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Cancer associated venous thromboembolism and P-selectin: A review

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ABSTRACT

Background: Venous Thrombo Embolism (VTE) is the third most common cause of vascular mortality worldwide and comprises Deep-Vein Thrombosis (DVT) and Pulmonary Embolism (PE). It is also the second most common cause of death among cancer patients. VTE contributes immensely to the morbidity and mortality of cancer patients, with a life threaten PE being 3 times more common in cancer patients compared to non-cancer patients. Cancer patients are said to have a 5 to 7 fold increased risk of developing VTE. P-selectin can serve as a promising marker which could help to increase the precision of predicting the risk of VTE among cancer patients when combine with established validated tools.

Aim: This study seeks to unravel the increasing trend of cancer associated VTE and the intricate and multifaceted role of P-selectin in cancer associated VTE.

Method: A vigorous literature search was performed via the internet search engines linked to academic databases including PubMed, Google Scholar, Ebsco, Hinari, Scopus, etc.

Conclusion: This review underscores the dynamic of cancer associated VTE and context-dependent role of P-selectin in cancer associated VTE respectively. As we poke into the relationship between cancer, VTE and P-selectin, as this will create an insight for therapeutic intervention.

Keywords: cancer, venous thrombo embolism, P-selectin

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INTRODUCTION

Venous Thrombo Embolism (VTE) is the third most common cause of vascular mortality worldwide and comprises Deep-Vein Thrombosis (DVT) and Pulmonary Embolism (PE) [1]. The development of VTE often starts in the valve sinus where several features surrounding these valves make the site predisposed to thrombosis. These include abnormal and reduced blood fl w, reduced shear stress, and hypoxia leading to an intact but dysfunctional endothelium [2]. Besides, leukocytes and platelets have a propensity to become trapped in valve pockets [3]. The risk factors for VTE can be subdivided into factors that promote venous stasis, factors that promote blood hypercoagulability, and factors causing endothelial injury or inflammation and that these three broad categories, frequently taught as "Virchow's triad", have formed the basis for the mechanism and categorizing the risk factors of VTE for over a century [1]. In cancer patients, tumours can compress veins, resulting in venous stasis, leading to thrombosis. VTE contributes immensely to the morbidity and mortality of cancer patients, with a fatal PE being 3 times more common in cancer patients compared to non-cancer patients [4, 5]. Cancer patients are said to have a 5-fold to 7-fold increased risk of developing VTE and those who develop VTE at diagnosis of cancer or within the year tend to have a remarkably poor prognosis when compared with cancer patients without VTE [6-9]. Venous Thrombo-Embolism is a fatal complication in a patient with active cancer. Theestimated incidence throughout 12 months is approximately 6%-8% but varies with tumour type [9]. Venous Thrombo-Embolism is associated with increase morbidity and mortality, and poor performance state this can interfere with the management of cancer patients [10]. Trousseau was the first to show the relationship between VTE and malignancy where he described thrombophlebitis as the presenting sign of visceral malignancy. Since then, there has been increased awareness of VTE as a potentially fatal event and one of the lethal pre-operative complications. However, despite increased monitoring and prevention of thrombosis tumour patients, there has been a surge in the incidences of VTE [11]. A study conducted by Choi et al. in korea to determine the epidemiology of Thrombo Embolism (TE) in Korean children with cancer reviewed incidence rate was quite low among Korean children with cancer, but higher in the general paediatric population and among children hospitalized for diseases other than cancer [12]. In another study, conducted in the US, to determine the national annual incidence and examine the trend of cancer-associated

VTE in the US over the years reported 1.18% which was non-signifi ant downward trend in the incidence of cancer-associated VTE over the years [13]. Patients who had cancer-associated VTE were signifi antly older than patients without VTE. Similarly, another study by Mulder et al., also show that due to novel cancer therapies, improved survival ad high resolution imaging the incidence of Venous Thrombo Embolism (VTE) in cancer patients might have changed in the past decade, with a 2.3% cumulative incidence of VTE in 12 months, which increases from 1.0% (95% CI, 0.9% to 1.2%) in 1997 to 3.4% (95% CI, 2.9% to 4.0%) in 2017, and this was attributed increase use of targeted therapies, chemotherapy and computed tomography scans [14]. Moreso this study also discovered a nine fold steady increase risk of VTE in cancer compare to general population. Furthermore, in the same direction, another study also found that cancer-associated thrombosis is a far reach consequent for patients with cancer and is associated with inferior survival. Similarly, another study by Wang et al., on the clinical characteristics and prognosis of cancer patients with venous thromboembolism review that of the 18,531 patients diagnosed with a malignant tumour, 280 (1.51%) patients presented with VTE at first diagnosis or during the disease course of these 26 had incidental Pulmonary Embolism (PE) and dyspnea was the predominant symptom in the PE group (51.65%), while lower limb swelling in the DVT group (65.27%). In a similar study, Caiano et al. using systematic review and meta-analysis to evaluate the outcomes among patients with cancer [15-17]. It was observered that in cancer patients, incidental VTE was associated with a lower rate of VTE recurrence when compared to symptomatic VTE, with an increased risk of major bleeding events. Douce et al, evaluated the risk factors for CAT, among patients starting chemotherapy an institution and the impact of incorporating longitudinal hospitalization into risk assessment [18]. Th y found out that when time-to-event data were included into CAT risk assessment, male sex, prior VTE, and hospitalization were important risk factors [18]. Another study on venous thromboembolism in patients with cancer undergoing surgical exploration was carried out by Ruff et al. He reported that malignancy and surgery are both independent risk factors for Venous Thrombo Embolism (VTE) events, and that the current NCCN guidelines recommend VTE prophylaxis for up to 28 days after major abdominal or pelvic surgery for malignancy [19].

LITERATURE REVIEW

Studies on epidemiology of cancer-related VTE

Th re is ethnic variation in the of incidence of VTE, a study from America shows that African-Americans have 5-fold increase risk than Asian-ancestry populations, while European and Hispanic populations do have intermediate risk [20]. A study by Zakai showed that the incidence of VTE is 30%-60% higher in blacks than in whites [21]. A study in Uganda by Muleledhu et al. showed that DVT occurs in 5% of post-surgical patients and cancer was found to be the commonest risk factor in aff cted persons [22]. Similarly, a case-control study conducted by Fall et al. showed that cancer was a risk factor for DVT in 3.81% of 105 patients evaluated during the study [23]. However, studies conducted in South Africa and Cameroon by Alsheri and Kingue et al. respectively, reported a prevalence of 4.1% and 22.2% [24, 25]. Fernandes et al reported that the relevance Cancer-Associated Thrombosis (CAT) is being given concern both for physicians in the Venous Thrombo Embolism (VTE) space and for oncologists [26].This review that the annual incidence of VTE in patients with cancer is 0.5% compared to 0.1% in the general population and that active cancer accounts for 20% of the overall incidence of VTE. Th y also found out that VTE is the second most prevalent cause of death in cancer. Furthermore, a study conducted in Ibadan, southwest of Nigeria by Kotila et al. reported that CAT patients constitute 12.2% of all cancers treated at the Haematology department [27]. Theseshow that there is paucity and inconsistency in the available information on cancer-associated VTE in our environment. Yao and Xu. studied the progress of cancer-associated venous thromboembolism [28]. Lee et al. in their study on the systematic review on the epidemiology of cancer-associated thrombosis in Asia [29]. Show that the incidence of CAT in Asia is signifi antly higher than non-cancer-associated VTE in the general population and cancer is perhaps the most important risk factor for VTE [29]. Another study by Imura et al. on the incidence of VTE among cancer patients after remission [30]. Th y reported that the risk of developing VTE decreased to the same level as that in patients without cancer 2 years after cancer remission. Ording et al. determine the increasing incidence and declining mortality after cancer-associated venous thromboembolism focusing on a nationwide cohort study in Denmark, this reported a cumulative incidence of 1.8% to 2.8% and mortality of 52.4% to 45.8% [31]. Similarly, another Danish study by. Gade et al. on the epidemiology of venous thromboembolism after a second cancer, review that the incidence rate of VTE was highest within the first 6 months after the second cancer was diagnosed, with no changes based on the duration when the cancer was first diagnosed. A similar longitudinal study was conducted by Martens et al. on epidemiology of cancer-associated venous thromboembolism in patients with solid and hematologic neoplasms in the veteran's affairs health care system [32, 33]. It was reported that a consistent high incidence of VTE was observed.

Studies on pathophysiology of VTE in cancer

Themechanisms predisposing cancer patients to thromboembolic conditions are yet to be fully understood. However, mechanisms that can activate hypercoagulable states in cancer patients have been previously studied. Prominent among these mechanisms are the direct mechanisms involved in cancer-associated thrombosis and the indirect mechanisms which promote thrombosis in cancer. Pavlovic et al. reported that the clinical manifestation of cancer-related thrombotic events mainly aff cts the venous side, and manifests in various forms, including unusual sites of venous thrombosis [34]. Behravesh et al. also found out that beyond postsurgical and trauma-related cases, stasis plays a major role in the development of venous thrombosis, and this begins at the valve [35]. Furthermore Leiva et al. evaluated the common pathophysiology in cancer, atrial fi rillation, atherosclerosis and thrombosis [36]. He found out the coincidence of cardiovascular disease, such as atrial fi rillation and atherosclerosis, patients with cancer live longer, also cancer and cardiovascular disease shared several risk factors and underlying pathophysiologic mechanisms, including inflammation, cancer-related factors including treatment eff cts, and alterations in platelet function. Similar finding was reported by Noble and Pasi in epidemiology and pathophysiology of cancer-associated thrombosis [37]. Furthermore, another study by Walker et al. in 2022 surveyed factor VIII as a potential player in cancer pathophysiology. The study has showed evidence

of the potential independent role for FVIII in cancer-associated thrombosis pathophysiology [38]. In another study, by Falanga and Marchetti evaluating the awareness and pathophysiology of cancer-associated thrombosis [39]. Th y reported that both venous and arterial, are leading cause of morbidity and mortality in patients with cancer two centuries ago. Clinico-pathological correlation between deep vein thrombosis and malignancy cancer was studied by Chhabhaya et al [40]. The researchers explained that Cancer Associated Thrombosis (CAT) is the target of intense interest in recent medical literature, including its epidemiology, pathophysiology, and challenges in diagnosis, prophylaxis, and treatment. Cancer types, stages, treatment, and comorbidities are among the risk factors for developing VTE. The study showed that there was no correlation between diff rent types of cancer with deep venous thrombosis, neither with a diff rent approach of treatment had it shown any signifi ant results nor with any comorbidity [41]. However, they found a correlation between diff rent cancers with various comorbidity.

Studies on the direct mechanisms of cancer-associated thrombosis

The direct mechanisms of cancer-associated thrombosis include the following;

- Tissue Factor (TF):

This is not normally expressed in quiescent endothelium. However, malignant tissue involving endothelial and tumour cells express TF constitutively. Tissue Factor triggers haemostasis immediately after vascular injury and it is profusely expressed on sub-endothelial cells such as pericytes, fi roblasts, and vascular smooth muscles [27].

- Micro Particles (MP):

These are very small membrane vesicles measuring between 0.1 μm-1μm such as P-selectin, that are released from apoptotic or activated normal cells, or resting malignant cells. MP procoagulant activity has been attributed to the surface expression of active TF [41, 42].

- Plasminogen Activator Inhibitor-1 (PAI-1):

A key inhibitor of fi rinolysis which is highly expressed in pancreatic cancer cells [43]. Increased PAI-1 in plasma reduces fi rinolytic activity, increasing the risk of thrombosis [44].

Other mechanisms that activate coagulation and are associated with cancer-associated thrombosis include cancer procoagulants and tumour-derived platelet agonists. Risk factors that lead to CAT and TAC include cancer type, chemotherapy, radiotherapy, hormonal therapy, anti-angiogenesis therapy, surgery, or supportive therapy with hematopoietic growth factors.

Studies on the indirect mechanisms of cancer-associated thrombosis

The cells that are actively involved in promoting thrombosis in cancer include; platelets, endothelial cells, and leukocytes. The indirect mechanisms of cancer-associated thrombosis include microparticles, inflammatory cytokines, adhesion molecules, neutrophil extracellular traps, mucins, hypoxia, Damage-Associated Molecular Patterns (DAMPs) Cancer-associated chemotherapy, coagulation gene defect, and decreased coagulation inhibitors.

- Microparticles:

Th y are released from activated endothelial cells and monocytes in response to cancer.

- Inflammatory cytokines:

Th y could be synthesized and secreted by tumour cells which are thrombogenic and capable of promoting procoagulant phenotype in host endothelial cells.

Tumours can also cause reactive responses [45]. The presence of cancer is a well-recognized independent risk factor for VTE [39]. About one-fi h of all new VTE events are due to active cancer. It is estimated that approximately 4%-20% of cancer patients will experience VTE at some stage with the risk more in the initial period following diagnosis. Several studies have also shown that the risk of VTE is signifi antly higher in cancer patients [45, 46]. A similar study by Blom et al. showed that this risk for VTE was seven-fold higher in a patient with cancer than in those without malignancy [47]. Another study by Prandoni et al. has reported that the risk for recurrent VTE is four times higher [48]. Furthermore, Stein et al. also reported an increased incidence of VTE among hospitalized cancer patients compared to non-cancer hospitalized patients [46]. Also, cancer patients with previous VTE are at high risk of recurrent VTE compared to those without malignancy [46, 47]. Moreso, it has been reported that the VTE is four times higher in cancer patients concurrently receiving chemotherapy [39]. However, the rate of VTE varies from one sub-group of cancer patients and depends on the presence of various factors such as patient, tumour, and trauma-related factors [39]. The age, BMI, co-morbidities, and immobilization are said to increase the risk of VTE in the general population as well as in cancer patients [49]. The primary site and degree of the metastatic disease contribute signifi antly to the risk of thrombosis among cancer patients with the highest incidence reported among patients with brain, pancreatic, and gastric. Furthermore, lymphoma and multiple myeloma patients are also at high risk. Other contributing factors to VTE in cancer include chemotherapy, antiangiogenic agents, hormonal therapy, surgery, and erythropoiesis-stimulating agents [50].

Studies on P-selectin in cancer patients

P-selectin is an adhesion receptor that normally recognizes vascular mean glycoproteins bearing the carbohydrate structure [51]. Several studies independently correlated clinical prognosis and tumour metastasis with P-selectin [52]. Since metastasis is thought to involve the interaction between tumour platelet leucocyte and the endothelium [53]. In another study, P-selectin defici ncy in mice was associated with a signifi antly slow cancer progression rate [26]. Another study showed a correlation between an increased level of P-selectin and a hypercoagulability state among patients with Haematological malignancies [54]. Another study has also shown that the use of D-dimer and P-selectin has demonstrated to be a potentially useful tool to predict thromboembolic events either independently or in a prediction score [26]. A well-defined association has been established between elevated P-selectin levels which can serve as a predictive tool for thromboembolism in cancer patients undergoing chemotherapy. Selectins characterize a family of three structurally and functionally related adhesion molecules: E-selectin, P-selectin, and L-selectin. The lectin-like domains are primarily in control of Ca^{2+} dependent interactions with

fucosylated, mucin-like ligands. Functionally, the rapid association and dissociation rate constants that characterize selectin-mediated adhesion allow selectins to function as vital initiators of leukocyte adhesion to endothelium under conditions of shear fl w. A role for selectins as signal-transducing receptors is also now becoming evident [55]. P-selectin is stored in the alpha granules of platelets and in the Weibel-Palade bodies of Endothelial Cells (EC) [56]. Exposure to an activating stimulus such as thrombin results in rapid translocation of P-selectin to the cell surface, avoiding the need for transcription or translation [56]. E-selectin is upregulated after the initiation of thrombosis in a transcription-dependent fashion. P-selectin can be secreted into the circulation as a component of EC and platelet-derived Micro Particles (MP) or, in small quantities, as a free, alternatively spliced version lacking a transmembrane domain [57]. These two forms of soluble P-selectin are elevated in humans in association with atherosclerosis and thrombosis and are predictive of future adverse cardiovascular events, including myocardial infarction and stroke [56, 57]. Soluble P-selectin levels are also elevated at times of overwhelming systemic thrombosis and consumption, such as disseminated intravascular coagulation and heparin-induced thrombo cytopenia. P-selectin defici nt mice demonstrate a haemophilic phenotype with marked bleeding tendencies [57]. In animal models of DVT, we, and others, have demonstrated that P-selectin expression regulates fi rin deposition and thrombus size [58]. We have also shown that associations exist between P-selectin and E-selectin deletions and reduced thrombosis, with the thrombi exhibiting diminished fi rin content. In a primate model of stasis-induced DVT, P-selectin blocking antibodies or antibodies blocking the P-selectin receptor, PSGL-1, inhibit thrombosis and promote recanalization [59]. A reduction in the fi rin content of thrombi formed in the presence of P-selectin inhibition is likely contributory, as leukocyte-platelet interactions leading to fi rin deposition are P-selectin dependent [57].

Studies on P-selectin and cancer-associated VTE in cancer

Cells in our body do interact with their environment via diverse Cell Adhesion Molecules (CAMs). P-Selectin (SELP) is an adhesion molecule that belongs to the Selectin family of proteins, which are expressed by diff rent cell types such as platelets, endothelial and immune cells, as well as several types of cancer cells. The increase expression of P-selectin by activated platelets makes it a pivotal component in the pathogenesis of thrombosis, in general, and in Cancer-Associated Th rombosis (CAT), in particular. Hence, the mechanisms by which P-selectin mediates CAT are associated with tumour-promoting processes such as inflammation and metastasis. Moreover, P-selectin was shown to have a role in tumour-host interactions and cancer immunity. However, P-selectin has been the focus of several studies exploring its role in cancer progression. Fernandes et al. reported that D-dimer and P-selectin could serve as a biomarker for the risk of VTE in cancer patients [26]. Furthermore, in a cancer and thrombosis study conducted by Kanz et al. at the Medical University of Vienna, the authors reported that P-selectin remains a signifi ant predictor of VTE in cancer patients [60]. Similarly, in a CAT study by Ay et al. P-selectin levels were signifi antly elevated among cancer patients who developed VTE and it was a predictor of VTE [61]. Celle et al. in another study reported an elevated level of P-selectin in myeloproliferative neoplasm [62]. Similarly, Leinoe et al. showed that low P-selectin expression in acute myeloid leukaemia and is attributed to the reduced platelet synthesis as well as the alpha granules dysfunction [63]. Khorana also reported that P-selectin, tissue factor, D-dimer, C-reactive protein, platelet and leucocytes counts are potential promising biomarkers, predictive of VTE in cancer [64]. Hrncar et al. also showed that P-selectin and factor VIII are the best predictive tools for assessing the risk of VTE in hepatocellular carcinoma [65].

CONCLUSION

This review underscores the dynamic of cancer associated VTE and context the dependent role of P-selectin in cancer associated VTE respectively. As we poke into the relationship between cancer, VTE and P-selectin, as this will create an insight for therapeutic intervention.

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