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Indonesian Prostate Cancer Risk Calculator (IPCRC): An application for Predicting Prostate Cancer Risk (a Multicenter Study)

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ABSTRAK

Tujuan: *mengembangkan model prediksi kanker prostat berdasarkan populasi Indonesia.* ***Metode:*** *kami mengikutsertakan seluruh pasien pembesaran prostat jinak (BPH) dan kanker prostat yang menjalani biopsi prostat dan prostatektomi pada Januari 2009 dan Desember 2013 dari 5 pusat urologi di Indonesia. Setelah itu, dicari hubungan antara kemungkinan kanker prostat dengan berbagai variabel, seperti: umur, nilai PSA, volume prostat (menggunakan pemeriksaan ultrasonografi transabdominal atau transrektal), dan pemeriksaan colok dubur. Kami menghitung persamaan skor prediktif untuk memprediksi terjadinya kanker prostat menggunakan analisis chi-square, uji Kolmogorov-Smirnov, regresi logistik multipel, dan kurva ROC. Selanjutnya kami mendesain suatu aplikasi untuk memprediksi risiko kanker prostat yang dinamakan Indonesian Prostate Cancer Risk Calculator (IPCRC).* ***Hasil:*** *terdapat 784 pasien kanker prostat dan 1.173 pasien BPH yang digunakan dalam pengembangan kalkulator risiko ini. Rata-rata umur adalah 66,9±8,1 tahun; PSA adalah 72,4±248,9 ng/ml; dan volume prostat adalah 49,6±28,2 ml. Pemeriksaan colok dubur yang abnormal ditemukan pada 637 pasien kanker prostat dan 56 pasien BPH. Kami mengikutsertakan umur, nilai PSA, hasil pemeriksaan colok dubur yang abnormal dalam analisis dan didapatkan hasil yang bermakna dengan nilai p<0,05 pada model univariat. Walaupun tidak bermakna, kami juga menyertakan volume prostat (p=0,157) karena kepentingan klinisnya. Analisis ROC menunjukkan nilai AUC sebesar 0,935; sensitivitas sebesar 90,1%; dan spesifisitas sebesar 80% dalam memprediksi kanker prostat pada populasi indonesia.* ***Kesimpulan:*** *pengembangan Indonesian Prostate Cancer Risk Calculator (IPCRC) mengikutsertakan umur, nilai PSA, pemeriksaan colok dubur, dan volume prostat sebagai variabel-variabelnya. Kedepannya, dibutuhkan studi prospektif untuk memvalidasi kalkulator risiko ini.*

Kata kunci: *kanker prostat, kalkulator risiko, deteksi dini.*

ABSTRACT

Aim: *to develop a prediction risk model of prostate cancer based on Indonesia population.* ***Methods:*** *we included all benign prostate hyperihrophy (BPH) and PCa patients who had prostate biopsy and prostatectomy between January 2009 and December 2013 from 5 urology centers in Indonesia. The relationship between the possibility of PCa with the following variables including: age; PSA level, prostate volume (by transabdominal ultrasound or transrectal ultrasound) and digital rectal examination (DRE) finding. We calculated a predictive scoring equation to predict the possibility of PCa using chi-square analysis, Kolmogorov-Smirnov test, multiple logistic regression and ROC curve. Then, we designed an application for predicting prostate cancer risk called Indonesian Prostate Cancer Risk Calculator (IPCRC).* ***Results:*** *there were 784 PCa and 1173 BPH patients were used for developing the risk calculator in our study. The mean ages, PSA and prostate volume are 66.9±8.1 years old; 72.4±248.9 ng/ml and 49.6±28.2 ml, respectively. Abnormal DRE was found in 637 PCa and 56 BPH. We included age, PSA level, abnormal DRE finding (all showed significant $p<0.05$ in univariate model). Additionally, although not significant, we included prostate volume ($p=0.157$) due to its clinical importance. The corrected ROC analysis showed AUC 0.935, sensitivity of 90.1% and specificity 80% in predicting the prostate cancer in our population.* ***Conclusion:*** *we have developed the Indonesian Prostate Cancer Risk Calculator which includes age, PSA, DRE, and prostate volume as its variables. Future prospective study to validate the risk calculator is needed.*

Key words: *prostate cancer, risk calculator, early detection.*

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in men worldwide. It was estimated 914,000 new cases were found and responsible for 6% (258 400) of total cancer deaths in men in 2008.[1-3] Unlike in western countries, PCa is relatively rare in Indonesia.[4] Indonesian Society of Urologic Oncology (ISUO) in the period 2006-2010 reported 971 PCa cases in Indonesia with the mean of age 68.3 years and PCa was found in 563 (57.9%) cases by prostate biopsy.[5]

Since 30 years ago, considerable knowledge has been gained for finding the factors that may identify a low or high risk of PCa with opportunistic screening. The discovery of prostate specific antigen (PSA) was a cornerstone finding to develop many strategies to detect PCa.[6] Since the introduction of PSA testing in 1987, serum PSA has become a useful tool in screening for PCa. However, it is still difficult to differentiate prostate cancer from benign prostatic disease since PSA levels depend on age, prostate size, and the inflammatory state of the prostate. In addition to total PSA, there are other clinical factors that improve the detection rate of prostate cancer, such as age, digital rectal examination (DRE) findings, transrectal ultrasound (TRUS) findings, PSA density (PSAD), PSA velocity, PSAD of transition zone volume (PSADT), percent of free PSA (% free PSA), and age-specific PSA.[7] Serum prostate-specific antigen (PSA) screening for PCa is controversial because the test lacks specificity and therefore can induce many unnecessary prostate biopsies and lead to overdiagnosis of PCa.[8] This disadvantage can be reduced by using individual risk estimation.[9] In the last decade, several nomograms and artificial neural networks have been developed to predict prostate cancer, either on initial or repeat biopsy. In general, these models have been based on PSA values, a DRE and age, but have also used other variables, including race, family history, year of biopsy, prostate volume, number of needle cores, percentage free PSA (% fPSA), number of previous negative biopsies and PSA velocity.[10] Among prediction tools, nomograms provide superior, individualized, disease-related risk estimations that facilitate management-related decisions. The ability of the nomograms to predict PCa diagnosis, stage, and prognosis has been confirmed. In general, it has been demonstrated that these predictive models perform better than clinical judgment when predicting probabilities of outcome.[11]

In recent years, several nomograms have become available to the clinician, assisting in the risk stratification of prostate cancer (PCa) at needle biopsy.[12] The Prostate Cancer Prevention Trial – Risk Calculator (PCPT-RC) was one of the first online tools to revolutionize the approach to predicting PCa and the newest The European Randomized Study of Screening Prostate Cancer (ERSPC) Risk Calculator are the best known nomograms incorporating known risk factors.[2,13] The Prostate Cancer Prevention Trial (PCPT) was developed from 18,882 men in North American double-blind randomized study of the chemoprevention effects of finasteride versus placebo on prostate cancer development.[14-17] The European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator has been developed based on 6,288 men, mostly Caucasian, participants in the screening arm of ERSPC study.[18-20] There are few studies investigating the validity of the ERSPC-RC or the PCPT-RC in Asians.

During the period of 3 years (September 1994-August 1997), Djoko et al.[4] reported 344 cases with prostate symptom without urinary retention which consisted of 332 BPH patients and 12 PCa patients. With a new cut-off point, most patients (69%) had PSA less or same as 8 ng/ml and none of them had PCa. In intermediate PSA level (8.1-30 ng/mL), we found 90 patients, with only 1 patient had PCa. In PSA above 30 ng/ml 11 from 18 patients (61%) had PCa. By accepting the recommended western cut-off levels, there were numerous unnecessary biopsies had been done, and the specificity of this cut-off was limited (71.9% for PSA less than 4.0 ng/ml). These data were incomparable to the data from western countries.[4] This might be due to a different our population charateristic related to PSA expression. Therefore, we decided to create a model that assigns a probability of detecting prostate cancer base on age, prostate volume, PSA and digital rectal examination (DRE) in Indonesian population.[1]

METHODS

Study Population

In this prognostic study, we included all benign prostate hypertrophy (BPH) and PCa patients who had prostate biopsy and prostatectomy between January 2008 and December 2013 from five urology centers (Cipto Mangunkusumo Hospital Jakarta, Soetomo Hospital Surabaya, Sardjito Hospital Yogyakarta, Hasan Sadikin Hospital Bandung and Adam Malik Hospital Medan) in Indonesia. Data obtained from medical records were age, prostate volume measured by trans-abdominal ultrasonography (TAUS) or transrectal ultrasonography (TRUS), PSA, DRE and histopathological examination. Standard forms were used to make the same data that collected in each center. We excluded patients below 40 years old and volume below 10 ml. We analyzed 1957 patients who had complete medical record data from total of 2577 samples.

Variables

We chose several factors to evaluate the following important predictors for PCa predictions, e.g : age, total PSA level, prostate volume and DRE findings. PSA was measured using PSA Enzyme Immunoassay using PSA monoclonal antibody. The prostate was measured in three dimensions, and its volume was estimated using a modification of the prolate ellipsoid formula and recorded in cm3 (0.523 [length (cm) × width (cm) × height (cm)]) by TAUS/TRUS. DRE was classified as normal or abnormal (any prostatic nodule or induration). The biopsy specimens were examined for the presence of cancer and were categorized using the Gleason score by a pathologist. All variables data were collected from medical record.

Statistical Analysis

The relationship between the possibility of prostate cancer and its variables were evaluated. The association of each factor with its diagnosis was assessed by simple logistic regression analysis. Multiple logistic regression analysis with backward selection was used to determine which factor were independent predictors of PCa in the model-building set. A prediction equation for prostate cancer prediction was developed based on the final logistic regression model. We calculated a predictive scoring equation to predict the possibility of PCa using chi-square analysis, Kolmogorov-Smirnov test, multiple logistic regression and receiver operating

characteristic (ROC) curve. We regarded a p value <0.05 as statistically significant.

The logistic model is as follows;

ln(odds) : β0 + β1(lpsa-lpsac) + β2(lvol-lvolc) + β3(lage-lagec) + β4(DRE abnormal).

Odds is defined as p/(1–p) where P (in the case of this example) is the probability to detect prostate cancer.

In addition, we assessed the performance of the final model by internal validation using the bootstrap procedure. We generated 1000 bootstrap samples and draw 1000 random sample from the original study population. The simple and multiple logistic regression procedure was subsequently employed to the validation samples. All data analyses were performed with SPSS version 20.

Risk Calculator Application

An android application was made by transfering the diagnostic model to a software called Microsoft Visual C# 2010. The application is called Indonesian prostate cancer risk calculator (IPCRC).

RESULTS

In this study, we included 1957 subjects. The characteristics of the subjects can be found in **Table 1**. In total, mean of ages, PSA and prostate volume are 66.9±8.1 years old; 72.4±248.9 ng/ml and 49.6±28.2 ml, respectively. Abnormal DRE findings were found in less than 45% of the patients. Interestingly in Hasan Sadikin hospital, less than seven percent of the patients had abnormal DRE. Most patients were diagnosed as BPH (59.9%). Compared with the others center, Cipto Mangunkusumo Jakarta had more patients diagnosed with PCa (50.3 %, 232 patients). Their mean PSA level was also doubled.

Age, PSA levels and abnormal DRE finding showed significant association level with the diagnosis ($p<0.05$) in univariate model. Additionally, although not significant, we included prostate volume due to its clinical importance. Positive weak correlation with PCa were shown for age ($r=0.045$), PSA ($r=0.278$) and prostate volume ($p=0.048$), while abnormal DRE showed strong significant negative correlation with diagnosis of Pca ($r = -0.784$, $p< 0.001$). (**Table 2**)

From the logistic regression analysis we obtained the model for IPCRC:

ln(odds) = -1.883 + 0.621 (lpsa - 4.25) + 0.041(lvol - 5.47) – 1.199 (lage-6.05) + 3,999 (DRE abnormal). Patient's risk to get PCa increases in younger patients had normal DRE, higher PSA and larger prostate volume. BPH

Table 1. Characteristic of patients in each center

Variables	Total (n=1957)	Cipto Mangunkusumo (n=461)	Soetomo Surabaya (n=539)	Sardjito Yogyakarta (n=266)	Hasan Sadikin Bandung (n=496)	Adam Malik Medan (n=200)
Age X±SD (Median)	66.9±8.1 (67)	66.9±7.5 (67)	64.3±7.8 (65)	70.1±8.6 (71)	67.4±8.1 (68)	68.0±7.4 (68)
Prostate specific antigen (PSA) X±SD (Median)	72.4±248.9 (16.75)	132.2±405.3 (17.17)	68.6±207.3 (20.6)	46.1±102.7 (14.45)	46.6±185.9 (12.5)	43.7±38.1 (31.6)
Prostate Volume X±SD (Median)	49.6±28.2 (43.5)	51.1±31.5 (42.9)	43.9±23.8 (39)	48.6±32.7 (43.7)	54.1±27.6 (53.4)	51.6±23.7 (45.6)
DRE findings n(%) Abnormal	693 (35.4)	211 (45.8)	191 (35.6)	127 (48.1)	33 (6.7)	131 (65.5)
Nodule n(%) Positive	553 (28.3)	127 (27.5)	191 (35.6)	119 (45.1)	28 (5.6)	88 (44.2)
Consistency n(%) Hard	596 (30.5)	214 (46.4)	191 (35.6)	106 (30.2)	32 (6.5)	53 (26.6)
Diagnosis n(%)						
PCa	784 (40.1)	232 (50.3)	224 (41.7)	93 (35.2)	116 (23.4)	119 (59.8)
BPH	1173 (59.9)	229 (49.7)	313 (58.3)	171 (64.8)	380 (76.6)	80 (40.2)

Table 2. Bivariate analysis

Variables	PCa	BPH	p value	r
Age, X±SD (Median)	67.3±8.6 (68)	66.6±7.7 (67)	0.004*	0.045
Prostate specific antigen (PSA), X±SD (Median)	157±377.1 (56)	15.9±19.1 (10)	<0.001*	0.278
Prostate volume, X±SD (Median)	51.3±34.2 (43)	48.5±23.4 (44)	0.157*	0.048
DRE findings n(%) Abnormal	637 (81.3)	56 (4.8)	<0.001#	- 0.784$

* Kolmogorov-Smirnov test # Chi square $ significant correlation (p<0.001)

patients will have a higher score compared to Pca patients.

The ROC analysis revealed a sensitivity of 90.1% and specificity 80% in predicting the prostate cancer in our population with area under curve (AUC) of 0.938. In **Table 3**, we showed the callibration of score (in 10 percentiles) to the diagnosis. The higher the score percentiles, the higher chance diagnosis of Pca were obtained.

Table 3. Scores accuration with diagnosis (callibration)

Scores (in percentiles)		Diagnosis		Total
		BPH	CaP	
Percentile 10	n	187	8	195
	% within scores	95.9	4.1	100.0
Percentile 20	n	179	8	187
	% within scores	95.7	4.3	100.0
Percentile 30	n	173	15	188
	% within scores	92.0	8.0	100.0
Percentile 40	n	174	32	206
	% within scores	84.5	15.5	100.0
Percentile 50	n	194	26	220
	% within scores	88.2	11.8	100.0
Percentile 60	n	159	38	197
	% within scores	80.7	19.3	100.0
Percentile 70	n	82	112	194
	% within scores	42.3	57.7	100.0
Percentile 80	n	20	175	195
	% within scores	10.3	89.7	100.0
Percentile 90	n	4	186	190
	% within scores	2.1	97.9	100.0
Percentile 100	n	1	184	185
	% within scores	0.5	99.5	100.0
Total	n	1173	784	1957
	% within scores	59.9	40.1	100.0

Internal Validation

Both bootstrap samples and the random sampling set show consistency with the original data set. Age, PSA levels and abnormal DRE findings showed significant association levels with the diagnosis ($p<0.05$), while prostate volume showed the opposite. From the bootstrap samples, we got a mean ROC of 0.938, while from the random set we got a mean ROC of 0.941, resulting in optimism corrected ROC of 0.935. (**Figure 1**)

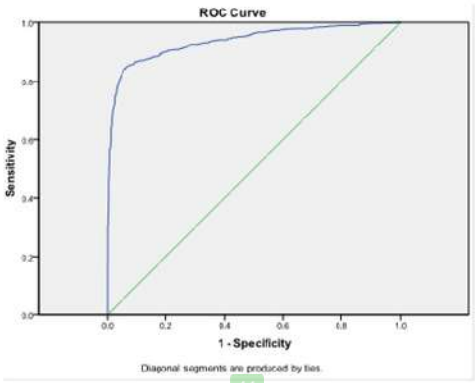

Figure 1. ROC of Indonesian prostate cancer risk calculator (IPCRC)

Indonesian Prostate Cancer Risk Calculator (IPCRC)

We showed the display of the application in **Figure 2A-B**. **Figure 2A** depicts the predictions for a 67-yr-old man with a PSA of 2.8 ng/ml and a prostate volume of 45.3 cm^3. If all the other predictors are set on zero, the probability of PCa are 2,61%. An abnormal DRE outcome

(**Figure 2B**) would increase this man's risk for PCa to 59.4%.

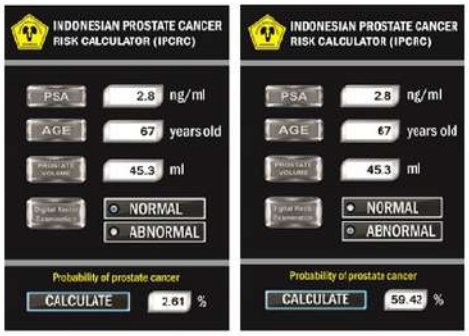

Figure 2. Indonesian prostate cancer risk calculator (IPCRC)

DISCUSSION

In this study, we have developed the Indonesian Prostate Cancer Risk Calculator using the risk factors variables: age, PSA, DRE, and prostate volume of patients. These variables were included in the calculator based on data from 1957 patients in five urology centers in Indonesia. (**Figure 2**)

General practitioners and urologists are increasingly confronted with requests for early detection of PCa. Several risk assessment tools have been developed to support decision making on which diagnostic tools should be conducted to screen suspected PCa patient, a PSA test or a prostate biopsy.[11] However, using PSA for screening purposes, may not be suitable since the prevalence may be related on individualized risk. A limited list of additional risk factors such as age, comorbidity, prostate volume, family history, ethnicity, digital rectal examination and previous biopsy status have been identified to modify risk and are important for consideration in routine practice.[20,21]

Characterizing risk based solely on serum PSA findings presents inherent difficulties. PSA is specific for prostate tissue but not for prostate cancer. Elevated values of serum PSA are found in many benign conditions involving enlargement of the prostate, including BPH and acute prostatitis. Conversely, a high body mass index erroneously lowers PSA values as a result of haemodilution. Thus, the interpretation of PSA values is prone to error arising from nonspecific sources. Furthermore, serum tPSA values are poor indicators of the aggressiveness of prostate cancer, regardless of the threshold chosen. Because PSA does not correlate well with aggressiveness, there is a trend in clinical practice toward overdiagnosis and consequent over-treatment of prostate cancer.[22,23] Recently, a noninvasive urinary test for the prostate cancer gene 3 (PCA3) has been developed. PCA3 is an emerging gene-based marker that is highly specific for prostate cancer.[24,25]

In the last 20 years, there has been extensive development of predictive tools called normogram, which cheap and simple, to aid clinicians in predicting PCa diagnosis, stage and prognosis. And a number of these risk assessment tools are readily available online for an individual man to assess his individual risk for PCa.[6,26] In men with a known PSA, risk calculators may hold the promise of identifying those who are at increased risk of having PCa and are therefore candidates for biopsy.[21,24] Therefore, it is justifiable in our nomogram to include age, PSA, prostate volume and DRE findings.

There were two known common risk calculators for screening in the world; ERSPC-RC and PCPT-RC. ERSPC-RC is a better prediction tool of prostate cancer after biopsy than the PCPT-RC.[2,26] Several studies showed that the performance of the PCPT-RC for predicting prostate cancer is superior to the prediction accuracy of PSA testing alone.3,10,27 and ERSPC.[26] However, in several study, PCPT-RC has been shown as not universally applicable in the population of men with elevated PSA (above 3.0 ng/mL).[3,12,28] The PCTP-RC may overestimate the risk of finding prostate cancer.15 This result could be due to that the PCPT-RC model was fitted on a population of primarily healthy men with PSA less than 3.0 ng/mL and above 55 years of age.[28,29] The accuracy of the PCPTRC on such a healthy population of men is not ruled out by the current validation study since no cohorts of this type were included.[15,28]

ERSPC selected predictor variables based on multivariable analysis including all predictors

irrespective of statistical significance, whereas PCPT included only predictors that were statistically significant. It is unclear whether models that included all predictor variables were overfitted and unstable, potentially increasing bias. PCPT and ERSPC did not report calibration measures. For model validity assessment, internal validation was performed using a 4 to 10-fold cross-validation for PCPT not ERSPC. During development, external validations were carried out for both ERSPC and PCPT. All studies were reported between 2002 and 2012. Countries evaluating the models were mainly from North America (Canada and the USA), Europe (Austria, Belgium, France, Germany, Finland, Italy, The Netherlands, Portugal, and Sweden), and Asia (Japan and South Korea). In total, PCPT and ERSPC RC3 models were validated in 43,072 and 11,536 patients, respectively. Reported median ages ranged from 61-70 years. Overall PSA ranged from 0.1-3210 ng/mL. The proportion of patients with PCa ranged from 21.6-60.7%. In general, ERSPC RC3 validation studies reported overestimation of PCa risk.[30]

A study in a Korean population showed the PCa was diagnosed in 125 (24.1%) men. For prostate cancer prediction, the area under curve (AUC) of the ERSPC-RC was 77.4%. This result was significantly greater than the AUCs of the PCPT-RC and the PSA (64.5% and 64.1%, respectively, $p<0.01$), but not significantly different from the AUC of the PSA density (PSAD) (76.1%, $p=0.540$). The ERSPC-RC was better than PCPT-RC and PSA in predicting prostate cancer risk in the present study. However, the difference in performance between the ERSPC-RC and PSAD was not significant. Therefore, the Western based prostate cancer risk calculators are not useful for urologists in predicting prostate cancer in the Korean population.[3] It seems that PCa in Korean men exhibit poor differentiation regardless of the initial serum PSA level or clinical stage at presentation unlike Western population. This may be due to smaller PV of an Asian population, which was suggested by another study. This may be due to the difference between the populations, on which the calculators were based.[17] External validations of the objectivity of nomograms are important to confirm the performance of these tests because they are often useful only for the cohorts from which they were developed. In addition, there is a limited efficacy of nomograms when externally validated with other study cohorts.

From the logistic regression analysis as a model for IPCRC, there were some differences compared to other risk calculator. Coefficient for PSA in IPCRC was 0.62 lower than ERSPC, of 1.1 and PCPT 0.85. it was similar with prostate volume of 0.04 in IPCRC lower than ERSPC of 1.36. But IPCRC had higher coefficient in DRE findings of 3.99 than ERSPC of 0.8 and PCPT 0.91. The differences was due to low incidence of PCa in our population and most of our patients came in a more severe conditions and were not suitable for screening (e.g had urinary retention). The ROC analysis of IPCRC showed high sensitivity and specificity in predicting prostate cancer with area under curve (AUC) 0.938 (95% CI 0.93-0.95) in our study population. The AUC was higher than the PCPT (AUC 0.70) and the ERSPC (AUC 0.79).[12] This indicated that IPCRC might be better in differentiating patient with PCa and BPH. A further validation in a larger population is needed to confirm this finding.

This study had several limitations. First, the results may have been influenced by the heterogenecity of patients, tumours and biopsy techniques. Second, this study had fewer sample compared to the others. Indonesian prostate cancer risk calculator was developed from 1957 men in Indonesian but PCPT was developed from 18,882 men[16,17] while ERSPC developed from 6,288 men.[13,19] Third, we did not consider race as one of the predictive variable in this calculators because of incomplete medical data. Four, Family history of PCa was not account for its predictive. However, we believed that IPCRC can be useful and had a good predictive value in diagnosing Pca in our population.

CONCLUSION

We have developed the Indonesian Prostate Cancer Risk Calculator which includes age, PSA, DRE, and prostate volume as its variables. Future studies to validate this risk calculator are needed.

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