



Complication of trans-rectal prostate biopsy based on Clavien index: 5 years of experience

Adhitya Fajar Prasetya*, Johan Renaldo

Department of Urology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia

ABSTRACT

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Trans-rectal prostate biopsy has become the gold standard for early diagnosis of prostate cancer in developing countries. Despite its low risk, there are some post-procedural complications. The complications are classified by using a modified Clavien-Dindo system. The study aimed to recognize complications of trans-rectal prostate biopsy procedure by using Clavien-Dindo classification index. All patients undergoing trans-rectal prostate biopsy procedure in the Department of Urology, Dr. Soetomo General Hospital between January 2015-December 2019, were retrospectively analyzed in terms of post-procedural complaints, underlying comorbidities and ongoing additional examinations. The complaints were compiled into Clavien-Dindo classification. Univariate analysis of various predictors of post-procedural complications was also conducted. It was found 98 complication events from 400 patients (24.5%). Most complications were 1st degree (dysuria, hematuria, urinary retention, fever, rectal pain and bleeding, erectile dysfunction, and constipation). In univariate analysis, positive results of urinary culture correlated to the emergence of post-procedural complications. In conclusion, the incidence of post-trans-rectal prostate biopsy complication in Dr. Soetomo General Hospital reached 24.5%. From all of the risk factors, positive urinary culture is related to the post-biopsy complication. Most complications are in the 1st grade of Clavien index, suggesting that the procedure is relatively safe and has a low risk.

ABSTRAK

Biopsi prostat trans-rektal telah menjadi standar emas bagi diagnostik awal karsinoma prostat di negara berkembang. Meskipun relatif berisiko rendah, terdapat sejumlah komplikasi pasca-tindakan. Komplikasi tersebut diklasifikasi menggunakan sistem Clavien-Dindo yang dimodifikasi. Penelitian ini bertujuan untuk mengetahui komplikasi dari prosedur biopsi prostat trans-rektal dengan menggunakan indeks klasifikasi Clavien-Dindo. Semua pasien yang menjalani prosedur biopsi prostat trans-rektal di Departemen Urologi, RSUD Dr. Soetomo, Surabaya dari bulan Januari 2015-Desember 2019, dianalisis secara retrospektif dalam hal keluhan pasca-tindakan serta komorbid yang mendasari dan pemeriksaan penunjang yang telah dilalui. Keluhan tersebut dikompilasi dalam sistem klasifikasi Clavien-Dindo. Analisis univariat dari berbagai prediktor komplikasi pasca-tindakan juga dilakukan. Ditemukan 98 kejadian komplikasi yang muncul dari antara 400 pasien (24.5%). Sebagian besar komplikasi berada di derajat I. Dalam analisis univariat, hasil kultur urine yang positif berhubungan dengan timbulnya komplikasi pasca-tindakan. Dapat disimpulkan, insidensi komplikasi pasca-biopsi prostat trans-rektal di RSUD Dr. Soetomo mencapai 24.5%. Dari semua faktor risiko, kultur urine positif berhubungan dengan komplikasi pasca-biopsi. Sebagian besar komplikasi termasuk dalam indeks Clavien derajat I, menunjukkan bahwa prosedur ini relatif aman dan berisiko rendah.

Keywords:

Clavien;
complication;
trans-rectal prostate biopsy;
dysuria;
hematuria;

INTRODUCTION

Trans-rectal ultrasound (TRUS) of the prostate is a sonographic imaging procedure mostly carry out by urologists.¹ This procedure is often followed by prostate biopsy, which has become the standard procedure since 1989.² It is mostly conducted due to specific clinical indication, either increasing prostate specific antigen (PSA) level or abnormal finding on rectal toucher.¹ Sextant biopsy hasn't been considered adequate. At least 8 systematic biopsies are recommended in prostates measuring \pm 30 cc. In larger prostates, 10-12 core biopsies are recommended.³

Although being considered relatively safe out-patient procedure, the incidence of post-biopsy complications is attached to the procedure itself.⁴ Potential complications on trans-rectal prostate biopsy include hematospermia (6.5-74.4%), hematuria (<14.5%), and rectal bleeding (2.2%).⁵ There have been historical concerns about performing trans-rectal prostate biopsy for patients on anticoagulation/antiplatelet therapy due to its bleeding complications. However, Raheem *et al.*⁶ reported that there was no statistical difference in rectal bleeding event between treatment (with anti-coagulation/anti-platelet therapy) and control groups (without anti-coagulation/anti-platelet therapy), suggesting the safety of continuation of anti-coagulant/anti-platelet treatment before trans-rectal prostate biopsy.

Other post-biopsy complications are infection (6.6%), severe rectal bleeding (1%), urinary obstruction (<4.6%), acute bacterial prostatitis, and urosepsis (0.3%).⁵

Due to the lack of a uniform reporting system, there is a considerable inconsistency from the available data. Terms like major and minor complications have been used, but not standardized, which causes difficulties in comparison of complications. The absence of consensus in grouping and inhomogeneity within reporting system has added the obstacles.⁷ To resolve the problems, Clavien *et al.*⁸ proposed a classification of surgical complications based on experience and analysis from 650 patients who underwent cholecystectomy.⁸ In 2004, Dindo *et al.*⁹ improved the classification system, and the so-called Clavien-Dindo classification system has been standardized for the registration of surgical complications since then.¹⁰ This system is composed of 5 grades and the suffix "d" (for "disability") is used to denote any post-operative impairment,¹¹ as seen in TABLE 1. The stratification of this system depends on the severity of the complication and the invasiveness of the required intervention. Although not being designed for urologic surgery, the application of Clavien-Dindo system has been validated, and it has been proven to be simple, reproducible, and applicable in urologic field.¹

TABLE 1. Clavien-Dindo classification of complications¹²

Grade	Definitions
I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, or radiologic intervention. Allowed therapeutic regimens include anti-emetics, antipyretics, analgesics, diuretics, and so on. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacologic treatment with medications/pharmacologic interventions other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic, or radiologic intervention.
IIIa	Intervention not under general anesthesia.
IIIb	Intervention under general anesthesia.
IV	Life-threatening complications (including central nervous system [CNS] complications) requiring intermediate care/intensive care unit management.
IVa	Single organ dysfunction (including dialysis).
IVb	Multi-organ dysfunction.
V	Death of a patient.

Brain hemorrhage, ischemic stroke, subarachnoid bleeding. This excludes transient ischemic attacks (TIAs).

The purpose of this study is to recognize complications of trans-rectal prostate biopsy procedure by using Clavien-Dindo classification index. A retrospective study was conducted by means of medical records of all patients who underwent trans-rectal prostate biopsy in our institution between January 2015-December 2019. Before collecting data from medical records, we ensured if all medical records have attached informed consent to extract data for scientific purposes. By reviewing all medical records, we sought to identify patients' demographic and prostate biopsy variables associated with post-biopsy complications.

MATERIALS AND METHODS

Design and subjects

The study was conducted retrospectively with analytic descriptive design. The data of 400 patients diagnosed with benign prostate hyperplasia or suspicious prostate cancer who

underwent trans-rectal prostate biopsy between January 2015 to December 2019 in the Urogenital Invasive Unit of Dr. Soetomo General Hospital, Surabaya, Indonesia were analyzed. The protocol of study has received approval from the Ethical Committee for Medical Research in Dr. Soetomo General Hospital (number of certificate 1856/109/XII/2019).

Protocol of study

We ensured if all medical records have attached informed consent to extract data for scientific purposes. The data collection was conducted by obtaining all patients' register numbers, then tracing in register books and printed or electronic medical records. We therefore recorded the patients' identities, such as age, comorbidity, PSA value, average prostate volume, urinary culture, pathological results, post-procedural symptoms. We also looked for pathological results from the Anatomical Pathology Department, urinary culture from the Clinical

Microbiology Department, and PSA value from Clinical Pathology Department. The inclusion criteria were all patients who underwent trans-rectal prostate biopsy in our institution between 2015 to 2019, regardless of pre-biopsy diagnosis and PA result, and the biopsy had to be done in, at least, 10 sites in the prostate. Patients were excluded from this research if the procedure of prostate biopsy was performed from other approaches, for example trans-perineal or trans-urethral prostate biopsy, and less than 10 sites in the prostate (eg. sextant-core biopsy).

Statistical analysis

The data were descriptively analyzed. The complications were

graded according to the Clavien-Dindo classification system. The system is highly recommended due to its simplicity and comprehensive nature, after which the data were presented in graphics. The factors which led to post-procedural complications were analyzed by means of univariate analysis and chi-square test by utilizing SPSS 18.0 software.

RESULTS

Descriptive data of trans-rectal prostate biopsy patients is presented in TABLE 2. Overall, there are 312 patients (78%) who underwent 10-core biopsy and the remaining 88 (22%) underwent 11 and 12-core biopsy due to hypoechoic area in the ultrasonography screen.

TABLE 2. Descriptive data on patients who underwent trans-rectal prostate biopsy.

Variable	Total patients
Age (mean ± SD year)	65.18 ± 7.78
Mean PSA value (ng/mL)	119.69 ± 492.29
Mean prostate volume (mL)	50.02 ± 26.81
Mean PSA density (ng/mL)	3.04 ± 14.17
Urinary culture [n (%)]	
• Positive	197 (49.25)
• Negative	203 (50.75)
Total core biopsy [n (%)]	
• 10 core	312 (78.00)
• 11 core	84 (21.00)
• 12 core	4 (1.00)
PA results [n (%)]	
• BPH/no malignancy	272 (68.00)
• PIN	4 (1.00)
• Prostate adenocarcinoma	105 (26.25)
• TCC	5 (1.25)
• SCC	1 (0.25)
• Prostatitis (acute and chronic)	10 (2.50)
• Tuberculous prostatitis	3 (0.75)

PSA: prostate specific antigen; SD: standard of deviation; PIN: prostate intra-epithelial neoplasia; TCC: transitional cell carcinoma; SCC: squamous cell carcinoma

TABLE 3 shows post-procedural complications classified according to modified Clavien-Dindo classification. Overall, there are 98 complication events of 400 patients (24.5%), divided

in 5 grades (I, II, IIIa, IIIb, and IV). It could be seen from TABLE 3 that most complications are in the 1st grade (82 complications (20.5%)).

TABLE 3. Post-operative grade of complication according to modified Clavien-Dindo classification system

Grade of complications	Total complications
Grade I [n (%)]	82 (20.50)
• Fever	10 (2.50)
• Rectal pain	9 (2.25)
• Dysuria	26 (6.50)
• Rectal bleeding	3 (0.75)
• Constipation	1 (0.25)
• Urinary retention	11 (2.75)
• ED	2 (0.50)
• Hematuria	20 (5.00)
Grade II [n (%)]	13 (3.25)
• UTI	10 (2.50)
• Anemia	2 (0.50)
Grade IIIa [n (%)]	1 (0.25)
Clot retention without surgical intervention (manual irrigation)	
Grade IIIb [n (%)]	1 (0.25)
Clot retention with surgical intervention (cystoscopy and clot evacuation)	
Grade IV [n (%)]	2 (0.50)
Sepsis	

ED: erectile dysfunction; UTI: urinary tract infection

TABLE 4 presents univariate analysis from various predictors of complication after trans-rectal prostate biopsy. Only positive pre-biopsy urinary culture significantly correlated

with the increased post-biopsy rate of complications ($p=0.042$). Whereas, the other predictors were not considered statistically significant ($p >0.05$).

TABLE 4. Univariate analysis of complication predictors of trans-rectal prostate biopsy

Variable	n	Complication		p
		Yes	No	
Diabetes mellitus	49	9	40	0.795
Hypertension	193	37	158	0.433
Other cardiovascular diseases	37	9	28	0.463
Cancer other than prostate/urology	13	6	7	0.310
Cerebrovascular accident	19	3	16	0.301
Other neurological disorders	3	1	2	0.553
Respiratory tract disorders	9	1	8	0.510
Pulmonary infections	16	4	12	0.590
Other infections	11	4	7	0.160
Melena	1	0	1	0.619
Core >10	88	16	72	0.676
Pre-biopsy positive urinary culture	197	47	150	0.042*

DISCUSSION

Trans-rectal ultrasound biopsy is a useful modality for all urologists to diagnose prostate cancer. The complications of trans-rectal prostate biopsy are reported up to 50% cases and range from minor complications which only need reassurance for the patients like hematuria, hematospermia, rectal bleeding, acute urinary retention, until worse complications which requires medical or surgical interventions, such as anemia, syncope, febrile UTI, and septic shock.^{4,13} It is showed from this study that the overall complication rates according to Clavien-Dindo classification system reached 24.5%.

Post-biopsy complications include hematuria, infection, lower urinary tract symptoms (LUTS), and pain, and its hospitalization rates are required in a minority of patients.¹⁴ As reported in English literature, the complication rate ranges between 3-11% and severe sepsis rate is estimated <1%.¹⁵ In this study, only fever and UTI complication rates are 2.5% and 2.5% from overall cases, lower than that report. The rates have been graded according to the Clavien index. Fever can

accompany other complications such as UTI and sepsis.

From the entire patients who underwent trans-rectal prostate biopsy, there were 2 (0.5%) who suffered erectile dysfunction. The number is far lower than reported by Yanaral *et al.*¹⁶ who recorded ED event ranging from 28.8% for mild ED until 5% for severe ED. The exact etiology of post-biopsy ED is unknown, possibly because of inflammation within immediate post-procedural time, and little damage in neuro-vascular bundles due to the biopsy needle. There are some speculations that the ED's components may be related to the psychological impact on cancer or accepting prostate cancer diagnosis.¹⁷ Despite of that, ED complaint won't be durable, as studied by Wibisono *et al.*¹⁸ who found out the improved erection hardness score (EHS) and international index of erectile function-5 (IIEF-5) scores in the first week after prostate biopsy.¹⁸

In 2013, a systematic review reported that bleeding symptoms such as hematuria and rectal bleeding ranged from 5-19% and 1.3-45%, respectively. In this study, hematuria was found in

5% patients, and rectal bleeding was 0.75%. Minor bleeding symptom could be neglected; thus it was not reported. Most bleeding events were only mild and transient.¹⁹

Post-biopsy urinary retention urine was found in 2.75% patients, higher than reported in literature (0.2-1.7%). There are many factors influencing the incidence of post-procedural urinary retention, such as large prostate size, transitional zone to total prostate volume ratio, and higher IPSS score. It seems that there is no correlation between the number of biopsy cores taken or the number of repeat serial biopsies performed and LUTS.¹⁷

Overall, the 3rd-grade complication (clot retention) occurred in one patient (0.25%), which resulted in clot evacuation procedure with regional anesthesia. Besides, there was one patient (0.25%) who suffered clot retention, but could be treated just by catheter irrigation. Efesoy *et al.*²⁰ reported that 0.25-0.7% hematuria event could cause either clot retention or anemia which required transfusion.²⁰

The 4th-grade complication consists of dysfunction of single or multi-organs which requires intensive care. It was visible in 0.5% cases, in accordance with a report in an English literature which mentioned that severe sepsis event was less than 1%. The proposed mechanism related to infection is the possibility of bacteria entering the bladder and blood flow from rectum, where the most common organism responsible for the infection event is *Escherichia coli*. The factors which could predict the infection event were: underlying medical comorbidity, especially diabetes mellitus, urethral catheterization, and previous hospitalization.¹⁵

In this study, univariate analysis of certain factors seemingly resulting in complication of surgical procedure was also performed. It was found that the positive pre-procedural urinary culture might have a relation with the

significantly increasing complication incidence. The study of Bruyère *et al.*²¹ suggested that routine pre-biopsy urinary culture had no benefit after the administration of antibiotic prophylaxis and enema. Instead, they suggested to take pre-procedural urinary culture in patients who had previous UTI history.

We acknowledge several limitations, which could be attributed to the retrospective nature of our study. Many participants may forget the complications they have experienced, causing the complications themselves may not be written in medical records. The result of our study may not exactly mirror the study from a larger heterogeneous because it is conducted in a single institution (which makes our study population smaller). It is also partly caused by the short period of this retrospective study (5 years). Because of that, our study isn't powered adequately to query all potential predictive variables of interest.

The modified Clavien system categorizes complication in standardized manner. The system could also be utilized to assess internal quality and evaluate learning curve for certain procedures.²² However, the Clavien system indeed has some shortcomings. There may be a variation of a complication grade between many institutions. A procedure routinely performed without anesthesia in one institution (grade IIIA) may be carried out under general anesthesia (grade IIIB) in other institutions. The subdivision of group III is only based on anesthetic type, not on its surgical procedure. Indication for intensive care also differs across hospitals. The rates of intensive care admission are determined by various factors, such as economical consideration of the patient, hospital's policy, physicians' preference, and insurance policy. Intensive care may also be indicated due to anesthetic complications, not merely surgical one. Besides, there is no

consensus whether some events must be considered as a complication or routine sequel of a surgery.⁸ For example, acute urinary retention due to trans-rectal prostate biopsy is considered as a minor complication in a study, but major one in another study.^{23,24} Elkoushy *et al.*²⁵ reported that inter-urologist understanding level in application of revised Clavien-Dindo classification could be said good.

CONCLUSION

In conclusion, the incidence of overall complications of post-trans-rectal prostate biopsy in Dr. Soetomo General Hospital, Surabaya reaches 24.5%. From all of the risk factors, pre-biopsy positive urinary culture is related to the post-biopsy complication. Most complications are in the 1st grade of Clavien index, suggesting that the procedure is relatively safe and has a low risk. The Clavien-Dindo system is simple and useful in classifying post-surgical/procedure complication despite many limitations. Further investigation is needed to minimize the recording bias with a prospective approach.

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