CARDIOVASCULAR RISK FACTORS AMONG NEWLY DIAGNOSED PROSTATE CANCER PATIENTS

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ABSTRACT

Introduction: *Patients with prostate cancer (PCa) are less likely to die of prostate cancer than of non-prostate causes such as cardiovascular disease (CVD). Recently, Jakarta Cardiovascular Risk score prediction models were developed and validated with good reliability in predicting 10-year cardiovascular events in the Indonesian population.* ***Objective:*** *This study aims to describe cardiovascular risk factors among newly diagnosed prostate cancer patients.****Material& Methods:*** *This is a cross-sectional, retrospective study of patients with newly diagnosed prostate cancer at Hasan Sadikin Academic Medical Center from 2013 to 2023. The Jakarta CV Risk score was calculated on all populations and among groups according to tumor extension: local (T1-T2), locally advanced (T3-T4), and metastatic. A score of -7 to 1 was considered a low risk for CV event, 2 – 4 was intermediate risk, and >4 was considered high-risk.* ***Results:****There were a total of 118 subjects included in this study. The mean age was 67.5 ± 9.7 years, the mean BMI was 22.3 ± 2.79 kg/m2. The average Jakarta cardiovascular score in this population was 7.25 ± 2.24. In the local PCa group (T1-T2) was 6.97 ±1.99 (high risk); in the locally advanced PCa group (T3-T4) was 7.30 ± 1.70 (high risk); and in the metastatic group was 7.14 ± 2.08 (high risk). Unfortunately, there are 22 (19.5%) patients who will be planned to receive Androgen-deprivation therapy based on staging.* ***Conclusion:*** *Patients with newly diagnosed PCa commonly have high cardiovascular risk and it should be our consideration for giving ADT treatment.*

Keywords: *Prostate cancer, cardiovascular disease, Jakarta cardiovascular risk score, androgen-deprivation therapy.*

ABSTRAK

Pendahuluan: *Pasien dengan kanker prostat memiliki kemungkinan yang lebih kecil untuk meninggal akibat kanker prostat itu sendiri dibandingkan dengan akibat lain seperti penyakit kardiovaskular. Baru-baru ini, model prediksi Jakarta Cardiovascular Risk Score telah dikembangkan dan divalidasi dengan reliabilitas yang baik dalam memprediksi kejadian kardiovaskular dalam 10 tahun pada populasi Indonesia.* ***Tujuan:*** *Penelitian ini bertujuan untuk mendeskripsikan faktor risiko kardiovaskular pada pasien yang baru terdiagnosis kanker prostat.* ***Bahan & Cara:*** *Penelitian ini merupakan studi retrospektif dengan desain potong lintang pada pasien yang baru terdiagnosis kanker prostat di RSUP Dr. Hasan Sadikin dari tahun 2013 hingga 2023. Jakarta Cardiovascular Risk Score dihitung pada seluruh populasi dan pada kelompok berdasarkan perluasan tumor: local (T1-T2), locally advanced (T3-T4), dan metastatik. Skor -7 hingga 1 dikategorikan sebagai risiko rendah untuk kejadian kardiovaskular, skor 2–4 sebagai risiko menengah, dan skor >4 dianggap sebagai risiko tinggi.* ***Hasil:*** *Terdapat total 118 subjek yang diikutsertakan dalam penelitian ini. Rerata usia adalah 67.5 ± 9.7 tahun, dan rerata IMT adalah 22.3 ± 2.79 kg/m². Rerata Jakarta Cardiovascular Risk Score pada populasi ini adalah 7.25 ± 2.24. Pada kelompok local (T1-T2), skornya adalah 6.97 ± 1.99 (risiko tinggi); pada kelompok locally advanced (T3-T4) adalah 7.30 ± 1.70 (risiko tinggi); dan pada kelompok metastatik adalah 7.14 ± 2.08 (risiko tinggi). Terdapat 22 (19.5%) pasien yang direncanakan untuk menerima terapi deprivasi androgen berdasarkan stadium penyakitnya.* ***Simpulan:*** *Pasien yang baru terdiagnosis kanker prostat umumnya memiliki risiko kardiovaskular yang tinggi, dan hal ini harus menjadi pertimbangan penting dalam pemberian terapi deprivasi androgen.*

Kata Kunci: *Kanker prostat, penyakit kardiovaskular, Jakarta Cardiovascular Risk Score, terapi deprivasi androgen.*

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INTRODUCTION

Prostate cancer is the most common malignancy and the leading cause of cancer death in men in Western countries, causing 94.000 deaths in Europe in 2008 and more than 28.000 deaths in the United States in 2012. In Asia, the average incidence of prostate cancer is 7.2 per 100,000 men per year. In

Indonesia, the number of prostate cancer patients in three central educational hospitals (Jakarta, Surabaya and Bandung) from 2010-2018 was 1.102 patients with an average age of 67.18 years. According to Golobocan data in 2020, the prevalence of prostate cancer is the third most common cancer in men in Indonesia.[1] Patients with prostate cancer (PCa) are actually less likely to die of prostate cancer than of non-prostate causes such as cardiovascular disease (CVD). A recent trial showed that nearly all patients (99%) with prostate cancer had at least 1 uncontrolled modifiable risk factor, and more than half (51%) had 3 or more uncontrolled modifiable risk factors.[2]

Androgen deprivation therapy (ADT) has long been used in advanced prostate cancer and more recently in localized disease with clear survival benefits alone or with radiotherapy.[3] ADT has been linked to various side effects, including cardiovascular disease.[2] The most common form of ADT is gonadotropin-releasing hormone (GnRH) agonist, which has been strongly associated with cardiovascular issues. For example, a study from D'Amico et al showed an earlier onset of fatal myocardial infarctions among patients over the age of 65 on GnRH agonists from a pooled analysis of 3 large, randomized clinical trials.[4] In addition, a large Surveillance, Epidemiology, and End Results–Medicare analysis suggested that GnRH agonists were associated with a 16% increased risk of coronary heart disease, an 11% increase in myocardial infarction, and a 16% increase in sudden cardiac death. [5] RADICAL-PC (A Randomized Intervention for Cardiovascular and Lifestyle Risk Factors in Prostate Cancer Patients), a large prospective study that includes standardized assessment of cardiovascular risk factors in patients with prostate cancer, the authors surprisingly found that nearly all patients (99%) with prostate cancer had at least 1 uncontrolled modifiable risk factor, and more than half (51%) had 3 or more uncontrolled modifiable risk factors, they are dyslipidemia, high blood pressure, physical inactivity, and older age.[6]

Administration of ADT significantly increases cardiovascular risk; however, no CV risk assessment is rarely conducted on such patients. Given the high risk of cardiovascular mortality experienced by the demographic of patients who get prostate cancer and given the additional risk of cardiac harm posed by ADT, it is important to address the CV risk factors among newly diagnosed prostate cancer patients. A developing country like Indonesia requires a simple measure for preventing cardiovascular disease. Recently, Jakarta Cardiovascular Risk JCVR score prediction models were developed and validated. It has good reliability in predicting 10-year cardiovascular events in the Indonesian population. The JCVR score had sensitivity 77.9%, specificity 90.0%, positive predictive value 92.2%, negative predictive value 72.8% in predicting 10-year cardiovascular event. It is expected that the results of this study to be a basis for considering the decision for ADT administration and controlling cardiovascular risk factors in patients with prostate cancer.[7]

OBJECTIVE

This study aims to describe cardiovascular risk factors among newly diagnosed prostate cancer patients.

MATERIAL &METHOD

This is adescriptive retrospective aiming to evaluate the cardiovascular risk factors among patients with newly diagnosed prostate cancer. The subjects of this study were patients newly diagnosed with prostate cancer and admitted to Hasan Sadikin Academic Medical Center, Bandung, Indonesia, from 2013 to 2023. Inclusion criteria were patients with prostate cancer of age ≥ 18 by histopathological confirmation:

This study aims to evaluate cardiovascular risk factors in all patients with Prostate cancer without any specific subgroup, the only exclusion criteria in this study was incomplete data. Subjects were recruited by consecutive sampling method. Data were collected from patients with newly diagnosed prostate cancer who came to the Urology polyclinic of the Dr. Hasan Sadikin General Hospital, Bandung. Patients with diagnosis of prostate cancer regardless of the stage and confirmed by histopathological anatomy were included. Informed consent were asked to patients who met for inclusion and exclusion criteria. The approval letter would be put into the patient's medical record and marked as part of the research. After obtaining patient's consent, we conducted anamnesis and physical examination. Patients who met the inclusion and exclusion criteria were included to the study and were treated according to the current guideline for prostate cancer.

Data including demographic factors, comorbidities, smoking history, blood pressure, and body mass index, was taken from medical records.

The Jakarta Cardiovascular Risk score was calculated on all population and among groups according to tumor extension: local (T1-T2), locally advanced (T3-T4), and metastatic. The JCVR score employed several parameters described on Table 1.

The score between –7 to 1 was considered low risk (CV event within 10 years < 10%), the score between 2 to 4 was considered moderate risk (CV event within 10 years = 10–20%), the score ≥ 5 was considered high risk (CV event within 10 years > 20%).

Normality test was using the Kolmogorov-Smirnov if sample >50 or Saphiro-wilk test if sample <50. Median and interquartile range was presented if data were not normally distributed, otherwise, mean and standard deviation was presented. This is a descriptive study, thus statistical analysis to compare mean between group was not conducted.

Table 1. Jakarta Cardiovascular Risk Score.[7]

Risk Factor	Score
Sex	
Female	0
Male	1
Age	
25-34	-4
35-39	-3
40-44	-2
45-49	0
50-54	1
55-59	2
60-64	3
Blood Pressure	
Normal	0
High Normal	1
Grade 1 Hypertension	2
Grade 2 Hypertension	3
Grade 3 Hypertension	4
Body Mass Index (kg/m^2)	
13.79-25.99	0
26.00-29.99	1
30.00-35.58	2
Smoking	
Never	0
Ex-smoker	3
Smoker	4
Diabetes Mellitus	
No	0
Yes	2
Physical Exercise/ Activity	
No	2
Low	1
Medium	0
High	-3

RESULTS

The total number of patients with newly diagnosed prostate cancer who came to the Urology clinic of the Dr. Hasan Sadikin General Hospital Bandung from 2013 to 2023 was 144 patients. 26 patients were excluded due to incomplete data, thus final analysis was conducted on 118 patients. The mean age was 67.5 ± 9.7 years, mean BMI was

Table 2. Baseline characteristics of the study.

Characteristics	Total, n=118
Age (year), mean ± SD	67.5 ± 9.7
Body mass index (kg/m2), mean ± SD	22.3 ± 2.79
Blood pressure	
Systolic blood pressure (mmHg), mean ± SD	129.94 ± 15.10
Diastolic blood pressure (mmHg), mean ± SD	80.47 ± 8.30
Smoking Status	
Never	34 (28.81)
Ex-smoker	2 (1.69)
Smoker	82 (69.49)
Diabetes mellitus (n), %	2 (1.69)
Androgen deprivation therapy (ADT) (n), %	22 (19.5%)
Gleason Score (n), %	
1	11 (9.32)
2	12 (10.17)
3	13 (11.02)
4	13 (11.02)
5	24 (20.34)
unknown	45 (38.14)
Jakarta Cardiovascular Score, mean ± SD	7.25 ± 2.24
Low risk (<2)	1 (0.85)
Intermediate risk (2-4)	8 (6.78)
High risk (=5)	109 (92.37)

Table 3. Patient's characteristics based on tumor extension.

Characteristics	Local (n=30)	Locally advanced (n=10)	Metastasis (n=37)
Age (year), mean ± SD	66.33 ± 5.37	62.1 ± 8.36	69.19 ± 8.89
Body mass index (kg/m2), mean ± SD	22.74 ± 2.76	22.63 ±3.25	21.54 ± 2.98
Blood pressure			
Systolic blood pressure (mmHg), mean ± SD	128.13 ± 11.16	131.5 ±17.49	128.35 ± 13.64
Diastolic blood pressure (mmHg), mean ± SD	79.40 ± 8.81	79.0 ±10.07	79.94 ± 8.50
Smoking Status			
Never	21 (70.0)	4 (40.0)	30 (81.08)
Ex-smoker	0 (0)	5 (50.0)	6 (16.22)
Smoker	9 (30.0)	1 (10.0)	1 (2.70)
Diabetes mellitus (n), %	0(0)	0 (0)	2 (5.40)
Androgen deprivation therapy (ADT) (n), %	1 (3.33%)	2 (20.0)	15 (40.54)
Jakarta Cardiovascular Score, mean ± SD	6.97 ± 1.99	7.30 ± 1.70	7.14 ± 2.08

22.3±2.79kg/m^2. The average Jakarta cardiovascular score in this population was 7.25 ± 2.24 (score of ≥ 5 was considered as having high cardiovascular risk with a 20% chance of cardiovascular event in ten years time).Most of the population in this study had high cardiovascular risk 109 (92.37%).Other

characteristics of the subjects were presented in Table 2.

We divided patients into 3 groups based on tumor extension, they are local tumor (T1-T2), locally advanced (T3-T4), and metastatic. However, there were 41 subjects with unclassified PCa, thus they were not included in any of the 3 groups. Overall, the 3 groups had similar characteristics, except that metastatic group had a higher number of patients receiving ADT. Furthermore, the local PCa group had a lower Jakarta Cardiovascular score than locally advanced and metastatic group. Unfortunately, there are 22 (19.5%) patients who will be planned to receive ADT based on staging.

DISCUSSION

Patients with PCa are more likely to die due to non-prostate cancer cause such as cardiovascular event, thus assessing cardiovascular risk factor is mandatory in such patient to either predict prognosis of the patients or decide whether ADT should be given. The population in this study included all newly diagnosed PCa patients in Dr. Hasan Sadikin General Hospital, Bandung, within the determined period. The mean age was 67.5 ± 9.7 year, which was similar to GLOBOCAN study 2018 that found average age of diagnosis of PCa of 67 years.[1] Prostate cancer incidence and mortality rates are strongly related to age with the highest incidence being seen in elderly men (> 65 years of age).[8] Prostate cancer may be asymptomatic at the early stage and often has an indolent course. Many prostate cancers are detected based on elevated plasmatic levels of prostate-specific antigen (PSA > 4 ng/mL), a glycoprotein normally expressed by prostate tissue. However, because men without cancer have also been found with elevated PSA, a tissue biopsy is the standard of care to confirm cancer's presence. Old age at diagnosis was associated with higher risk of prostate cancer death even after adjustment for cancer characteristics, primary treatment, year of diagnosis, mode of detection and comorbidity. Thus, it may raise further concern to address additional risk factors for death including cardiovascular risk in such patients.[9]

In this study, 82 (69.49%) were smokers.Cigarette smoking is a well-known cancer-causing behavior and a leading cause of death from cancer. Smoking has an inverse association with PCa incidence. Al-Fayez et al found that the risk of prostate cancer incidence in current smokers compared to nonsmokers showed an inverse association with an RR of 0.84 (95% CI: 0.78-0.91).[10] Although inversely correlated with PCa incidence, smoking was associated with higher mortality in PCa patients. Meta-analysis by Al-Fayez et al. showed that current smokers had a 42% higher risk of death from prostate cancer when compared to non-smokers with a relative risk of 1.42 (95% CI: 1.20-1.68). Thus, addressing cardiovascular risk including smoking status, was expected to better predict mortality in patients with PCa.[10]

In this study, a total of 50 (42.37%) of patients were on either Gleason score grade 3,4 or 5. In clinical practice, Grade Group 1 is histologically considered "low grade," Grade Group 2 is "intermediate grade," and Grade Group 3 or higher is "high grade" disease. Study by Mahal et al, showed that Gleason 6 (grade 1) disease was associated with a lower risk of prostate cancer death (206 of 83645 [0.25%]) compared with Gleason 7 to 10 (grade 2-5) disease (1481 of 108579 [0.77%]) (aHR, 0.25; 95% CI, 0.22-0.30; P<.001).[11]

The average Jakarta Cardiovascular score in this study was 7,25 ± 2,24. The Jakarta Cardiovascular Score was divided into low-risk (-7-1) with CV10 <10%, average-risk (2-4) with CV10 = 10-20%, high-risk (score > 5) with CV10 >20%. This is the first study that evaluate Jakarta Cardiovascular score in PCa cancer patient in Indonesia. We prefer to use Jakarta Cardiovascular score to assess cardiovascular risk since there were not any cardiovascular risk scoring that specific for Indonesian population other than the Jakarta Cardiovascular score. Jakarta Cardiovascular Score is simple method that require minimal parameters to assess cardiovascular risk in the Indonesian population. It is well correlated with Framingham score and had sensitivity 77.9%, specificity 90.0%, positive predictive value 92.2%, negative predictive value 72.8%, degree of agreement 82.67%,with kappa 0.652 and p = 0.000.[7] In our study, Most of the population had high cardiovascular risk [109 patients (92.37%)]. Previous study by Leong et al, found that among patients with PCa, 69% had a Framingham risk score consistent with high cardiovascular risk. Participants in whom androgen deprivation therapy was planned had higher Framingham risk scores than those not intending to receive androgen deprivation therapy, and this risk was abolished after adjustment for confounders.[12] Other study by Sun et al. evaluates cardiovascular

risk in US veteran with prostate cancer. They found that 35.7% had uncontrolled blood pressure, 19.8% had uncontrolled cholesterol levels, and 19.1% had uncontrolled glucose levels. Overall, 54.1% had at least 1 uncontrolled cardiovascular risk factor.13 Cardiovascular disease (CVD) is a common concomitant condition in patients with prostate cancer and according to the European Association of Urology guidelines, CV mortality now exceeds prostate cancer as the most common cause of death.[2]

Despite the high Jakarta CV score, unfortunately, there are 22 (19,5%) patients who will be planned to receive ADT based on staging. ADT has been known to increase cardiovascular risk and mortality in patients with PCa. Meta-analysis by Zhao et al showed that the incidence of CVD was 10% higher in ADT groups, although no significant association was observed (HR = 1.10, 95%CIs: 1.00-1.21; P = 0.06). For different types of ADT, CVD was related to gonadotropin-releasing hormone (GnRH) (HR = 1.19, 95%CIs: 1.04-1.36; P,0.001) and GnRH plus oral antiandrogen (AA) (HR = 1.46, 95%CIs: 1.03-2.08; P = 0.04), but not with AA alone or orchiectomy. The meta-analysis also demonstrated that ADT was associated with higher cardiovascular mortality (HR = 1.17, 95%CIs: 1.04-1.32; P = 0.01).[14] It is not clear whether this association is primarily due to ADT, established CV risk factors (eg, underlying CV disease, a family history of CV events), or a combination of both. ADT may increase CV risk by several mechanisms: (1) ADT may increase large artery stiffness, (2) luteinizing hormonreleasing hormone (LHRH) agonists may increase plaque vulnerability, potentially through stimulation of gonadotropin-releasing hormone (GnRH) receptors on T-lymphocytes that increases the risk of atherosclerotic plaque destabilization, potential for rupture, and subsequent thrombotic complications; (3) weight gain; (4) ADT leads to the development of insulin resistance and changes in lipid profile, which also increase the risk of CV disease. . PCa patients with pre-existing CV disease or risk factors may not be receiving optimal medical management of their CV health. Thus, known and underlying CV risk factors may not be addressed in patients with advanced PCa, potentially leading to increased CV events during the treatment of their PCa, including ADT.[15]

After comparing subject's characteristics among 3 groups based on tumor extension, it was concluded that overall, the 3 groups had similar characteristics, except that metastatic group had higher number of patients receiving ADT and the local PCa group had a lower Jakarta Cardiovascular score than locally advanced and metastatic group. Several studies demonstrated the association between cardiovascular risk and prostate cancer severity with conflicting results. Study by Nunzio et al. enrolled a total of 584 prostate cancer patients and found that high to moderate cardiovascular risk (based on the European Association of Cardiology guideline) was significantly associated with an increased risk of Gleason score >7 (OR: 2.154, CI: 1.076-4.314; P = 0.030).[16] Contrary, a smaller study by Jeon et al. showed that prostate cancer patients with metabolic syndrome had significantly lower Gleason scores (average, 6.63±1.92) than did prostate cancer patients without MS (average, 7.54±1.71; p=0.029).[17] The Genes Environment Prostate Cancer (GECAP) study showed that the presence of metabolic was associated with an increased PCa risk in African-American men (OR: 1.71, 95%CI 0.97-3.01) but not in white men (OR: 1.02, 95%CI 0.64-1.62).[18] Those findings indicated that the association between cardiovascular risk with prostate cancer severity differed among different populations.

The limitation of this study was using Jakarta CV scores that have not been validated externally in a large population. The small number of population and lack of statistical analysis were also limiting for further discussion in this study. Nevertheless, the findings of this study may raise concerns for evaluating CV risk and treating controllable CV risk in newly diagnosed PCa patients, especially for those receiving ADT.

CONCLUSION

Most of newly diagnosed PCa patients had high cardiovascular risk. Mitigating CV risk and treating controllable CV risk should be performed in such population to reduce mortality and morbidity especially for those receiving ADT.

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