in Figure 1. Cumulative incidences were obtained in competing risk analysis, accounting for all-cause mortality as competing outcome event.

VTE = venous thromboembolism.

CRP RISE AS TIME-DEPENDENT RISK FACTOR FOR VTE. To account for the time-dependent nature of longitudinal CRP changes after treatment initiation, we evaluated the association between CRP rise and subsequent VTE risk using a multistate model. CRP rise was implemented as a time-dependent covariate in a competing risk regression model, where it was associated with an increased risk of VTE (transition HR: 2.18; 95% CI: 1.02-4.69). Figure 3 visualizes the cumulative estimates of VTE risk in a landmark analysis, stratifying patients based on whether a CRP rise occurred within the first 3 months of ICI therapy.

EXTERNAL VALIDATION OF CRP CHANGES AND VTE RISK. A cohort of patients with cancer treated with ICI at the Medical University of Graz, Graz, Austria, served as an external validation cohort (n = 417). Baseline characteristics of this cohort are summarized in Supplemental Table 2. The association between an early CRP rise after ICI initiation and subsequent VTE risk was confirmed in multivariable analysis (adjusted sdHR: 2.25; 95% CI: 1.03-4.94). The cumulative incidence of VTE in patients with an early CRP rise was 22.9% (95% CI: 9.7%-39.3%), compared with 10.8% (95% CI: 7.4%-15.1%) in those without a CRP rise (Grayś method: $P = 0.015$) (Supplemental Table 3).

SENSITIVITY ANALYSIS. In the derivation cohort (n = 405), 70 patients (17.3%) were receiving continuous anticoagulation at baseline. In a sensitivity analysis excluding these patients, the cumulative incidence of VTE in those with a CRP rise was 22.3% (95% CI: 9.4%-38.6%), compared with 8.1% (95% CI: 2.5%-18.0%) in those without a CRP rise (Grayś method: $P = 0.008$). In multivariable analysis, adjusting for age, sex, cancer type, stage, ECOG performance status, and comorbidity burden, the sdHR for VTE in patients with a CRP rise was 4.57 (95% CI: 1.43-14.59).

In the external validation cohort (n = 417), 106 patients (25.4%) were receiving anticoagulation at baseline. After excluding these patients, the cumulative incidence of VTE in those with a CRP rise was 22.8% (95% CI: 8.1%-41.9%) compared with 11.2% (95% CI: 7.1%-16.3%) in those without a CRP rise (Grayś method: $P = 0.046$). The sdHR for VTE in multivariable analysis for patients with a CRP rise in the validation cohort was 2.43 (95% CI: 0.97-6.07). All details regarding the type and indication of anticoagulation, as well as sensitivity analyses in both the development and validation cohorts, are available in the Supplemental Appendix (Supplemental Tables 4 to 7).

DISCUSSION. Utilizing 2 cohorts of cancer patients treated with ICI therapy, we observed an independent association between early longitudinal CRP trajectories and subsequent VTE risk

(Central Illustration). An early increase in CRP levels after ICI initiation was associated with a higher prothrombotic risk. These findings were confirmed through external validation in an independent cohort and remained significant after controlling for potential confounding factors, including key clinical covariates, the time-dependent nature of CRP trajectories, the correlation with baseline CRP values, disease progression during follow-up, and a sensitivity analysis excluding patients receiving anticoagulation.

Our observations suggest a potential association between the ICI-associated systemic inflammatory response, as reflected by an early CRP rise, and hypercoagulability. Mechanistically, systemic inflammation is closely connected with the hemostatic system, through a complex interplay of inflammatory pathways, platelets, plasmatic coagulation, endothelial homeostasis, and fibrinolysis.[32] ICI therapy induces a systemic immune response through various physiologic mechanisms, including increased T-cell activation, proinflammatory cytokines, autoantibody-mediated mechanisms, and complement-mediated inflammation.[6] Phenotypically, immune-related adverse events induced by ICI resemble autoimmune diseases and share common pathophysiologic pathways with these conditions.[6] Intriguingly, autoimmune and inflammatory diseases in the noncancer population have been linked to an increased risk of VTE.[33,34]

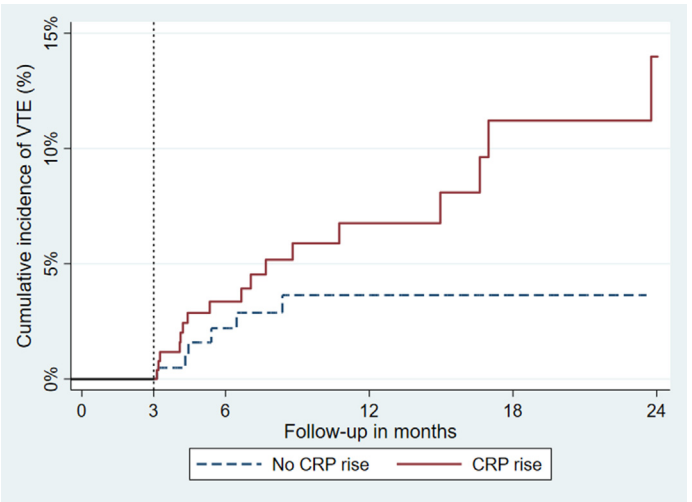
To the best of our knowledge, this study is the first to report a potential association between the ICI-induced inflammatory response, represented by an early CRP rise, and clinically overt hypercoagulability leading to VTE. Recent murine studies have suggested a potential pathophysiologic role for the upregulation of tumoral tissue factor and the release of tissue factor-bearing extracellular vesicles after ICI treatment, resulting in increased thrombus formation in ICI-treated mice.[35] Moreover, recent research has reported increased formation of prothrombotic neutrophil extracellular traps and circulating platelet-neutrophil aggregates in ICI-treated mice,[36] further supporting the concept of immunothrombosis as a potential cause of ICI-associated VTE. Therefore, we propose that VTE is an underappreciated immune-related adverse event of cancer immunotherapy, which may partly explain the high rates of VTE observed with ICI therapy.

Beyond their potential pathophysiological implications, our findings hold important clinical relevance for patients treated with ICI. Currently, primary thromboprophylaxis for ambulatory cancer patients is recommended based on risk stratification using the Khorana score or other validated models.[37] However, the Khorana score and other existing risk stratification tools were developed before the advent of immunotherapy, and recent validation studies in patients treated with ICI have reported conflicting results.[3,13,17,38] Additionally, established clinical risk factors for cancer-associated VTE have been shown to underperform in the context of ICI therapy, with consistently high VTE rates observed regardless of cancer type, stage, or patient characteristics.[3,13,38,39]

Data on biomarkers for predicting the risk of ICI-associated VTE are sparse, with only 1 exploratory subcohort from a retrospective study investigating inflammatory biomarkers before ICI initiation in 25 treated patients. This study found that higher pretreatment values of myeloid-derived suppressor cells, interleukin 8, and soluble vascular cell adhesion protein 1 were observed in patients who subsequently developed VTE compared with those who did not.[15] Therefore, our study highlights the potential of longitudinal evaluation of inflammatory biomarkers, such as CRP, for predicting VTE during ICI therapy.

STUDY LIMITATIONS. Several limitations need to be considered when interpreting the results of our study. First, despite using a widely available

FIGURE 3 Landmark Analysis of VTE Risk Based on Early CRP Rise Within 3 Months After ICI Initiation



A landmark time-dependent analysis was conducted using a 3-month timepoint after ICI initiation, comparing patients with and without a CRP rise during this period. The results confirm a higher risk of VTE in patients with an early CRP rise during ICI therapy compared to those without. Abbreviations as in Figure 2.

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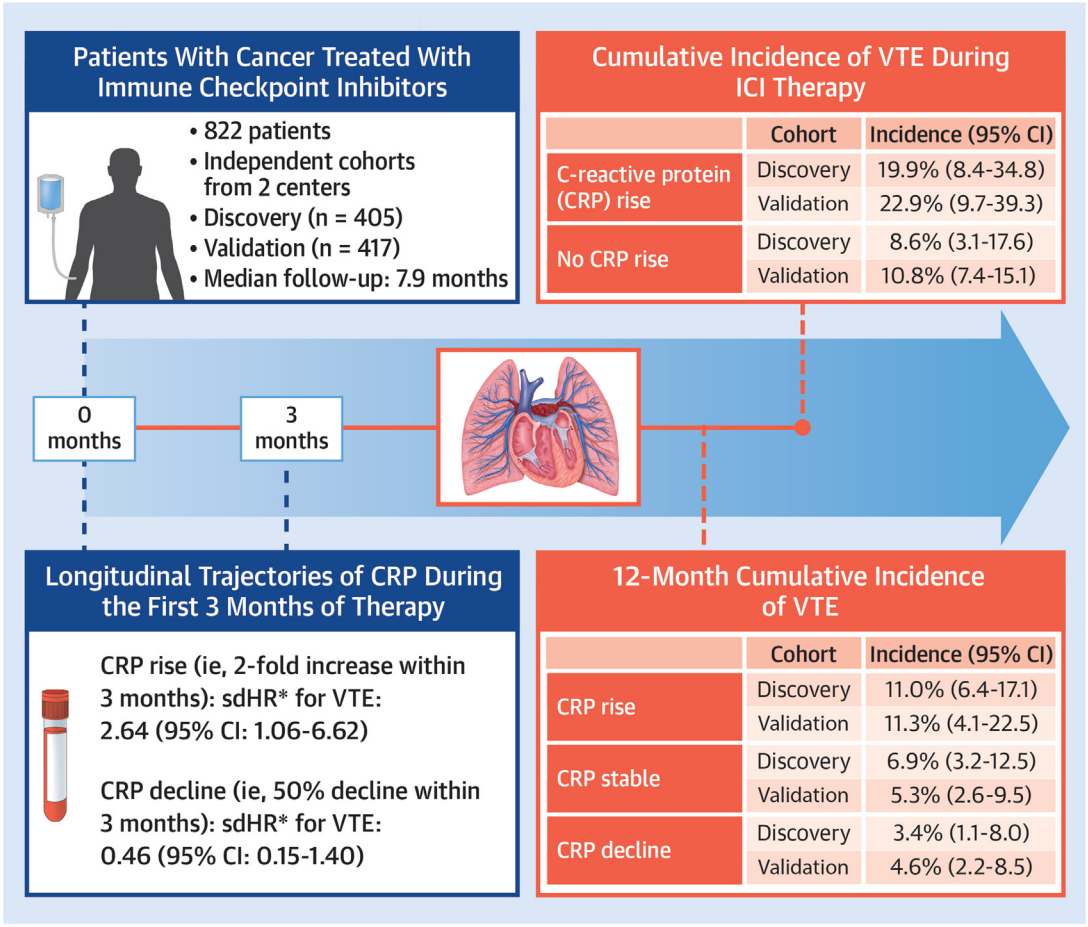
CENTRAL ILLUSTRATION **Longitudinal C-Reactive Protein Trajectories and Venous Thromboembolism Risk in Patients With Cancer Treated With Immune Checkpoint Inhibitors**



Moik F, et al. JACC CardioOncol. 2024;6(6):965-975.

Association between longitudinal C-reactive protein (CRP) trajectories and venous thromboembolism (VTE) risk in cancer patients treated with immune checkpoint inhibitors (ICIs), showing study cohorts, CRP group allocation methods, and key findings with an emphasis on increased VTE risk in patients with an early CRP rise after ICI initiation. Patients are stratified into groups based on the pattern of longitudinal CRP levels during the first 3 months of ICI therapy: CRP rise (defined as a ≥2-fold increase from baseline), CRP decline (defined as a ≥50% decrease from baseline), and CRP stable (no rise or decline from baseline). *Multivariable sdHR obtained in competing risk regression, accounting for all-cause death as competing event and adjusting for age, sex, cancer type, stage, ECOG performance status, and comorbidity burden. 95% CI = 95% confidence interval; CRP = C-reactive protein; ICI = immune checkpoint inhibitor; sdHR = subdistribution hazard ratio; VTE = venous thromboembolism.

biomarker and externally validating our findings in an independent cohort, the retrospective design limits generalizability. Longitudinal laboratory monitoring during ICI therapy, including routine CRP measurements, is standard practice in both study centers. However, due to the retrospective nature of the study, measurement timepoints were not standardized, and the exact reasons for individual CRP measurements or potential noncompliance with the practice could not be captured. Therefore, prospective studies using a standardized approach to longitudinally measure biomarker levels at fixed timepoints are needed.

Similarly, despite controlling for potential clinical confounders in multivariable analysis and validating our finding in time-dependent analyses, the

longitudinal CRP trajectories are influenced by complex confounding factors that may affect the association between CRP levels and VTE risk. These factors could include increased CRP levels due to infection, clinical deterioration, or cancer progression, which would be better controlled in a prospective study. Previous studies have linked rising CRP levels to an increased risk of progression in ICI therapy.[24]

Furthermore, cancer progression is linked to hypercoagulability.[40,41] In evaluating the potential confounding effect of underlying cancer progression dynamics, we found that a subset of VTE occurred in close association with disease progression. However, an independent association between rising CRP levels and VTE risk, regardless of disease progression during follow-up, was observed.

Additionally, the previously reported association between early transient CRP elevations after ICI initiation and improved clinical outcomes suggests that clinical deterioration and disease progression are not the sole drivers of increased VTE risk in patients with rising CRP levels.[22,23,25]

Moreover, despite CRP being an established surrogate of systemic inflammation, the retrospective design of our study limited the ability to explore more specific immune-mediated biomarkers and pathways involved in the inflammatory response. Future studies should aim to unravel the complex ICI-associated inflammatory response and its correlation with hypercoagulability biomarkers and VTE risk.

Lastly, currently available risk assessment models for cancer-associated VTE rely on variables available at treatment initiation,[20] and incorporating longitudinal biomarker measurements into risk stratification strategies may be challenging in clinical practice. Furthermore, before clinical implementation, the exact timing and frequency of measurements needed to optimize risk stratification must be determined through prospective studies with standardized CRP monitoring. However, established VTE risk models have limited predictive utility in patients treated with ICI. Therefore, more nuanced risk assessment strategies that incorporate longitudinal data could improve the ability to develop personalized prediction and prevention strategies in the future.[10,16,20,39]

CONCLUSIONS

In summary, the observed association between early changes in CRP levels and subsequent VTE risk suggests that ICI-induced systemic inflammation may contribute to clinically overt hypercoagulability, manifesting as VTE. An early increase in CRP levels could serve as a promising biomarker to identify cancer patients receiving ICI therapy who are at high risk for developing VTE and may benefit from risk-stratified thromboprophylaxis strategies, pending confirmation in future studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In cancer patients treated with immune checkpoint inhibitors, early increases in the inflammatory biomarker C-reactive protein are associated with a significantly higher risk of venous thromboembolism.

TRANSLATIONAL OUTLOOK: Further research is needed to explore the potential pathophysiologic relationship between immune checkpoint inhibitor–associated inflammation and systemic hypercoagulability.

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KEY WORDS **cancer, C-reactive protein, immune checkpoint inhibitors, thrombosis, venous thromboembolism**

APPENDIX **For supplemental figures and tables, please see the online version of this paper.**