1. Introduction

Prostate cancer is the second most common cancer among men in the world and has become a significant health problem in developed and developing countries. The studies have shown that there was an association between cancer and hemostasis. Malignancy and increased age are the main risk factors for coagulation activation and thrombosis. The increased risk of thrombosis in cancer patients may be associated with high levels of coagulation markers such as fibrinogen and D-dimer. The aim of this study is to examine the levels of D-dimer and fibrinogen in patients with prostate cancer and compare them to those in patients with benign prostate hyperplasia. Further studies that include large number of patients are needed to determine the relationship between prostate cancer and coagulation disorder.

Conclusion: The present study demonstrated that plasma D-dimer level was higher in patients with prostate cancer. Further studies that include large number of patients are needed to determine the relationship between prostate cancer and coagulation disorder.

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2. Materials and methods

A prospective study that includes patients who underwent transrectal ultrasound guided prostate biopsy and prostate surgery was performed between January 2015 and January 2016. Plasma prostate specific antigen (PSA), free PSA (fPSA), percentage PSA, D-dimer, and fibrinogen levels were measured before the procedures (prostate biopsy and transurethral resection). Prostate biopsy was performed under local anesthesia with at twelve cores. Percentage IPSA was calculated as IPSA/PSA × 100. Venous blood samples were collected into citrate tubes by sterile atraumatic venipunctures. Plasma D-dimer and fibrinogen levels were measured by Enzyme-linked immunosorbent assay (ELISA) (Diagnostic Stago, France) and Clauss method (Sysmex, Japan). Plasma fibrinogen levels were considered to be normal between 175mg/dL and 350mg/dL and D-dimer levels were considered to be normal between 0ug/mL and 0.5ug/mL.

Patients with a history of coagulopathy, venous or pulmonary embolism, using anticoagulant therapy, a history of acute or chronic prostatitis, radiotherapy, prostate surgery or biopsy previously and a pathological report of high grade prostate intraepithelial neoplasia and atypical small acinar proliferation, were excluded from the study. The PSA, fPSA, percentage fPSA, D-dimer, and fibrinogen levels, and patient age and pathology reports were recorded. The patients were divided into two groups: Group 1 had benign prostate hyperplasia and Group 2 consisted of patients with prostate cancer. The statistical analyses were performed using MedCalc Statistical Software demo version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The data of groups were compared with the independent sample t test and P < 0.05 was considered as statistically significant.

3. Results

There were 76 patients in the present study. Of these, 53 patients were in Group 1 and 23 patients were in Group 2. The mean age of the patients was 65.33 ± 7.47 years and 66.08 ± 6.7 years in Group 1 and Group 2, respectively. The 12 prostate biopsy cores were performed in all patients. The patients' characteristics are shown in Table 1. There was a statistically significant difference for IPSA between the groups. In Group 2, D-dimer levels were higher (1.09ug/mL and 0.50ug/mL, P = 0.03) than in the patients in Group 1. There were no significant differences in PSA, percentage of IPSA, fibrinogen, and age between the groups. The patients were diagnosed using transrectal ultrasound guided prostate biopsy and transurethral prostate surgery. Transrectal prostate biopsy and transurethral surgery were performed in 64 and 12 patients, respectively.

With the cancer group, 13 patients and six patients were reported as Gleason 6 and Gleason 7, respectively. Gleason 8 and Gleason 9 were detected in two patients. Of these patients, four were treated with hormonal therapy and eight were treated with radical prostatectomy. Radiotherapy was performed in six patients and the remaining five patients refused the treatment options.

4. Discussion

Prostate cancer is one of the most common cancer among men.1 The use of screening methods including digital rectal examination and PSA testing are important to detect prostate cancer. These screening methods may lead to prostate biopsy, which is necessary to confirm the diagnosis of prostate cancer. Transrectal ultrasound guided prostate biopsy can be performed, which is the gold standard method for histopathological diagnosis of prostate cancer.2 Although transrectal ultrasound guided sextant prostate biopsy was described by Hodge et al, six-core biopsy is an inaccurate means of cancer detection and has a 10–30% false negative rate.3 European Association of Urology 2015 guidelines suggest 10–12 systematic cores for initial diagnosis.4 The authors reported the prostate cancer detection rate was 13.3–35% in patients who underwent six and 12 prostate biopsies, respectively.5 The 12 prostate biopsy protocol was performed in all patients in the current study.

The pathogenesis of cancer-associated thrombosis depends on patient characteristics, tumor histology, stage, and treatment-related factors.5 Abnormalities of the coagulation system have been investigated in cancer patients and it is reported that plasma levels of factors were altered.3,14 In cancer patients, systematic activation of coagulation occurs and this activation leads to augmented thrombin generation followed by fibrin formation.5 It has been suggested that fibrin may contribute to tumor growth and facilitate the tumor invasion and metastasis by promoting angiogenesis and formation of a protective fibrin shield on tumor cells that makes the tumor cells resistant to endogenous defense mechanisms. The interaction of fibrin, platelets, and tumor cells leads to the formation of aggregates that promote endothelial adhesion and metastatic potential.6 Fibrin degradation products have a strong angiogenic efficacy.

Fibrinogen is one of the important coagulation system factors and systemic inflammatory markers which enhances the progression and invasive potential of tumor cells through several mechanisms.5 Firstly, fibrinogen is deposited around solid tumors and provides a table framework to the extracellular matrix of the tumor. It also serves as a scaffold to support some growth factors to tumor cells such as vascular endothelial growth factor, and fibroblast growth factor, and promotes tumor proliferation and angiogenesis. Tumor cells have fibrinogen receptors; intercellular adhesion molecule-1 and α5β1 integrin. These receptors play a role as a bridging factor between fibrinogen and tumor cells, thus enhancing the endothelial adhesion of tumor cell emboli in the vasculature of target organs, leading to the occurrence of metastasis. Additionally, fibrinogen promotes β3-integrin-mediated adhesion of tumor cells to platelets, and the platelet-tumor cell aggregates thus formed could shield tumor cells from the immune system and lead to increase of metastatic tumor cells.6 The fibrinogen levels are increased because of tumor-associated cytokines or endogenous synthesis by tumor cells themselves in cancer patients.7 The endogenous fibrinogen has a key role in promoting the growth of lung and prostate cancer cells through interaction with fibroblast growth factor.15 D-dimer is one of the fibrin degradation products and the level of D-dimer is a result of fibrinolysis activation.8 Elevated plasma D-dimer levels are seen in patients with various cancer types, because procoagulant factors lead to constitutive activation of the
coagulation cascade with resultant thrombin generation followed by fibrin formation. Fibrin may also conversely form a protective shield on malignant tumor cells, to protect them from endogenous defense mechanisms and promoting angiogenesis, invasion, and metastasis of the tumor. Tumor cells themselves may convert fibrinogen to fibrin and the fibrin is used for support, to appear new vessels, invasion and remodeling tumor stroma.

Elevated D-dimer levels have been reported in patients with breast, prostate, gynecologic, and lung cancers without clinical thrombosis. D-dimer levels were highest in patients with pancreatic cancer and lowest in patients with prostate cancer. The authors from the Vienna Cancer and Thrombosis Study reported that elevated D-dimer level was a prognostic parameter associated with increased mortality risk in patients with lymphomas, brain tumors, pancreatic, prostate, breast, lung, stomach, and colorectal cancers. The authors from Korea found that D-dimer levels were significantly higher in patients with prostate cancer than the patients without prostate cancer at prostate biopsy. In another study, the investigators showed a significant increase of D-dimer level in patients with advanced prostate cancer compared with age-matched controls and patients with localized prostate cancer. By contrast, Caine et al. investigated the D-dimer levels after radical prostatectomy and found no significant difference 3 months and 12 months after surgery. The present study demonstrated that the D-dimer level was higher in patients with prostate cancer than the other patients without cancer, with a significant difference (P < 0.05).

The authors found strong evidence that an elevated plasma fibrinogen level was an independent predictor of worse overall survival in patients with solid tumors. The patients with increased level of fibrinogen have a significantly poorer disease-free survival and cancer-specific survival. Thurner et al. found that there was a significant association between an elevated plasma fibrinogen level and poor cancer specific survival and overall survival in patients with prostate cancer. Caine et al. found the significant fall in fibrinogen level after radical prostatectomy 3 months and 12 months after the surgery. By contrast, Hong et al. found that there was no difference between fibrinogen levels in patients with prostate cancer compared with others. That study showed higher fibrinogen levels in patients with advanced prostate cancer than patients with organ confined disease, without a significant difference. In the current study, there was no significant difference in plasma fibrinogen levels between the groups (P = 0.886).

This study includes a small number of patients and coagulation parameters (fibrinogen, D-dimer) were not checked again after first measuring the levels. Other hemostatic system factors were not analyzed. The stage of the patients with prostate cancer was not homogenous and the conditions that affect coagulation parameters, such as trauma and inflammatory process, could not be eliminated.

In conclusion, patients with prostate cancer had higher plasma D-dimer levels than the other patients. If studies support our findings in the future, plasma D-dimer level may be a diagnostic marker for prostate cancer. Further studies are needed to define the relationship between the coagulation system and prostate cancer.

**Conflict of interest**

There is no conflict of interest.

**References**

1. Monn MF, Tatem AJ, Cheng L. Prevalence and management of prostate cancer among East Asian men: current trends and future perspectives. Urol Oncol 2016;34:58.e1–9.
2. Alghamdi KG, Hussain B, Alghamdi MS, El-Sheeney MA. The incidence rate of prostate cancer in Saudi Arabia: an observational descriptive epidemiological analysis of data from the Saudi Cancer Registry 2001–2008. Hematol Oncol Stem Cell Ther 2014;7:18–26.
3. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. J Clin Oncol 2009;27:4821–6.
4. Kohli M, Fink M, Spencer HJ, Zent CS. Advanced prostate cancer activates coagulation: a controlled study of activation markers of coagulation in ambulatory patients with localized and advanced prostate cancer. Blood Coagul Fibrinolysis 2002;13:1–5.
5. Caine GJ, Ryan P, Lip GYP, Blann AD. Significant increase of D-dimer after radical prostatectomy in prostate cancer patients. Cancer Lett 2007;251:296–301.
6. Wen J, Yang Y, Ye F, Huang X, Li S, Wang Q, et al. The preoperative plasma fibrinogen level is an independent prognostic factor for overall survival of breast cancer patients who underwent surgical treatment. Breast 2015;24:745–50.
7. Ay C, Dunkler D, Pirker R, Thaler J, Quehenberger P, Wagner O, et al. High D-dimer levels are associated with poor prognosis in cancer patients. Blood Coagul Fibrinolysis 2012;97:1158–64.
8. Ghafouri M, Velayati M, Ghasabeh MA, Shabkia M, Alavi M. Prostate biopsy using transrectal ultrasonography; the optimal number of cores regarding cancer detection rate and complications. Iran J Radiol 2015;12:13257.
9. Vasudeva P, Kumar N, Kumar A, Singh H, Kumar G. Safety of 12 core transrectal ultrasound in patients on aspirin. BJU Int 2015;41:1096–100.
10. Mochtar CA, Atmoko W, Umbai R, Harid ARAH. Prostate cancer detection rate in Indonesian Men. Asian J Surg 2017 [Article in press].
11. Mottet N, Bellmunt J, Briere E, van den Bergh RCN, Bolla M, van Casteren NJ, et al. EAU Guidelines on Prostate Cancer. 2015.
12. Hanna DL, White RH, Wun T. Biomolecular markers of cancer-associated thromboembolism. Crit Rev Oncol Hematol 2013;88:19–20.
13. Bick RL. Coagulation abnormalities in malignancy: a review. Semin Thromb Hemost 1992;18:353–72.
14. Constantini V, Zacharski LR. Fibrin and cancer. Thromb Haemost 1993;69:406–14.
15. Ay C, Vornittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 2009;27:4124–9.
16. Thurner EM, Pilko SK, Langsenlehner U, Stajokovic T, Pichler M, Gerger A, et al. The association of an elevated plasma fibrinogen level with cancer-specific and overall survival in prostate cancer patients. World J Urol 2015;33:1467–73.
17. Sahni A, Simpson-Haidaris PJ, Sahni SK, Vaday GG, Francis CW. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemost 2008;6:176–83.
18. Khoury JD, Adcock DM, Chan F, Symanski JT, Tiefenbacher S, Goodman O, et al. Increases in quantitative D-dimer levels correlate with progressive disease better than circulating tumor cell counts in patients with refractory prostate cancer. Am J Clin Pathol 2010;134:964–9.
19. Hong SK, Ko DW, Park J, Kim IS, Doo SH, Yoon CY, et al. Alteration of angiopoietin-1 and angiopoietin-2 after radical prostatectomy in prostate cancer patients. Cancer Lett 2007;251:296–301.
20. Thurner EM, Dalaker A, St discuss the impact of serum D-dimer levels on the risk of venous thromboembolism in patients with cancer.