Saudi Pharmaceutical Journal 30 (2022) 1193–1199

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Immune checkpoint inhibitors and potential risk of thromboembolic events: Analysis of the WHO global database of individual case safety reports

Eman A. Alghamdi *, Hadir Aljohani, Waad Alghamdi, Fawaz Alharbi

Saudi Food and Drug Authority, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 26 January 2022
Accepted 17 June 2022
Available online 21 June 2022

Keywords:
Checkpoints inhibitors
Pulmonary embolism
Deep vein thrombosis
Acute coronary syndrome
VigiBase

ABSTRACT

Introduction: Thromboembolic events with the use of immune checkpoint inhibitors (ICIs) in patients with cancer have been reported in few studies. However, the detailed profile of these cases remains mostly uncertain.

Method: A descriptive analysis of Thromboembolic events associated with ICIs retrieved from the VigiBase, between 1967 to November 2020. We extracted the data using the terms of 'pulmonary embolism' OR 'deep vein thrombosis' OR 'acute coronary syndrome' OR 'myocardial infarction' OR 'ischemic stroke' (preferred term (PT) (MedDRA).

Results: We included 161 cases from 26 countries in our descriptive analysis. Patients' ages were reported in 141 (87.6%) cases, with a median of 68 years (interquartile range 61–74), and 63.4% of the patients were male. Indications for ICIs were reported in 151 (93.8%) cases, as follows: lung cancer (n = 85, 52.8%), renal cell carcinoma (n = 24, 14.9%), melanoma (n = 20, 12.4%), urethral carcinoma (n = 12, 7.45%), breast cancer (n = 4, 2.48%), adenocarcinoma of the gastroesophageal junction (n = 3, 1.9%), gastric cancer (n = 2, 1.24%), and skin cancer (n = 1, 0.62%). Nivolumab was reported as a suspected drug in 76 cases (47%), pembrolizumab in 46 cases (28.5%), atezolizumab in 21 cases (13%), durvalumab in 14 cases (8.6%), and avelumab in four cases (2.4%).

The time to onset of thromboembolic events was reported in 127 (78.8%) cases. Most of these patients (n = 109, 85.8%) reported thromboembolic events within the first six months. The causality assessment of included cases showed that 50.3% of reported thromboembolic events were possibly related to the suspected reported medication, 13.7% were probably related, 13% were unlikely to be related, and 23% were not assessable due to insufficient information.

Conclusion: This study demonstrates a possible association between the use of ICIs and thromboembolic events. Further epidemiological studies are needed to assess this association and to elucidate the underlying mechanism.

Abbreviations: PD-1, Programmed Cell Death-1; PD-L1, Programmed Cell Death Ligand 1; ICIs, Immune Checkpoint Inhibitors; VTE, Venous Thromboembolism; ATE, Arterial Thromboembolism; irAEs, Immune-Related Adverse Events; WHO, World Health Organization; UMC, Uppsala Monitoring Centre; ICSRs, Individual Case Safety Reports; ADRs, Adverse Drug Reactions; PE, Pulmonary Embolism'; DVT, Deep Vein Thrombosis'; ACS, Acute Coronary Syndrome'; MI, Myocardial Infarction; PT, Preferred Term; MedDRA, Medical Dictionary For Regulatory Activities; IC, Information Component; IQR, Interquartile Range; LMWH, Low-Molecular-Weight Heparin; UFH, Unfractionated Heparin; TTO, Time To Onset; RR, Risk Ratio.

* Corresponding author.
E-mail addresses: emanian@live.com (E.A. Alghamdi), hijohani@sfda.gov.sa (H. Aljohani), e.aghamdi@sfda.gov.sa (W. Alghamdi), Ffharbi@sfda.gov.sa (F. Alharbi).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2022.06.010

1. Introduction

Immunotherapy has emerged as an effective treatment for solid tumors and hematological malignancies. Pembrolizumab, nivolumab, and cemiplimab comprise a subclass of immunotherapy targeting programmed cell death-1 (PD-1) checkpoint inhibitors. Atezolizumab, avelumab, and durvalumab target programmed cell death ligand 1 (PD-L1) receptors. These immune checkpoint inhibitors (ICIs) are indicated for the treatment of several types of cancer, such as metastatic melanoma and lung cancer, gastric cancer, gastric-esophageal junction cancer, and mesothelioma.(Garon et al., 2015; Robert et al., 2019) The antineoplastic effect occurs by selective inhibition of the interaction between PD-1 and its ligands PD-L1 and PD-L2, which suppresses T-cells and tumor growth, boosts anti-tumor responses, and facilitates tumor rejection.(González-Rodríguez and Rodríguez-Abreu, 2016; Robert et al., 2014).

The associations between malignancy and venous thromboembolism (VTE) and arterial thromboembolism (ATE) have been confirmed in several studies.(Cohen et al., 2017; Goldenberg et al., 2003; Grilz et al., 2018; Maraveyas and Johnson, 2009) In fact, VTE occurs in as many as 10% of patients with cancer.(Falanga et al., 2013; Pabinger et al., 2013; Timp et al., 2013a) It is hypothesized that thromboprophylaxis targeting patients with cancer at particularly high risk of thrombosis might improve their prognosis. The risk of VTE and ATE depends on the interaction between tumor cells, the hemostatic system, patient characteristics, and therapy-associated factors. Furthermore, the identification of risk factors for cancer-related venous thrombosis will help to improve the understanding of thrombosis pathophysiology in patients with cancer.

Since there is widespread use of ICIs to treat different types of cancers, and this is still expected to increase in the future, the toxicity of this group should be closely monitored. ICIs are well known to cause immune-related adverse events (irAEs), such as pneumonitis, colitis, hepatitis, immune thrombocytopenia, and rheumatoid arthritis. Most irAEs are moderately severe and classified as grade three to four toxicity.(Le Burel et al., 2017) The majority of irAEs can be reversed by corticosteroids and supportive care. Generally, the associated responses are good and enable the continued administration of ICIs, but in some cases, more aggressive therapy is needed.(Le Burel et al., 2017) Furthermore, irAEs can occur from two weeks to nine weeks after initiation based on the type of toxicity.(Weber et al., 2012).

The relationship between VTE and ATE with the use of ICIs has been addressed in some studies in literature. Recently published cohort studies demonstrated that the rate of VTE in patients receiving ICIs was between 6% and 18%, and, several case reports in the literature described serious and fatal thromboembolic events during the use of ICIs.(Ando et al., 2019; Boutros et al., 2018; Hegde et al., 2017; Ibrahimi et al., 2017; Nichetti et al., 2020).

Generally, thromboembolic events are not considered irAEs. However, the immune system activation associated with the use of ICIs could provoke the growth and destabilization of atherosclerotic lesions, causing acute coronary syndrome (ACS).(Tomita et al., 2017) Moreover, the proatherogenic T-cell response is downregulated by PD-1, and that inhibition of PD-1 may increase the risk of cardiovascular complications.(Cochain et al., 2014) Indeed, studies conducted in mice deficient of PD-1 resulted in enhanced infiltration of activated CD4 + and CD8 + T-cells in the atherosclerotic lesion, confirming the important role of the PD-1 pathway in vascular inflammatory diseases. The atherogenesis was accelerated early after the PD-1 blockade.(Bu De-xiu et al., 2011) This evidence strongly suggests that PD-1 inhibition may accelerate the development of atherosclerotic plaques and inflammation, which may induce vascular complications, such as ischemic heart disease and pulmonary embolism (PE).(Bar et al., 2019).

The aim of this study was to describe cases of VTE and ATE reported with the use of ICIs using real-world data from VigiBase, the World Health Organization (WHO)'s global database of individual case safety reports (ICSRs). Moreover, the study aimed to assess the causality between these events and the use of ICIs using the WHO-Uppsala Monitoring Centre (UMC) causality system.

2. Methods

2.1. Study setting

The WHO Programme for International Drug Monitoring was established in 1968 in Geneva, Switzerland. Since 1978, the UMC in Sweden has had the technical and operational responsibility of the WHO Programme, including the maintenance of VigiBase. One of the main tasks of the UMC is to collect and analyze worldwide data on ICSRs.("UMC | VigiBase," n.d.) VigiBase contains more than 20 million ICSRs, which are forwarded by national pharmacovigilance centers from over 145 countries to the UMC.("UMC | WHO programme members," n.d.) These ICSRs contain information about patients, suspected and concomitant drugs, suspected adverse drug reactions (ADRs), the reporter, and other relevant clinical information.

In VigiBase, drugs are coded according to the WHO Drug Dictionary, which uses the WHO Anatomical Therapeutic Chemical classification system, while ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) or the WHO Adverse Reaction Terminology.("UMC | VigiBase," n.d.) VigiBase is compliant with both MedDRA and WHO Adverse Reaction Terminology.

2.2. Study procedure and outcomes

We performed a search in VigiBase for adverse events associated with anti–PD-1 agents (nivolumab, pembrolizumab, cemiplimab) and anti–PD-L1 agents (atezolizumab, durvalumab, avelumab) between 1967 and November 2020.(Lindquist, 2008) VTEs included deep vein thrombosis (DVT) and PE.(Ay et al., 2008) ATEs included ACS and ischemic stroke.(Grilz et al., 2018).

Cases were first identified by the following MedDRA terms: 'pulmonary embolism' OR 'deep vein thrombosis' OR 'acute coronary syndrome' OR 'myocardial infarction' OR 'ischemic stroke' (reaction preferred term [PT] [MedDRA]). All serious cases with completeness scores of $\geq$ 0.85 were included.("UMC | vigiMethods," n.d.).

All relevant information included in ICSRs, such as that related to rechallenge and dechallenge, was retrieved using VigiLyze, a tool developed by the UMC for data mining and analysis of ICSRs in VigiBase.("UMC | vigiMethods," n.d.) The information component (IC) for the ICIs–ADR combination was also collected. The IC value is a measure of the disproportionality of a drug–ADR pair in the database. A positive IC025 value (the lower border of the credible interval for the IC value greater than 0) is "a traditional threshold which indicates that a drug-ADR pair is reported more often than expected based on all reports in the database," thus showing a statistical signal.(Bate et al., 1998).

Furthermore, we collected the following information for each ICSR: patient demographics (i.e., age, sex, and medical history), the adverse drug reaction (i.e., date of occurrence and outcome), and exposure to the drug (i.e., date of introduction and withdrawal).

The causality assessment was performed using the WHO-UMC causality system (Appendix 1).(Organization (WHO), 2017).

2.3. Statistical analysis

We performed our statistical analyses using Jamovi software version 1.2.2.0. Age was summarized using the median. Other baseline characteristics of cases are presented as numbers and percentages.

3. Results

3.1. Descriptive analysis of cases

As of November 28, 2020, we identified a total of 1,287 ICSRs of thromboembolic events with the use of ICIs, including anti–PD-1 agents (nivolumab, pembrolizumab, cemiplimab) and anti–PD-L1 agents (atezolizumab, durvalumab, avelumab). Of these, 161 ICSRs had completeness scores of $\geq$ 0.85 and were included in the analysis. The ICSRs were reported from 26 countries—mainly from France (n = 34, 21.1%), followed by Germany (n = 29, 18%) and Japan (n = 28, 17.4%) (Table 1).

Age was reported for 141 (87.6%) ICSRs, with the median being 68 years (interquartile range [IQR] 61–74). One hundred and two (63.4%) patients were male, and 59 (36.6%) were female. Other Comorbidities were reported in 41 (25.5%) patients, which include hypertension (15), diabetes mellites (6), thyroid disorder (2), hyperlipidemia (10), cardiac disease (5), previous thrombotic event (3). Among the 161 included ICSRs, indications for ICIs were reported in 151 (93.8%) cases. Eighty-five patients (52.8%) were being treated for lung cancer, 24 (14.9%) for renal cell carcinoma, 20 (12.4%) for melanoma, 12 (7.45%) for urethral carcinoma, 4 (2.48%) for breast cancer, 3 (1.9%) for adenocarcinoma of the gastroesophageal junction, 2 (1.24%) for gastric cancer, and 1 (0.62%) for skin cancer.

Nivolumab was reported as a suspected drug in 76 cases (47%), pembrolizumab in 46 cases (28.5%), atezolizumab in 21 cases (13%), durvalumab in 14 cases (8.6%), and avelumab in only four cases (2.4%). Cemiplimab was not reported in any of the included cases.

Table 1
Number of reports per country.

Country	Number	% of Total
France	34	21.1%
Germany	29	18.0%
Japan	28	17.4%
Italy	12	7.5%
United States of America	12	7.5%
Australia	7	4.3%
The United Kingdom	7	4.3%
Netherlands	4	2.5%
Greece	3	1.9%
Sweden	3	1.9%
Belgium	2	1.2%
Canada	2	1.2%
Estonia	2	1.2%
Hungary	2	1.2%
Singapore	2	1.2%
Switzerland	2	1.2%
Czechia	1	0.6%
Denmark	1	0.6%
Finland	1	0.6%
India	1	0.6%
Ireland	1	0.6%
Korea	1	0.6%
New Zealand	1	0.6%
Poland	1	0.6%
Portugal	1	0.6%
Venezuela	1	0.6%

Table 2
Characteristics of included cases.

No. of cases/patients	N = 161
Sex	
Male	102 (63.4%)
Female	59 (36.6%)
Age at onset, years [median (IQR)] (n = 141)	68 yr. (IQR 61–74)
ICIs reported as individual suspected drug	**n = 122**
Nivolumab	76 (47%)
Pembrolizumab	46 (28.5%)
Atezolizumab	21 (13%)
Durvalumab	14 (8.6%)
Avelumab	4 (2.4%)
Indication	**n = 151**
Lung cancer	85 (52.8%)
Renal cell carcinoma	24 (14.9%)
Melanoma	20 (12.4%)
Urothelial carcinoma	12 (7.5%)
Unknown source of cancer	5 (3.1%)
Breast cancer	4 (2.5%)
Adenocarcinoma of the gastroesophageal junction	3 (1.9%)
Gastric cancer	2 (1.2%)
Ovarian cancer	2 (1.2%)
Bladder cancer	1 (0.6%)
Metastatic melanoma	1 (0.6%)
Skin cancer	1 (0.6%)
Squamous cell carcinoma of head and neck	1 (0.6%)
Type of reaction	**n = 161**
PE	83 (51.6%)
MI	40 (24.8%)
DVT	16 (9.9%)
DVT and PE	11 (6.8%)
ACS	8 (5.0 %)
Embolic stroke	3 (1.9%)
Use of thromboprophylaxis as co-medication	
Yes	30 (18.6%)
No	131 (81.4%)

Out of the 161 included cases, ICI was reported as an individual suspected drug in 122 ICSRs. Specifically, nivolumab in 63 (51.6%) cases, pembrolizumab in 35 (28.6%) cases, atezolizumab in 16 (13.3%) cases, and durvalumab in eight (4.9 %) cases. In the remaining cases (n = 27), ICIs were reported as a co-suspected drug with other drugs, such as anti–cytotoxic T lymphocyte antigen-4 monoclonal antibody, bevacizumab, paclitaxel, cabozantinib, naloxegol, lenvatinib, axitinib, gemcitabine, cisplatin, carboplatin, pemetrexed, and etoposide.

Furthermore, VTE was reported more frequently than ATE (n = 118, 73.3% and n = 43, 26.7%, respectively). PE was reported in 83 (51.6%) cases, followed by myocardial infarction (MI) and DVT, which were reported in 40 (24.8%) and 16 (9.9%) cases, respectively (Table 2).

Thrombolytic agents were used as co-medications in 30 (18.6%) reported cases. Of these, PE events were reported for 16 patients, while MI and DVT were reported for nine and three patients, respectively. ACS was reported for two patients, while one patient reported both DVT and PE (Fig. 1).

Of these, the anticoagulant agents were mainly low-molecular-weight heparin (LMWH) (five cases), apixaban (four cases), unfractionated heparin (UFH) (four cases), rivaroxaban (one case), and fondaparinux sodium (one case). On the other hand, the antiplatelet agents were aspirin (in 14 cases) and clopidogrel (one case). Of the 15 included patients on antiplatelet agents, one was on dual antiplatelets (aspirin/clopidogrel). (Fig. 2 &Fig. 3.).

Time to onset (TTO) of thromboembolic events was reported for 127 (78.8%) cases; most of the patients (n = 109, 85.8%) reported thromboembolic events within the first six months. TTO for patients on antithrombotic agents ranged from one day to 1,080 days, with a median of 60 (IQR 30–120) days following the

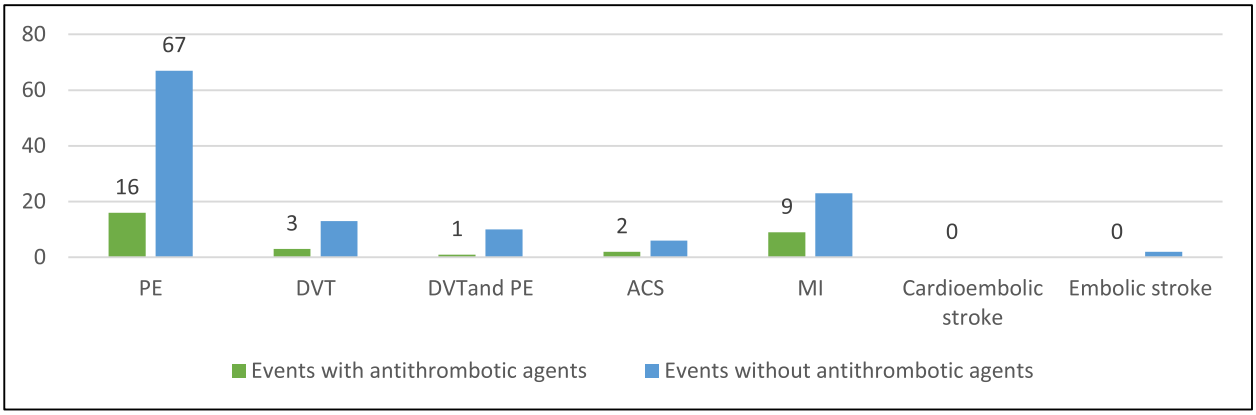

Fig. 1. Numbers of AVE and ATE events with and without antithrombotic agents.

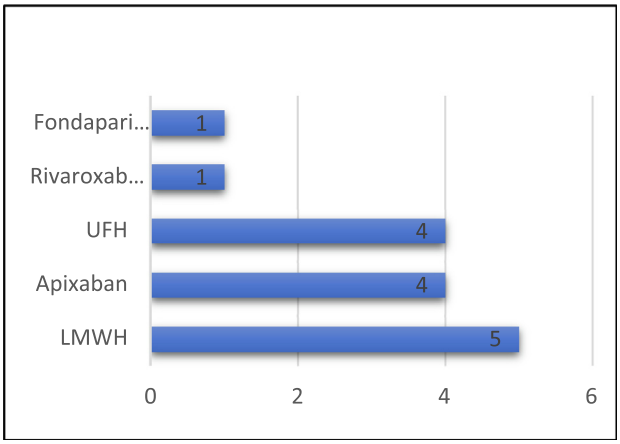

Fig. 2. The distribution of anticoagulants among ICSRs (n = 15).

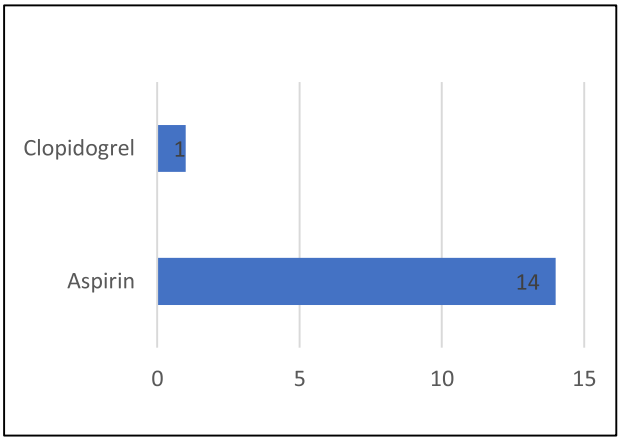

Fig. 3. The distribution of antiplatelets among ICSRs (n = 15).

initiation of ICIs. For patients not receiving antithrombotic agents, the TTO ranged from one day to 540 days, with a median of 45 (IQR 21.8–90) days. This difference was not statistically significant.

Reaction outcomes were as follows: fatal in 41 cases (25.5%), recovered in 82 cases (50.9%), recovered with sequelae in 10 cases (6.2%), not recovered in 21 cases (13.0 %), and not reported in the remaining cases.

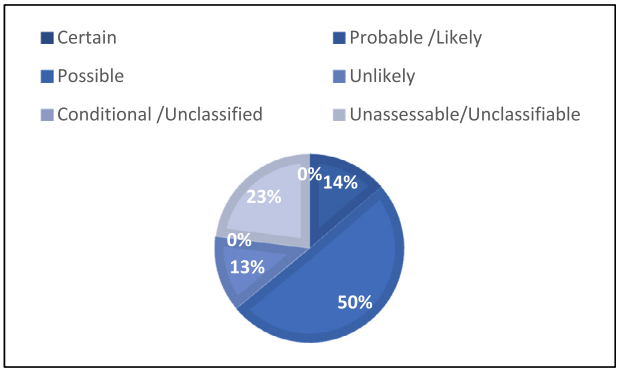

Fig. 4. Causality assessment of the ICSRs.

Table 3
Information Component (IC025) for ICIs and reported reactions.

Drug Name	*Type of thromboembolic event*				
	PE	DVT	MI	ACS	Embolic Stroke
Nivolumab	0.6	−0.4	−1.3	1.2	−1.5
Pembrolizumab	0.7	−0.7	−1.4	−0.0	−0.8
Atezolizumab	1.0	−0.4	−1.2	−1.3	−1.2
Durvalumab	1.2	−1.4	−2.3	−1.7	−0.1
Avelumab	0.6	−3.2	–	0.2	–

3.2. Causality assessment of cases

The causality assessment of included cases revealed that 81 (50.3%) reported thromboembolic events were possibly related to the suspected reported medication, 22 (13.7%) were probably related, and 21 (13%) were unlikely to be related. Thirty-seven cases (23%) were not assessable due to insufficient information (Fig. 4).

In particular, in the 22 cases that were probably related, ICI was indicated for lung cancer in nine (40%), melanoma in five (22.7%), renal carcinoma in four (18%), and urothelial carcinoma in two (9%). In these 22 cases, pulmonary embolism was reported in 11, myocardial infarction in nine, and PE and DVT in two each.

IC values were retrieved from VigiLyze in July 2021. We found positive IC values for all included ICIs with PE and nivolumab and ACS combination, while the IC value was negative for the remaining combinations in VigiBase (Table 3).

4. Discussion

To our knowledge, our study is the first to describe a large number of thromboembolic events reported with ICIs in VigiBase. We described ICI-induced VTE and ATE events for 161 cases. Of these cases, PE was reported in 83 cases (51.6%), followed by MI in 40 cases (24.8%), DVT in 16 cases (9.9%), DVT with PE in 11 cases (6.8%), ACS in eightcases (5.0%), and embolic stroke in 3 cases (1.9%). The most commonly reported ICIs as suspected drugs were nivolumab (47%) and pembrolizumab (28.5%). The main findings from the present study indicate the following: firstly, ICIs may have prothrombotic effects and increase the risks of VTE and ATE. Secondly, the TTO of thromboembolic events tended to be shorter in patients not receiving antiplatelet and anticoagulant treatments. Thirdly, patients with lung cancer receiving ICIs had an increased rate of all thrombosis events compared to patients with other types of cancer receiving ICIs (P = 0.02).

Overall, the results of this study align with those from prior studies documenting the increased risk of VTE and ATE events associated with the use of ICIs.(“Abstracts of 48th ESCP symposium on clinical pharmacy 23–25 October 2019, Ljubljana (Slovenia),” 2020; Alkhathlan et al., 2017; Ferreira et al., 2018; Kunimasa et al., 2018; Li et al., 2021; Sussman et al., 2021; Tomita et al., 2017; Tsukamoto et al., 2018) In terms of confounding factors, it has been argued that gender and age may increase the risk of thromboembolism in patients receiving ICIs. One study found that the event rate was higher in patients $\geq$ 65 years of age compared to younger patients and in male patients (59%) compared to female patients (41%).(Bar et al., 2019; Sussman et al., 2021) Similar results were found in the present study; the median age of patients who developed thromboembolic events was 68 (IQR 61–74) years, and the incident rate of thromboembolic events in cancer patients with ICIs was slightly higher for males (59%) than for females (41%). Notably, female patients with cancer who developed acute VTE had significantly lower rates of fatal bleeding (risk ratio [RR] 0.69; 95% confidence interval [CI] 0.47–0.99) and death (RR 0.90; 95% CI 0.83–0.97) and a non-significantly lower rate of PE recurrences compared to males.(“Gender differences in cancer patients with acute venous thromboembolism,” 2015).

Furthermore, previous literature has stated that VTE incidence rates were higher in patients receiving the combination of ICI (either PD-1 or PD-L1) and ipilimumab compared with those receiving single-agent ICI (16.7% vs. 5.0% at 6 months; 21.3% vs. 9.5% at 12 months, respectively; P = 0.02). The 6-month and 1-year cumulative ATE incidence rates were similar for patients receiving combination and single-agent ICI, respectively (2.5% vs. 1.5% at 6 months; 5.1% vs. 3.0% at 12 months, respectively; P = 0.50). (Sussman et al., 2021) These results supports those of the present study, which may suggest that the use of ipilimumab with ICIs could be a risk factor for developing thromboembolic events.

Malignancy is a well-known risk factor for an increased risk of thromboembolic events with poor outcomes, with a six-fold decrease in survival rate compared to patients without cancer. (Chew et al., 2006) According to a large Danish retrospective study, the most common cancer diagnosed during a thromboembolic event episode was pulmonary cancer (17%), followed by pancreatic cancer (10%), colon and rectal cancer (8%), renal cancer (8%), and prostatic cancer (7%).(SØrensen et al., 2000) Thus, it is difficult to conclusively state that ICIs increased the incident rates of VTE and ATE. To further assess the impact of ICIs on thromboembolic events, Li et al. found that found that ICIs showed a signal of PE compared with other chemotherapy. (Li et al., 2021) Considering the fact that protein kinase inhibitors and other chemotherapy are well documented to significantly increase VTE and PE risks. (Gervaso et al., 2020; Jiang and Lee, 2019; Moore et al., 2011).

One previous study showed that the median TTO of fatal cases was 31 (IQR 13–73) days, which was significantly shorter than that of non-fatal cases (50 [IQR 20–108] days) (P < 0.001).(Li et al., 2021) Another study argued that a higher rate of thromboembolic events was found during the first six months after initiation of ICIs than in later time periods (odds ratio 3.49, 95% CI 1.45–8.41; P = 0.002).(Bar et al., 2019) In the current study, only serious cases were included in the analysis; the median TTO of thromboembolic events for patients who were not on antithrombotic agents was 45 (IQR 21.8–90) days, and the TTO was 60 days (IQR 30–120) for patients who were receiving antithrombotic agents at the time of the event. The TTO found in the current study may support previous findings that a higher rate of thromboembolic events is found during the first six months after initiation of ICIs. Furthermore, the antithrombotic agent could play a role in delaying the onset of thromboembolic events in patients with cancer on ICIs. However, information about the previous history of VTEs or ATEs and details on antithrombotic therapy was not available in the reported cases to properly assess the relationship between the events and antithrombotic agents. In spite of the fact that the American Society of Clinical Oncology and the European Myeloma Network recommend the use of LMWH prophylaxis and aspirin in selected populations of cancer patients with solid tumors or patients with myeloma receiving immunomodulatory agents, the use of thromboprophylaxis has been controversial in clinical practice.(Hegde et al., 2017; Kearon et al., 2016; Khorana et al., 2014; Mandalà and Labianca, 2010; Streiff et al., 2018; Terpos et al., 2015; Watson et al., 2015) Therefore, larger studies should be conducted to assess the optimal regimen of thromboprophylaxis in special subpopulations.

This study has some limitations. The reported cases were captured from the WHO global database of ICSRs, which holds suspected cases that vary with regard to their sources and completeness. Thus, the authors could not validate the diagnoses of AVE and ATE. Due to the lack of denominator information in spontaneous reporting, this study cannot quantify the incidence of AVEs and ATEs associated with ICIs. The number of reports was small, so larger studies are needed to confirm or refute the hypotheses generated from the observations of this study. Furthermore, valuable information, such as disease stage, duration of anticoagulation, previous history of thromboembolic events, and lifestyle risk factors, were also not available, which may limit the findings of the current study.

5. Conclusion

This study proposes a possible association between the use of ICIs and thromboembolic events. Further epidemiological studies are needed to study the association between the occurrence of thromboembolic events and the use of ICIs and to elucidate the underlying mechanism. Healthcare providers are advised to educate patients about the signs and symptoms of thromboembolic events and to encourage them to seek medical attention if they experience any of these events while using ICIs.

6. Ethics Approval and Consent to Participate

As the study uses retrospective data from the WHO global database, ethical approval and consent for participation are not required for authorized professionals of countries participating in the WHO program for international drug monitoring.

7. Authors’ contributions

EA Conception/design.

EA, HA, and WA Provision of study material or patients.
HA Data analysis and interpretation.
EA, WA Manuscript writing.
FA Final review of manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abstracts of 48th ESCP symposium on clinical pharmacy 23–25 October 2019, Ljubljana (Slovenia): The digital revolution supporting clinical pharmacy through e-health, digital support systems, big data, and more, 2020. . Int J Clin Pharm 42, 217–292. https://doi.org/10.1007/s11096-019-00945-w

Alkhathlan, A.Z., Tofovic, D.S., Sullivan, C., Gupta, A., Rajagopalan, S., 2017. Ipilimumab-nivolumab therapy causing STEMI in a melanoma patient: a case report. Case Rep. Intern. Med. 4, 57. https://doi.org/10.5430/crim.v4n3p57.

Ando, Y., Hayashi, T., Sugimoto, R., Nishibe, S., Ito, K., Kawada, K., Ikeda, Y., Yamada, S., Imaizumi, K., 2019. Risk factors for cancer-associated thrombosis in patients undergoing treatment with immune checkpoint inhibitors. Invest. New Drugs 38 (4), 1200–1206.

Ay, C., Simanek, R., Vormittag, R., Dunkler, D., Alguel, G., Koder, S., Kornek, G., Marosi, C., Wagner, O., Zielinski, C., Pabinger, I., 2008. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna cancer and thrombosis study (CATS). Blood, J. Am. Soc. Hematol. 112 (7), 2703–2708.

Bar, J., Markel, G., Gottfried, T., Percik, R., Leibowitz-Amit, R., Berger, R., Golan, T., Daher, S., Taliansky, A., Dudnik, E., Shulman, K., Urban, D., Onn, A., 2019. Acute vascular events as a possibly related adverse event of immunotherapy: a single-institute retrospective study. Eur. J. Cancer 120, 122–131. https://doi.org/10.1016/j.ejca.2019.06.021.

Bate, A., Lindquist, M., Edwards, I.R., Olsson, S., Orre, R., Lansner, A., De Freitas, R.M., 1998. A Bayesian neural network method for adverse drug reaction signal generation. Eur. J. Clin. Pharmacol. 54 (4), 315–321.

Boutros, C., Scoazec, J.-Y., Mateus, C., Routier, E., Roy, S., Robert, C., 2018. Arterial thrombosis and anti-PD-1 blockade. Eur. J. Cancer 91, 164–166.

De-xiu, B.u., Margarite, T., Elena, M.-G., George, S., Goro, T., James, L., Petr, J., Freeman, G.J., Sharpe, A.H., Lichtman, A.H., 2011. Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation. Arterioscler. Thromb. Vasc. Biol. 31, 1100–1107. https://doi.org/10.1161/ATVBAHA.111.224709.

Chew, H.K., Wun, T., Harvey, D., Zhou, H., White, R.H., 2006. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch. Intern. Med. 166, 458–464.

Cochain, C., Chaudhari, S.M., Koch, M., Wiendl, H., Eckstein, H.-H., Zernecke, A., Ashour, H.M., 2014. Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice. PLoS ONE 9 (4), e93280.

Cohen, A.T., Katholing, A., Rietbrock, S., Bamber, L., Martinez, C., 2017. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. Thromb. Haemost. 117 (01), 57–65.

Falanga, A., Marchetti, M., Vignoli, A., 2013. Coagulation and cancer: biological and clinical aspects. J. Thromb. Haemost. 11, 223–233.

Ferreira, M., Pichon, E., Carmier, D., Bouquet, E., Pageot, C., Bejan-Angoulvant, T., Campana, M., Vermes, E., Marchand-Adam, S., 2018. Coronary toxicities of anti-PD-1 and anti-PD-L1 immunotherapies: a case report and review of the literature and international registries. Target. Oncol. 13 (4), 509–515.

Garon, E.B., Rizvi, N.A., Hui, R., Leighl, N., Balmanoukian, A.S., Eder, J.P., Patnaik, A., Aggarwal, C., Gubens, M., Horn, L., Carcereny, E., Ahn, M.-J., Felip, E., Lee, J.-S., Hellmann, M.D., Hamid, O., Goldman, J.W., Soria, J.-C., Dolled-Filhart, M., Rutledge, R.Z., Zhang, J., Lunceford, J.K., Rangwala, R., Lubiniecki, G.M., Roach, C., Emancipator, K., Gandhi, L., 2015. Pembrolizumab for the treatment of non–small-cell lung cancer. N. Engl. J. Med. 372, 2018–2028. https://doi.org/10.1056/NEJMoa1501824.

Gender differences in cancer patients with acute venous thromboembolism, 2015. . Thrombosis Research 135, S12–S15. https://doi.org/10.1016/S0049-3848(15)50433-7

Gervaso, L., Montero, A.J., Jia, X., Khorana, A.A., 2020. Venous thromboembolism in breast cancer patients receiving cyclin-dependent kinase inhibitors. J. Thromb. Haemost. 18 (1), 162–168.

Goldenberg, N., Kahn, S.R., Solymoss, S., 2003. Markers of coagulation and angiogenesis in cancer-associated venous thromboembolism. J. Clin. Oncol. 21 (22), 4194–4199.

González-Rodríguez, E., Rodríguez-Abreu, D., 2016. Immune checkpoint inhibitors: review and management of endocrine adverse events. Oncologist 21, 804–816. https://doi.org/10.1634/theoncologist.2015-0509.

Grilz, E., Königsbrügge, O., Posch, F., Schmidinger, M., Pirker, R., Lang, I.M., Pabinger, I., Ay, C., 2018. Frequency, risk factors, and impact on mortality of arterial thromboembolism in patients with cancer. Haematologica 103, 1549–1556. https://doi.org/10.3324/haematol.2018.192419.

Hegde, A.M., Stroud, C.R.G., Cherry, C.R., Yogarajah, M., Cherukuri, S.D., Walker, P.R., 2017. Incidence and impact of thromboembolic events in lung cancer patients treated with nivolumab. American Society of. Clini. Oncol. 35 (15_suppl), e20624.

Ibrahimi, S., Machiorlatti, M., Vesely, S.K., Malla, M., Modhia, F., Jones, S.A., Roman, D., Cherry, M.A., 2017. Incidence of vascular thromboembolic events in patients receiving immunotherapy: A single institution experience. Blood 130, 4864.

Jiang, M.D., Lee, M.A.I., 2019. Thrombotic risk from chemotherapy and other cancer therapies. Thromb. Hemost. Cancer, 87–101.

Kearon, C., Akl, E.A., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., Huisman, M., King, C.S., Morris, T.A., Sood, N., Stevens, S.M., Vintch, J.R.E., Wells, P., Woller, S.C., Moores, L., 2016. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 149 (2), 315–352.

Khorana, A.A., Otten, H.-M., Zwicker, J.I., Connolly, G.C., Bancel, D.F., Pabinger, I., 2014. Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. J. Thromb. Haemost. 12 (11), 1928–1931.

Kunimasa, K., Nishino, K., Kimura, M., Inoue, T., Tamiya, M., Kumagai, T., Imamura, F., 2018. Pembrolizumab-induced acute thrombosis. Medicine (Baltimore) 97. https://doi.org/10.1097/MD.0000000000010772.

Le Burel, S., Champiat, S., Mateus, C., Marabelle, A., Michot, J.-M., Robert, C., Belkhir, R., Soria, J.-C., Laghouati, S., Voisin, A.-L., Fain, O., Mékinian, A., Coutte, L., Szwebel, T.-A., Dunogeant, L., Lioger, B., Luxembourger, C., Mariette, X., Lambotte, O., 2017. Prevalence of immune-related systemic adverse events in patients treated with anti-programmed cell death 1/anti-programmed cell death-ligand 1 agents: a single-centre pharmacovigilance database analysis. Eur. J. Cancer 82, 34–44. https://doi.org/10.1016/j.ejca.2017.05.032.

Li, H., Sun, X., Sun, D., Zhao, J., Xu, Z., Zhao, P., Ma, Z., Zhang, Y., 2021. Thromboembolic events associated with immune checkpoint inhibitors: a real-world study of data from the food and drug administration adverse event reporting system (FAERS) database. Int. Immunopharmacol. 98, 107818.

Lindquist, M., 2008. VigiBase, the WHO global ICSR database system: basic facts. Drug Information J. 42 (5), 409–419.

Mandalà, M., Labianca, R., 2010. Venous thromboembolism (VTE) in cancer patients. ESMO clinical recommendations for prevention and management. Thromb. Res. 125, S117–S119.

Maraveyas, A., Johnson, M., 2009. Does clinical method mask significant VTE-related mortality and morbidity in malignant disease? Br. J. Cancer 100, 1837–1841. https://doi.org/10.1038/sj.bjc.6605091.

Moore, R.A., Adel, N., Riedel, E., Bhutani, M., Feldman, D.R., Tabbara, N.E., Soff, G., Parameswaran, R., Hassoun, H., 2011. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J. Clin. Oncol. 29 (25), 3466–3473.

Nichetti, F., Ligorio, F., Zattarin, E., Signorelli, D., Prelaj, A., Proto, C., Galli, G., Marra, A., Apollonio, G., Porcu, L., de Braud, F., Lo Russo, G., Ferrara, R., Garassino, M.C., 2020. Is there an interplay between immune checkpoint inhibitors, thromboprophylactic treatments and thromboembolic events? mechanisms and impact in non-small cell lung cancer patients. Cancers 12 (1), 67.

Organization (WHO), W.H., 2017. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. WHO, http://www.who-umc. org/graphics/4409. pdf.[Google Scholar].

Pabinger, I., Thaler, J., Ay, C., 2013. Biomarkers for prediction of venous thromboembolism in cancer. Blood 122, 2011–2018. https://doi.org/10.1182/blood-2013-04-460147.

Robert, C., Ribas, A., Schachter, J., Arance, A., Grob, J.-J., Mortier, L., Daud, A., Carlino, M.S., McNeil, C.M., Lotem, M., Larkin, J.M.G., Lorigan, P., Neyns, B., Blank, C.U., Petrella, T.M., Hamid, O., Su, S.-C., Krepler, C., Ibrahim, N., Long, G.V., 2019. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 20, 1239–1251. https://doi.org/10.1016/S1470-2045(19)30388-2.

Robert, C., Ribas, A., Wolchok, J.D., Hodi, F.S., Hamid, O., Kefford, R., Weber, J.S., Joshua, A.M., Hwu, W.-J., Gangadhar, T.C., Patnaik, A., Dronca, R., Zarour, H., Joseph, R.W., Boasberg, P., Chmielowski, B., Mateus, C., Postow, M.A., Gergich, K., Elassaiss-Schaap, J., Li, X.N., Iannone, R., Ebbinghaus, S.W., Kang, S.P., Daud, A., 2014. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. The Lancet 384, 1109–1117. https://doi.org/10.1016/S0140-6736(14)60958-2.

Sørensen, H.T., Mellemkjær, L., Olsen, J.H., Baron, J.A., 2000. Prognosis of cancers associated with venous thromboembolism. N. Engl. J. Med. 343 (25), 1846–1850.

Streiff, M.B., Holmstrom, B., Angelini, D., Ashrani, A., Bockenstedt, P.L., Chesney, C., Fanikos, J., Fenninger, R.B., Fogerty, A.E., Gao, S., Goldhaber, S.Z., Gundabolu, K., Hendrie, P., Lee, A.I., Lee, J.T., Mann, J., McMahon, B., Millenson, M.M., Morton, C., Ortel, T.L., Ozair, S., Paschal, R., Shattil, S., Siddiqi, T., Smock, K.J., Soff, G., Wang, T.-F., Williams, E., Zakarija, A., Hammond, L., Dwyer, M.A., Engh, A.M., 2018. NCCN guidelines insights: cancer-associated venous thromboembolic disease, version 2.2018. J. Natl. Compr. Canc. Netw. 16, 1289–1303. https://doi.org/10.6004/jnccn.2018.0084.

Sussman, T.A., Li, H., Hobbs, B., Funchain, P., McCrae, K.R., Khorana, A.A., 2021. Incidence of thromboembolism in patients with melanoma on immune checkpoint inhibitor therapy and its adverse association with survival. J. Immunother. Cancer 9 (1), e001719.

Terpos, E., Kleber, M., Engelhardt, M., Zweegman, S., Gay, F., Kastritis, E., van de Donk, N.W.C.J., Bruno, B., Sezer, O., Broijl, A., Bringhen, S., Beksac, M., Larocca, A., Hajek, R., Musto, P., Johnsen, H.E., Morabito, F., Ludwig, H., Cavo, M., Einsele, H., Sonneveld, P., Dimopoulos, M.A., Palumbo, A., 2015. European myeloma network guidelines for the management of multiple myeloma-related complications. Haematologica 100 (10), 1254–1266.

Timp, J.F., Braekkan, S.K., Versteeg, H.H., Cannegieter, S.C., 2013a. Epidemiology of cancer-associated venous thrombosis. Blood 122, 1712–1723. https://doi.org/10.1182/blood-2013-04-460121.

Tomita, Y., Sueta, D., Kakiuchi, Y., Saeki, S., Saruwatari, K., Sakata, S., Jodai, T., Migiyama, Y., Akaike, K., Hirosako, S., Fujisue, K., Yamamura, S., Miyazaki, S., Takashio, S., Izumiya, Y., Nakamura, K., Tsujita, K., Ichiyasu, H., Fujii, K., 2017. Acute coronary syndrome as a possible immune-related adverse event in a lung cancer patient achieving a complete response to anti-PD-1 immune checkpoint antibody. Ann. Oncol. 28 (11), 2893–2895.

Tsukamoto, J., Monteiro, M., Vale, S., Lemos, C., Scarpelli, T., Carvalho, L., Pezzutti, D., Brandão, R., 2018. Thromboembolic Events Related to Treatment with Checkpoint Inhibitors: Report of Two Cases. CRO 11, 648–653. https://doi.org/10.1159/000492463.

UMC | VigiBase [WWW Document], n.d. URL https://www.who-umc.org/vigibase/vigibase/ (accessed 8.30.20).

UMC | vigiMethods [WWW Document], n.d. URL https://www.who-umc.org/vigibase/vigilyze/vigimethods/ (accessed 5.31.21).

UMC | WHO programme members [WWW Document], n.d. URL https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/who-programme-members/ (accessed 5.19.21).

Watson, H.G., Keeling, D.M., Laffan, M., Tait, R.C., Makris, M., Haematology, B.C., for S. in,, 2015. Guideline on aspects of cancer-related venous thrombosis. Br. J. Haematol. 170, 640–648.

Weber, J.S., Kähler, K.C., Hauschild, A., 2012. Management of immune-related adverse events and kinetics of response with ipilimumab. J. Clin. Oncol. 30 (21), 2691–2697.