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Clinicopathologic Characteristics of Renal Cell Carcinoma in Prof. dr. I.G.N.G. Ngoerah General Hospital 2018 – 2022

Características Clínico-Patológicas do Carcinoma de Células Renais no Prof. I.G.N.G. Hospital Geral de Ngoerah 2018 – 2022

Características Clínico-Patológicas del Carcinoma de Células Renales en el Prof. dr. I.G.N.G. Hospital General Ngoerah 2018 – 2022

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Abstract
RCC is a tumor that manifests in proximal tubule epithelial cells and accounts for 3% of total adult neoplastic cases. In Indonesia, RCC cases are still deemed low, but show a tendency to increase annually. This study's objective is to provide a description on the clinicopathologic features of RCC patients in Prof. dr. I.G.N.G. Ngoerah General Hospital in the province of Bali from 2018 to 2022. This is a cross-sectional study which implemented total sampling in collecting secondary data from the laboratory of anatomical pathology in Prof. dr. I.G.N.G. Ngoerah General Hospital. There were 38 cases of RCC from a total of 108 kidney cases which underwent histopathologic examinations. Descriptive analysis showed that the majority of RCC cases were found in the age range of 51 – 60 years old (36.8%), males (76,3%), left tumor laterality (57,9%), operative procedures for specimen collection (94,7%), ccRCC subtype (63,2%), tumor size of >10 cm (50,0%), grade III – IV (57,9%), and pT3a stage (47,4%). The combination of these clinicopathologic findings suggested that the RCC patients in Bali were shown to be associated with worse prognosis and should consider further analytical studies.
Keywords: Renal cell carcinoma; Epidemiology; Characteristic.

Resumo
O CCR é um tumor que se manifesta nas células epiteliais do túbulo proximal e é responsável por 3% do total de casos neoplásicos em adultos. Na Indonésia, os casos de CCR ainda são considerados baixos, mas mostram uma tendência a aumentar anualmente. O objetivo deste estudo é fornecer uma descrição das características clinicopatológicas dos pacientes com CCR no Prof. I.G.N.G. Hospital Geral Ngoerah na província de Bali de 2018 a 2022. Este é um estudo transversal que implementou amostragem total na coleta de dados secundários do laboratório de anatomia patológica do Prof. I.G.N.G. Hospital Geral de Ngoerah. Houve 38 casos de CCR de um total de 108 casos renais submetidos a exames histopatológicos. A análise descritiva mostrou que a maioria dos casos de CCR foi encontrada na faixa etária de 51 a 60 anos (36,8%), sexo masculino (76,3%), lateralidade do tumor esquerdo (57,9%), procedimentos operatórios para coleta de espécimes (94,7%), subtipo CCRcc (63,2%), tamanho tumoral >10 cm (50,0%), grau III – IV (57,9%) e estágio pT3a (47,4%). A combinação desses achados clínico-patológicos sugeriu que os pacientes com CCR em Bali demonstraram estar associados a pior prognóstico e deveriam considerar estudos analíticos adicionais.
Palavras-chave: Carcinoma de células renais; Epidemiologia; Característica.

Resumen
El CCR es un tumor que se manifiesta en las células epiteliales del túbulo proximal y representa el 3% del total de casos neoplásicos en adultos. En Indonesia, los casos de CCR todavía se consideran bajos, pero muestran una tendencia a aumentar anualmente. El objetivo de este estudio es proporcionar una descripción de las características clínico-patológicas de los pacientes con CCR en el Prof. dr. I.G.N.G. Hospital General Ngoerah en la provincia de Bali de 2018 a 2022. Se trata de un estudio transversal que implementó un muestreo total en la recopilación de datos secundarios del laboratorio de patología anatómica del Prof. dr. I.G.N.G. Hospital General de Ngoerah. Hubo 38 casos de CCR de un total de 108 casos de riñón que se sometieron a exámenes histopatológicos. El análisis descriptivo mostró que la mayoría de los casos de CCR se encontraron en el rango de edad de 51 a 60 años (36,8%), hombres (76,3%), lateralidad izquierda del tumor (57,9%), procedimientos operativos para la recolección de muestras (94,7%), subtipo ccRCC (63,2%), tamaño tumoral >10 cm (50,0%), grado III – IV (57,9%) y estadio pT3a (47,4%). La combinación de estos hallazgos clínico-patológicos sugirió que los pacientes con CCR en Bali demostraron estar asociados con un peor pronóstico y deberían considerar estudios analíticos adicionales.
Palabras clave: Carcinoma de células renales; Epidemiología; Característica.

1. Introduction

Cancer has been one of the disorders which resulted in high mortality rates globally due to postponed medication. Cancer cases are presented with many variants based on the location of manifestation, types of cancer, and many other factors. One of the most common types of cancer affecting the urogenital system is Renal Cell Carcinoma (RCC). RCC or previously known as Grawitz tumor is one of the most prevalent kidney cancers which covers 85% of total cases worldwide. RCC is a tumor that manifests in kidney tubules epithelial cells and accounts for 3% of total adult neoplastic cases. The causes of RCC are currently still considered vague, complex, and multifactorial. However, several studies have found smoking and obesity to be common causes of RCC (Melisa et al., 2016).

The majority of RCC cases are found in Western developed countries, such as countries in East and North Europe, North America, and Australia whereas countries from Asia and Africa have lower number of cases. Despite having lower number of cases, socioeconomically developing countries have higher RCC mortality rates when compared to developed countries. RCC ranks third in the highest mortality rate caused by urogenital cancers and ranks twelfth in number of cancer-related deaths in the United States (Moch et al., 2016; Seno et al., 2011).

In Indonesia, RCC cases are considered quite low with incidence rate of approximately 2.4 cases every 100,000 civilians. A study conducted in Cipto Mangunkusumo Hospital in the capital of Indonesia from 1995 until 2009 found that there was an annual increase in number of RCC cases. There were only 17 cases of RCC reported from 1995 until 1999, which then increased to 30 cases from 2000 until 2004, and eventually reaching 52 cases from 2005 until 2009 (Seno et al., 2011). Despite being one of the types of cancer with low prevalence rate when compared to other types of cancer worldwide, RCC provides many potential areas of research since it presents unique histopathologic features, varying clinical findings, and is considered a complex type of neoplasm (Vargas et al., 2012). However, studies on the clinicopathologic characteristics of RCC are still rare across the globe. Therefore, the authors aimed to study the clinicopathologic characteristics of RCC in Prof. dr. I.G.N.G. Ngoerah General Hospital in the province of Bali from the year of 2018 until 2022.

2. Methodology

This study implemented an observational cross-sectional study design and was conducted in the laboratory of anatomical pathology in Prof. dr. I.G.N.G. Ngoerah General Hospital which served as Bali's central hospital. The method of total sampling was implemented in collecting all secondary data of kidney cases which underwent histopathologic examinations in the laboratory of anatomical pathology. The cases were then divided into categories of neoplastic and non-neoplastic cases. The neoplastic cases were further classified into RCC and non-RCC cases, whereas the non-neoplastic cases were further classified into infectious and anatomical causes (Merchán-Hamann & Tauil, 2021). This study had been approved

by the Ethical Commission of Udayana University (No: 925/UN14.2.2.VII.14/LT/2023)

Descriptive analysis was conducted on the RCC cases to acquire their clinicopathologic characteristics. All statistical analyses were conducted using IBM SPSS Statistics 20. Numerical variables were tested for normality using Shapiro-Wilk test and were presented in mean (± standard deviation, SD) for normally distributed data and in median (interquartile range, IQR) for abnormally distributed data. Categorical variables were presented in *n* (%).

3. Results

There was a total of 108 cases of kidney specimens sent to the laboratory of anatomical pathology to be histopathologically examined. The 108 kidney cases consisted of 61 neoplastic and 47 non-neoplastic cases. The neoplastic cases were further classified into 38 RCC cases and 23 non-RCC cases. Non-RCC cases included cases of Wilms tumor, urothelial carcinoma, sarcoma, angiomyolipoma, and other causes. The category of non-neoplastic cases was predominantly occupied by cases with infectious causes rather than anatomical (Table 1).

Table 1 - Total kidney cases in the laboratory of anatomical pathology.

Cases	***n* (%) (*n*=108)**
Neoplastic	
RCC	38 (35,2)
Clear Cell RCC (ccRCC)	24 (22,2)
Papillary RCC (PRCC)	11 (10,2)
Collecting Duct Carcinoma (CDC)	2 (1,9)
Mixed RCC	1 (0,9)
Non-RCC	23 (21,3)
Wilms tumor	7 (6,5)
Urothelial carcinoma	8 (7,4)
Sarcoma	2 (1,9)
Angiomyolipoma	2 (1,9)
Others	4 (3,7)
Non-Neoplastic	47 (43,5)
Infectious	32 (68,1)
Anatomical	15 (31,9)

Source: Authors (2023).

All 38 cases of RCC were further descriptively analyzed for their clinicopathologic characteristics. The results from our analysis found that from a total of 38 RCC cases, 29 patients (76.3%) were males. The mean (± SD) age of all patients was 53.0 (± 12.4) years old with the majority of patients being in the age range of 51 – 60 years old (36.8%). Almost all of the specimens delivered to the laboratory of anatomical pathology for histopathologic examinations were surgically collected, which accounted for 36 cases (94.7%) whereas 2 cases (5.3%) were collected through biopsy. The manifestation of RCC on the right kidney was found in 15 cases (39.5%) and on the left kidney in 22 cases (57.9%). There was 1 case (2.6%) which did not have laterality data stated in its medical record. The median (IQR) size of the tumor found in our study was 11.0 (7.88) cm with the majority of cases having tumor size of >10 cm (50.0%). There were 2 cases (5.3%) which did not have size data stated in their medical records. There were four histological subtypes found in our study which included 24 cases (63.2%) of ccRCC, 11 cases (28.9%) of PRCC, 2 cases (5.3%) of CDC, and 1 case (2.6%) of mixed RCC. Our study found that the most common RCC grade was grade II with 14 cases (36.8%) followed closely by grade III with 12 cases (31.6%) and grade IV with 10 cases (26.3%). Grade I was the least to be found, consisting of only 1 case (2.6%) together with another case (2.6%) which grade was not stated in its medical record. The most common pT stage in our study was pT3a with a total of 18 cases (47.7%),

whereas the least common were pT2, pT2a, pT3b, and pT3c with each only consisting of 1 case (2.6%). In addition, there were 3 cases (7.9%) which did not have pT stage data stated in their medical records (Table 2).

Table 2 - Demographics and clinicopathologic characteristics of RCC.

	***n* (%) (*n*=38)**
Age, years	53,0 (± 12,4)[a]
21 – 30	1 (2,6)
31 – 40	5 (13,2)
41 – 50	9 (23,7)
51 – 60	14 (36,8)
61 – 70	6 (15,8)
>70	3 (7,9)
Sex	
Male	29 (76,3)
Female	9 (23,7)
Tumor laterality	
Right	15 (39,5)
Left	22 (57,9)
Not available	1 (2,6)
Specimen collection method	
Surgical	36 (94,7)
Biopsy	2 (5,3)
Histologic subtypes	
ccRCC	24 (63,2)
PRCC	11 (28,9)
CDC	2 (5,3)
Mixed RCC	1 (2,6)
Tumor size, cm	11,0 (7,88)[b]
<7	11 (28,9)
7 – 10	6 (15,8)
>10	19 (50,0)
Not available	2 (5,3)
Grading	
Grade I	1 (2,6)
Grade II	14 (36,8)
Grade III	12 (31,6)
Grade IV	10 (26,3)
Not available	1 (2,6)
pT Staging	
pT1	3 (7,9)
pT1b	2 (5,3)
pT2	1 (2,6)
pT2a	1 (2,6)
pT2b	4 (10,5)
pT3	2 (5,3)
pT3a	18 (47,4)
pT3b	1 (2,6)
pT3c	1 (2,6)
pT4	2 (5,3)
Not available	3 (7,9)

[a] Mean (± SD); [b] Median (IQR)

Source: Authors (2023).

4. Discussion

The mean (± SD) age of patients at time of RCC diagnosis from all the samples found in this study was 53.0 (±12.4) years old with the majority of patients being in the 51 – 60 years old (36.8%) age range. These age findings were lower when compared to studies from the United States which reported 64 years old as the mean age and most patients were found to be in the 65 – 74 years old age range (Anand et al., 2020; Howlander et al., 2020). Another study by Capitano et al. (2018) which evaluated the effect of aging on RCC found that the risk for RCC increased progressively starting from the age of 40 – 44 years old and reached its peak between the age of 60 and 70 years old. The age findings from this study were still higher than that of ours. However, comparison with Asian countries showed similar age findings. The data from a cancer center hospital in Indonesia found that patients were mostly diagnosed with kidney cancer at the age range of 51 – 65 years old (Duha et al., 2022). A similar finding was reported from a tertiary care referral center in India where the median age at time of RCC diagnosis from their samples was 58 years old (Pallagani et al., 2021). The factors which led to relatively younger age of diagnosis in Asian countries when compared to Western countries still need to be further studied.

The comparison in sex category found that 76.3% of the RCC patients in our study were males. This finding is in accordance with the data from GLOBOCAN 2018 which showed that two-third of global RCC cases were found in males (Bray et al., 2018). The study by Capitanio et al. (2019) also showed that the proportion of male to female RCC patients was 1.5:1, whereas the study by Duha et al. (2022) found that the proportion was 2.3:1. The predisposition of higher RCC incidence in males compared to females are influenced by many factors, including lifestyle, jobs and occupations, comorbidities, hormones, and even genetics. Higher incidence rates in males have been associated with the prevalence of smoking and exposure to occupational-related toxins in several studies (Gelfond et al., 2018; Mancini et al., 2020; Peired et al., 2021; Pesch et al., 2000). In 2013, it was reported that 22.4% of mortalities in male RCC patients were associated with history of smoking (Dy et al., 2017). The tendency of men's choice of jobs and occupations also put them at higher risk for RCC manifestation. An epidemiological study which recruited 57,310 workers exposed to 2,4,5-Tricholorophenoxyacetic (2,4,5-T) herbicide found that only 2.7% of the workers were females. Another cohort study on the effect of metalworking fluids as RCC risk factor which recruited 33,421 workers also found that there were only 13.5% of female workers. Both 2,4,5-T herbicide and metalworking fluids exposures were shown to be associated with increased risk for RCC (Andreotti et al., 2020; Shrestha et al., 2016).

Hypertension was found to be an independent risk factor for RCC and was found to be more prevalent in male populations than that of females (Doumas et al., 2013; Macleod et al., 2013). This condition may be due to hypertension being a multifactorial disease often influenced by lifestyle factors, such as smoking which is more common in males. Males with hypertension were found to be 1.32 times more likely to develop RCC (Gelfond et al., 2018). This condition is further exacerbated by the findings which showed that the usage of antihypertensive drugs was associated with increased risk for kidney cancer incidence (Xie et al., 2020). Furthermore, hypertension also plays a role in the pathogenesis of chronic kidney disease which was also found to be a risk factor for the manifestation of RCC (Carrero et al., 2018; Peired et al., 2020).

Females tend to be diagnosed with RCC at much older age when compared to males. This suggested that higher female hormones during younger years could have played a protective role by preventing the pathogenesis of RCC (Hew et al., 2012). A study by Yu et al. (2013) found that RCC cells expressed estrogen receptor beta (ERβ) which could act as a tumor suppressor. The stimulation of estrogen and ERβ activation could inhibit RCC proliferation and also induce cell apoptosis. A cohort study by Setiawan et al. (2009) which recruited 106,036 females found that females who had experienced menarche above 15 years old were associated with a 42% increase in risk for RCC despite not being statistically significant ($p > 0.05$). There has not been any clear association of the use of hormonal contraceptives, age of menopause, and history of hysterectomy/oophorectomy with RCC incidence in females until now (Zucchetto et al., 2008). Another hormonal factor which

was found to influence the development of RCC was the expression of androgen receptors. However, the expression of androgen receptors could occur in both males and females without any significant differences (G. Zhu et al., 2014). The study by Noh et al. (2013) found that higher expression of androgen receptors in RCC was associated with more aggressive cancer characteristics and worse prognosis. The expression of androgen receptors could induce the proliferation of RCC cells by inhibiting miRNA-145 (Chen et al., 2015).

Genetically, there are differences in the metabolic pattern of RCC between males and females. The genes associated with immune response and inflammation were found to be predominantly expressed in male RCC patients, whereas female RCC patients expressed genes associated with catabolic processes (Brannon et al., 2012). A genomic study conducted by Laskar et al. (2019) found two sex-specific RCC gene loci. The DPF3 gene was associated with higher risk in females, whereas EPAS1 was associated with higher risk in males.

The distribution of RCC laterality in our study found a slightly higher frequency of left kidney cases (57.9%) with a 18.4% difference. The study by Pallagani et al. (2021) reported equal distribution between right and left kidney cases. Another study by Strauss et al. (2019) also reported equal distribution among 17,709 RCC patients. Despite RCC laterality tends to be equally distributed, it has been found to be one of the prognostic factors of RCC. The data from Surveillance, Epidemiology and End Results (SEER) and German Centre for Cancer Registry Data (ZfKD) reported that RCCs which manifested on the left kidney were frequently found in an advanced stage with lower cancer-specific survival (CSS) rate (Strauss et al., 2019). The study by Guo et al. (2019) also found that patients who had RCC on the right kidney tend to have better clinicopathologic features when compared to cases on the left kidney. Therefore, the slightly higher number of left kidney cases in our study could have indicated a tendency towards worse prognosis.

Almost all of the specimens sent for histopathologic examinations in our study were surgically excised (94.7%). This was in accordance with a study on clinicopathologic characteristics of RCC in Kenya where the majority of the specimens collected were also surgically excised (Mutuiri & Gakinya, 2022). Surgically collected specimens give the advantage of being able to determine more specific characteristics, such as pT staging which is based on tumor sizes, when compared to biopsy specimens which are only feasible for tumor grading. However, the implementation of biopsy in specimen collection has been increasing over the last few years (Williamson, 2019). Biopsy is used to consider whether to put a patient under surveillance or to carry out surgical procedures as means for RCC treatment. Metastatic cases proved to be a challenge for biopsy in determining cases of primary kidney cancer and in distinguishing clear cell from non-clear cell subtypes (Halverson et al., 2013). Another limitation of biopsy was difficulty in determining clear cell subtype in high grade cancers with poorly differentiated morphology (Taneja et al., 2019). There were 2 cases of RCC which were collected through biopsy in our study. This may have been due to the cases being determined as inoperable advanced stage cases. In such cases, biopsies are only conducted to diagnose and to determine appropriate chemotherapies.

The most common subtype found both regionally and globally is ccRCC. As much as 70-80% of RCC cases in Asia were dominated by ccRCC (Duha et al., 2022). Following ccRCC, the most common subtypes are PRCC and ChRCC. These three subtypes were reported as the most common subtypes starting from ccRCC, PRCC, then ChRCC sequentially by data from SEER, ZkKD, and the studies by Anand et al. (2020), Mutuiri and Gakinya (2022), and Pallagani et al. (2021). The most common subtypes found in our study were also ccRCC (63.2%) followed by PRCC (28.9%). However, the difference was that our study did not have any cases of ChRCC, but found 2 rare cases of CDC (5.3%) and 1 case of mixed RCC (2.6%) instead. When compared to other common subtypes, ccRCC cases that needed to be treated surgically were reported to have worse prognosis in general. However, this condition would not be relevant after adjusting the grade and stage of each subtype (Klatte et al., 2018). Patients with CDC subtypes were generally associated with worse prognosis independent of its stage and grade (Keegan et al., 2012). There was one CDC case in our study which was not graded since it was assumed as a subtype with

generally worse prognosis. There was also a case of mixed RCC in our study which showed both ccRCC and PRCC morphologies. The ideal method in determining the specific subtype in such cases is to perform immunohistochemistry (IHC) test. However, this case was restricted to routine histopathologic examinations using Hematoxylin and Eosin (H&E) staining and was reported as a case of mixed RCC in our study.

The median (IQR) size of tumor in our study was 11.0 (7.88) cm with the majority of cases having the size of more than 10 cm (50.0%). These findings differed greatly from SEER data which reported that ≥10 cm tumors only accounted for 10% of total cases and the majority of cases had tumor sizes below 4 cm (43.8%). However, the study by Mutuiri and Gakinya (2022) reported that the mean tumor size of RCC in their study was 9.7 cm which was also quite large. Large tumor sizes in RCC have been associated with worse prognosis. A study by Kurban et al. (2017) included 323 neoplastic cases of which 320 of them were RCC cases. This study analyzed the correlation of tumor size with grade and pT stage and found that 54 from 106 cases of neoplasm with the tumor size of >7 cm were either graded III or IV by the Fuhrman grading method and 71 from 106 cases had the pT stage of ≥ pT3a. These findings were in accordance to our study where the accumulated percentage of grade III and IV cases reaching up to 57.9% and the most prevalent pT stage being pT3a (47.4%). However, it should be taken into consideration that the grading in our study was conducted using the International Society of Urological Pathology (ISUP) method which may have had slightly different grading results from the Fuhrman method used in the study by Kurban et al. (2017), especially in determining grade II and III (Rabjerg et al., 2021). Another study by Zhi et al. (2020) specifically found a negative correlation between survival rate and size of ccRCC. In addition, large size tumors were also associated with higher risk for lymph node metastasis which would be represented in higher grades. There were 2 cases (5.3%) in our study which did not have size data in their medical records due to the specimens being collected through biopsy.

The data from SEER, ZfKD, and the study by Mutuiri and Gakinya (2022) reported that their findings on RCC grades were dominated by grade II cases. As much as 51.8% of SEER data and 65% of ZfKD data were grade II cases (Guo et al., 2019; Strauss et al., 2019), whereas the study by Mutuiri and Gakinya (2022) found a slightly lower result where 46% of their patients were grade II. In terms of the most common grade, these findings were still in accordance to our study where grade II was the most prevalent (36.8%). However, the distribution was quite even when compared directly to grade III (31.6%) and grade IV (26.3%). The accumulation of grade III and IV cases (57.9%) greatly outnumbered grade II cases unlike previous studies.

The proportion of pT stage in our study showed a major difference from the data from SEER, ZfKD, and the study by Pallagani et al. (2021). SEER and ZfKD data reported that 68% and 67% of the pT stage found in the datasets respectively were pT1 (Guo et al., 2019; Strauss et al., 2019). The study by Pallagani et al. (2021) also found that pT1 stage cases were the most common and accounted for 40.1% of the total samples. In contrast, our study had more invasive cases with the accumulated number of pT3 cases reaching up to 57.9% and specifically dominated by pT3a (47.4%). The pT3a stage was recommended to be further observed and analyzed as there were reports regarding different prognoses dependent of the invasive characteristics displayed. Hence, D. Zhu et al. (2020) proposed three new sub-classification criteria for pT3a which included type A, B, and C. Type A included pT3a tumors which invaded the pseudo-capsule and had a direct contact with the perinephric adipose tissues. Type B included pT3a tumors which protruded into the perinephric adipose tissues with a tongue-like appearance. Type C included pT3a tumors which had nodules distributed in the perinephric adipose tissues. There were significant differences in the recurrence rate among these three proposed criteria with type B and C being more recurrent in nature (Xu & Zhu, 2021; D. Zhu et al., 2020).

5. Conclusion

In our study, the age of RCC diagnosis was generally younger compared to studies and data from Western countries

and patients were predominantly males. The laterality distribution showed slightly higher number of left kidney cases. Almost all of the specimens sent for histopathologic examinations were surgically collected and the most common histologic subtype found was ccRCC. The RCC cases in our study presented large tumor sizes and were dominated by grade III and IV cases. The cases also presented invasive characteristics which were shown in pT3a being the most prevalent pT stage. The combination of these clinicopathologic characteristics suggested that the RCC patients in Bali were shown to be associated with worse prognosis and further studies are needed to analyze possible correlations between certain factors and the prognosis of RCC in Bali. Further studies should consider the addition of other variables, such as Body Mass Index (BMI), jobs and occupations, history of smoking or alcohol consumption, comorbidities, and history of prolonged drug use, for a more in-depth comprehension regarding possible RCC prognostic factors.

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