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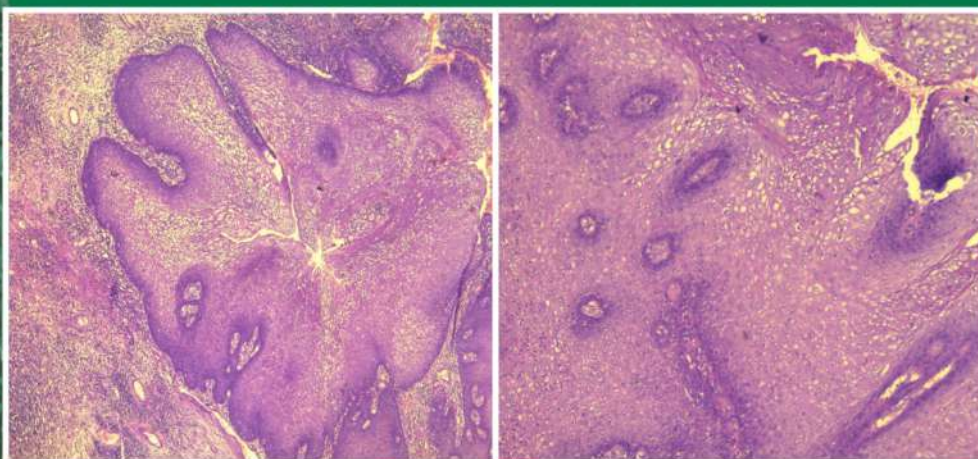
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# HISTOPATHOLOGICAL EXAMINATIONS PROFILE OF BLADDER DISEASES IN DR. SOETOMO GENERAL ACADEMIC HOSPITAL FROM JANUARY 2015 TO DECEMBER 2019

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## ABSTRACT

**Objective:** This study aimed to analyze the profile of bladder disease in Soetomo General Hospital based on histopathological examination. **Material & Methods:** This study was using secondary data. Histopathological examination data of patients with bladder disease were evaluated based on age, gender, and histopathological types. **Results:** There were 419 patients with bladder abnormalities. Non-neoplasm bladder diseases were found in 62 patients consisted of 56 patients (90.32%) with cystitis and 6 patients (9.67%) with glandular cystitis. Neoplastic bladder diseases were found in 357 patients and were divided into benign and malignant neoplasm. Benign neoplasms were found in 11 patients consisted of 5 patients (45.45%) with UP and 6 patients (54.54%) with IUP. Malignant neoplasms were found in 340 patients consisted of 300 patients (88.23%) with urothelial carcinoma, 26 patients (7.64%) with adenocarcinoma, 14 patients (4.12%) with SCC. Moreover, six male patients with PUNLMP were also reported. **Conclusion:** Histopathological examination in patients with bladder abnormalities shows that neoplastic bladder diseases (357/419, 85.20%) were more common than non-neoplastic bladder disease (62/419, 14.80%).

**Keywords:** Bladder disease, profile.

## ABSTRAK

**Tujuan:** Penelitian ini bertujuan untuk menganalisis profil penyakit kandung kemih di RSUD Dr. Soetomo berdasarkan pemeriksaan histopatologi. **Bahan & Cara:** Penelitian ini menggunakan data sekunder. Data pemeriksaan histopatologi pasien dengan penyakit kandung kemih dievaluasi berdasarkan usia, jenis kelamin, dan jenis gambaran histopatologi. **Hasil:** Terdapat 419 pasien dengan penyakit kandung kemih. Penyakit kandung kemih non-neoplasma ditemukan pada 62 pasien yang terdiri dari 56 pasien (90.32%) dengan sistitis dan 6 pasien (9.67%) dengan sistitis glandular. Penyakit neoplasma kandung kemih ditemukan pada 357 pasien dan terbagi menjadi neoplasma jinak dan ganas. Neoplasma jinak ditemukan pada 11 pasien yang terdiri dari 5 pasien (45.45%) dengan UP dan 6 pasien (54.54%) dengan IUP. Neoplasma ganas ditemukan pada 340 pasien yang terdiri dari 300 pasien (88.23%) dengan karsinoma urothelial, 26 pasien (7.64%) dengan adenokarsinoma, 14 pasien (4.12%) dengan karsinoma sel skuamosa. Selain itu, enam pasien laki-laki dengan PUNLMP juga dilaporkan. **Simpulan:** Pemeriksaan histopatologi pada pasien dengan kelainan kandung kemih menunjukkan bahwa penyakit kandung kemih neoplastik (357/419, 85.20%) lebih sering terjadi dibandingkan dengan penyakit kandung kemih non-neoplastik (62/419, 14.80%).

**Kata Kunci:** Penyakit kandung kemih, profil.

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## INTRODUCTION

Bladder disease comprises pathological conditions affecting either the structural and functional aspect of the bladder. Bladder diseases could be grouped into neoplastic and non-neoplastic

conditions according to histopathological characteristics.

Bladder neoplasm is a form of growing mass, both benign and malignant form, originating from the urinary tract whose incidence keeps on growing annually. WHO reported that bladder

neoplasm is one of the seventh global most common malignancies that continues to be increasing. In 2016, 330.380 new cases were reported worldwide.<sup>1</sup> In Indonesia, bladder malignancy was reaching the twelfth top of the most occurring malignancy in the whole country and keeps on growing by 15% every year with an incidence of, in men and women respectively, 5.8 and 1.1 per 100.000 population.<sup>2</sup> A previous study in Nusa Tenggara Barat, Indonesia, also found an increased incidence of bladder neoplasm, with 42 cases reported in 2017 and 48 cases in 2018.<sup>3</sup> In Surabaya, Soetomo General Hospital, as a regional hospital, reported an incidence of 126 cases with a dominance of male patients (81%).<sup>4</sup>

Chemical and carcinogenic substances exposure from environments were associated as a risk factor of bladder neoplasm, along with *Schistosoma haematobium* in parasitic infections. These factors happen to induce the occurrence of urothelial carcinoma (UC), squamous cell carcinoma (SCC), and adenocarcinoma in patients, while smoking habit currently associated as the main risk factor-induces UC. An increased risk was found along with longer duration and higher intensity in smoking.<sup>1</sup>

Meanwhile, the non-neoplastic form of bladder disease is commonly caused by inflammatory or reactive form.<sup>5</sup> Among pathologic conditions in this group, cystitis becomes the common cause of non-neoplastic bladder diseases and *Escherichia coli* becomes the chief etiologic agent for these occurrences.<sup>6</sup>

Studies of bladder disease in Indonesia, particularly in Surabaya, are still limited. This study was conducted to observe the profile of neoplastic and non-neoplastic bladder diseases in the Anatomical Pathology Laboratory of Soetomo General Hospital. The outcome of this study could provide baseline characteristics of bladder disease from a second-largest metropolitan city in Indonesia. It might provide clinical advances that could be made not only to furtherly develop the management of bladder neoplasm but also to make an advancement in its prevention regarding the types of diseases.

## OBJECTIVE

This study aimed to analyze the profile of bladder diseases in Soetomo General Hospital based on histopathologic examination.

## MATERIAL & METHODS

This was a descriptive retrospective study conducted from January 2015 to December 2019. Secondary data were used and included all patients with bladder diseases, both neoplasm, and non-neoplasm, that have been put through a histopathologic examination in the Anatomical Pathology Laboratory of Soetomo General Hospital. A consecutive sampling method involved a collection of secondary data on histopathological examination results through the medical records for being evaluated based on the characteristics of age, gender, their histopathological type. Data were processed and served in the form of appropriate tables. This study has been reviewed Medical Research Ethics Committee in Soetomo General Hospital.

## RESULTS

A total of 419 patients satisfying the inclusion criteria were included in the study (Table 1). Histopathological type distribution in the non-neoplasm group consisted of 56 patients with cystitis (90.32% of all non-neoplasm diseases) and 6 patients with glandular cystitis (9.67%). Distribution in the non-neoplasm group showed a predominance of male patients (35/62, 56.45% of all non-neoplastic cases) which tended to be higher in the adulthood age range, 19-65 years old (Table 1). Similarly, most patients with cystitis were found in the age category of 19 – 65 years old (47/56, 83.92% of all cystitis cases). Glandular cystitis was prevalently found in the age category of 19-65 (5/6, 83.33% of all glandular cystitis cases) with no gender predominance.

Histopathological distribution in benign neoplasm group consisted of 5 patients (45.45% of all benign neoplasms) with UP and 6 patients (54.54% of all benign neoplasms) with IUP. Most patients with UP were found in the age group of 19-65 while patients with IUP showed equal prevalence between adulthood and elderly (> 65 years old). There was no observed case in the pediatric group and all patients with IUP were male (Table 1).

Additionally, only six male patients were having PUNLMP which were more prevalent in the elderly group (> 65 years old). Histopathological type distribution in the malignant group consisted of 340 patients (81.15% of total bladder diseases) with

**Table 1.** Patients' distribution based on age, gender, and histopathological type

Age (years)	Sex	Histopathological type (n=419)							
		Non-Neoplasm		Benign		PUNLMP	Malignant		
		C	CG	UP	IUP		UC	AC	SCC
0 - 18	Male	3	-	-	-	-	-	1	-
	Female	2	-	-	-	-	-	-	-
19 - 65	Male	25	3	2	3	2	188	17	7
	Female	22	2	2	-	-	30	5	5
> 65	Male	4	-	1	3	4	74	3	1
	Female	-	1	-	-	-	8	-	1
All age	Male	32	3	3	6	6	262	21	8
	Female	24	3	2	-	-	38	5	6
Total case *		56	6	5	6	6	300	26	14
n (%)		(90.32)	(9.67)	(45.45)	(54.54)	(100.00)	(88.23)	(7.64)	(4.12)
		62 (14.79)		11 (2.63)		6 (1.43)	340 (81.15)		

\*upper row indicates total case in each histopathological finding; lower row indicates a total case in each histopathological characteristic: C, cystitis; CG, glandular cystitis; UP, urothelial papilloma; IUP, inverted urothelial papilloma; PUNLMP, papillary urothelial neoplasm of low malignant potential; UC, urothelial carcinoma; AC, adenocarcinoma, SCC=squamous cell carcinoma.

predominating UC cases (300/340, 88.23%), followed by adenocarcinoma (26/340, 7.64%), and SCC (14/340, 4.12%). Most patients with UC were found in the age category of 19-65 years old, followed by > 65 years old group with no pediatric cases observed. The majority of UC patients were male (300/340, 77.06% total UC cases). Similarly, adenocarcinoma was commonly found in the 19–60 years old group, followed by only 3 cases in the elderly (> 65 years old) and a case in pediatric (<19 years old). As adenocarcinoma, adulthood patients (19-65 years old) are the major contributor of reported SCC cases (12/14, 85.71%). Both adenocarcinoma and SCC cases were commonly observed in male patients (Table 1).

## DISCUSSION

This present study reported that cystitis was commonly found in aged 19 – 65 years old. Arora and Shoskes found a similar predominance of patients with cystitis at around 40 years old and reported an increased prevalence in the older groups.<sup>7</sup> While a study in Austria reported a different result with patients aged around 80 years old as the most prevalent ones, exceeding the number of patients younger than 65 years old.<sup>8</sup> Despite the difference, Berry et al. reported that the prevalence of cystitis was indeed increasing with a plus of age.<sup>8</sup> Rowe and Mehta also reported an older predominance in cystitis diagnosis, 65-74 years old.<sup>9</sup>

This study found a male predominance in the non-neoplasm group, particularly in cystitis. This result was in contrast with a study by Li and Leslie which reported that cystitis in males was less common than in female patients.<sup>10</sup> A study in Washington University also reported a similar result of female domination in the diagnosis of cystitis, with a ratio of 10:1 per 100.000 cases.<sup>8,10</sup> However, our contradictory results might be caused by the setting of our study in which only complicated cystitis, including males with cystitis, was referred to our tertiary hospital. Moreover, that all cystitis cases were not routinely undergone histopathological examination might result in this finding.

Patients in the age category of 19-65 years old were also the major contributor in UP, along with female predominance. Most studies have partially contradicted this result. As in previous studies, it was reported that the patients' age average having UP were 46 years old with male patients taking in two-third of the prevalence.<sup>11-12</sup> Meanwhile, this study found that IUP was found equally in the age group of 19-65 and > 65 years old. Accordingly, Limaïem et al. found that the IUP mostly occurred in patients in their fifth or sixth decade of life.<sup>13</sup> On the other hand, Cheng et al. found an age average of 37 years old in patients with IUP.<sup>14</sup>

The findings of Limaïem et al. seemed not only in line with the age predominance but also the gender dominance.<sup>14</sup> They found that the majority of IUP patients were male, confirming this study

finding.<sup>14</sup> They also were associating this predominance with a higher prevalence of smoking habit in male patients. The conflicting issue about this hypothesis was particularly found in the presence of p53 gene mutation. Most smokers are commonly positive for a mutation in the p53 gene, while IUP generally lacks it. But the probabilities of IUP are induced by the overexpression of the p53 gene is still abide.<sup>14</sup>

The domination of patients aged > 65 years old in PUNLMP in this study was along with the result of Kim et al. They reported that the mean age in PUNLMP patients was  $70.2 \pm 12.2$  years old.<sup>15</sup> This older age of PUNLMP patients was contradicted by Zhang et al.'s hypothesis that stated PUNLMP tended to be higher in younger patients as a result of higher mitotic rate in the younger ones, leading to higher progressivity and recurrence of PUNLMP in younger patients.<sup>16</sup> That study suggested that patients aged younger than 52 years old tended to have higher progressivity and recurrence of PUNLMP contrasted to the older group.<sup>16</sup> Zhang et al. also stated that younger age could be a predictor for a worse outcome in PUNLMP diagnosis.<sup>16</sup> Both this study and several other studies agreed that there was a domination of male patients in PUNLMP. This study even found all patients with PUNLMP are male, while Zhang et al. and Hentschel et al. with 3311 patients in 17 different health centers in Canada found a male predominance was almost 80% of the PUNLMP population and up to the ratio of 2.7:1.<sup>16-17</sup>

UC was found mostly in the 19-65 years old age category in this study, slightly followed by > 65 years old group. This finding was in line with a study in New York City that stated, epidemiologically, UC was commonly found in the age of 42-52 years old with a maximum range of 46-94 years old.<sup>13</sup> Similarly, a study in Nusa Tenggara Barat, Indonesia found a wider dominant range of age around 50-80 years old.<sup>5</sup> Theories of an existing role of genetic mutation were laid, suggesting an increase of down functioning genetic materials accumulation as the patients get older, specifically an inactivation in p5319 gene.<sup>5</sup> This study also showed that men were more likely to suffer from UC, confirming a similar study by Miyazaki and Nishiyama in 2017 that reported the same predominance of male patients in urothelial carcinoma.<sup>18</sup> and also corresponded with a study in Mohammad Hoesin Hospital, Palembang, in 2009-2013.<sup>19</sup> That male were more likely to have UC might be caused by the higher rate of carcinogenic exposure, such as cigarettes, in which eastern women was less likely to smoking.<sup>20</sup>

The current study observed that adenocarcinoma patients were commonly found in the age category of 19-65 years old, which was consistent with a study in the University of Pittsburgh and also a study by Dadhania et al. that found an age average of 57 years old in adenocarcinoma patients.<sup>21-22</sup> Slightly contrasting, a study in the Netherlands concluded an older result on age average of 66.4 years old.<sup>23</sup>

Moreover, male dominancy in adenocarcinoma cases was concordant with Ploeg et al. finding that 66% of adenocarcinoma suffered by male.<sup>23</sup> This might be caused by a high probability of discrepancies in health access between men and women, especially in the eastern countries, resulting in delayed management in female patients. This might also lead to a lower detection of adenocarcinoma in women. Furthermore, a lower prevalence of gross hematuria as a major symptom of adenocarcinoma in women is also adding to the treatment delay.<sup>24</sup>

Similarly, men became the primary contributor to SCC. A recent systematic review presented that male was indeed the dominant gender in the incidence of SCC, both in the Schistosoma and non-Schistosoma type.<sup>25</sup> Nevertheless, Martin et al. reported that females were the common ones and also noted that this predominance was highly related to the presence of several factors including chronic infection, recurring urinary tract infection, and a smoking habit.<sup>26</sup> Regarding reports on the age prevalence of SCC, several studies came up with diverse findings as this study results, with 45-49 years old as the most prevalent age group. Guo et al. reported a prevalent range of 41-77 years old while Martin et al. reported an average of 50 and 70 years old, respectively, in Schistosoma and non-Schistosoma type.<sup>26-27</sup> One study in Mansoura University surprisingly reported a much younger predominance in the age of 10-20 years old.<sup>28</sup>

Lower risk of bladder malignancy in the female has been linked with a history of older menarche age, parturition, and hormonal treatment of estrogen and progesterin.<sup>29</sup> Otherwise, a history of recurring urinary tract infections in women leads to a higher staging in diagnosis and poorer prognosis.<sup>29</sup> The long history of smoking, particularly in males, might also contribute to the higher prevalence of SCC in males, and probably older patients due to the dose-dependent effect of toxic substances in cigarettes. These factors could explain a variety of outcomes in the drug responses, the biology of the

neoplasm, and the occurrence of drug interaction in the management of SCC.

## CONCLUSION

Histopathological examinations in patients with bladder abnormalities admitted to the Soetomo General Hospital showed that neoplastic bladder diseases were more common than non-neoplastic bladder disease. This present study also reported that patients with non-neoplastic diseases were dominated by the male in the age group of 19-65 years old, with a histopathological type of cystitis; while patients with neoplasm diseases were also dominated by the male in the age group of 19-65 years old, with a histopathological type of urothelial carcinoma.

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