PROGNOSTIC FACTORS OF RENAL CANCER

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ABSTRACT

Objective: *Course of the disease of kidney cancer may be unpredictable. For example, between 4.2–7.1% of patients with tumours ≤ 4 cm that are usually slow-growing may have metastases at diagnostic and are at an elevated risk of disease-specific mortality. Conversely, as many as 40% of patients with lymph node metastases were diagnosed at nephrectomy are alive 5 year after surgery. Several approaches have been proposed to help predict the course of disease of kidney cancer and to distinguish between poor and favourable risk patients. In this study, we review the existing prognostic factors and compared with established prognostic models.* ***Material & methods:*** *This is an analytic descriptive study of all kidney cancer patients treated at Haji Adam Malik Hospital between 2011 and 2015. Individual patient data was collected from medical record and compiled.* ***Results:*** *The number of samples analyzed in this study were 38 patients. We found seven patients remain alive of the entire sample. From the results of the univariate test, the factors that have a significant relationship with the mortality rate were low KPS (<80), weight loss, and nephrectomy. From the results of multivariate analysis, nephrectomy is the only prognostic factor in patients with kidney cancer. Mortality rate was 0.056x lower in patients who underwent nephrectomy compared with patients who did not underwent nephrectomy.* ***Conclusion:*** *Despite the high mortality rate that is found in this study, nephrectomy still has a place in kidney cancer management, even in patients with advanced stage.*

Keywords: *Kidney cancer.*

ABSTRAK

Tujuan: *Perjalanan penyakit dari tumor ginjal mungkin dapat tidak terduga. Sebagai contoh, antara 4.2–7.1% dari pasien dengan tumor ≤ 4 cm yang pada umumnya lambat berkembang dapat mempunyai metastasis pada saat diagnosis dan mempunyai risiko disease-specific mortality yang meningkat. Sebaliknya, sebanyak 40% pasien dengan metastasis kelenjar getah bening yang didiagnosis pada saat nefrektomi, dapat hidup hingga 5 tahun paska pembedahan. Beberapa pendekatan telah diusulkan untuk membantu memprediksi perjalanan penyakit dari tumor ginjal dan untuk membedakan antara pasien dengan risiko baik dengan buruk. Dalam penelitian ini, kami meninjau faktor-faktor prognostik yang ada dan membandingkannya dengan model prognostik yang ada.* ***Bahan & cara:*** *Jenis penelitian ini adalah studi deskriptif analitik. Sampel penelitian adalah seluruh pasien yang telah didiagnosis dengan tumor ginjal yang berobat ke RSUP H. Adam Malik tahun 2011 hingga 2015. Data dikumpulkan dari rekam medis.* ***Hasil:*** *Jumlah sampel yang dianalisis pada penelitian ini adalah 38 pasien. Dijumpai tujuh pasien hidup dari seluruh sampel penelitian. Dari hasil uji univariat, faktor-faktor yang memiliki hubungan bermakna dengan tingkat mortalitas adalah KPS yang rendah (<80), penurunan berat badan, dan tindakan nefrektomi. Dari hasil uji multivariat, tindakan nefrektomi merupakan satu-satunya faktor prognostik pada pasien tumor ginjal. Tingkat mortalitas 0.056x lebih rendah pada pasien yang dilakukan nefrektomi dibanding pasien yang tidak dilakukan nefrektomi.* ***Simpulan:*** *Meskipun tingkat mortalitas yang tinggi yang dijumpai pada penelitian ini, tindakan nefrektomi masih memiliki tempat dalam penanganan tumor ginjal, bahkan pada pasien yang berobat dengan stadium lanjut.*

Kata Kunci: *Tumor ginjal.*

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INTRODUCTION

Course of disease of renal cancer may be unpredictable. For example, between 4.2–7.1% of patients with tumor ≤4 cm which are commonly slow in development may have metastasis by the time they were diagnosed and have increased disease-specific mortality.[1] On the other hand, 40% patients with lymph node metastasis diagnosed during nephrectomy, may live up to 5 years post surgery.[2]

Renal cancer incidence is 3% out of all malignancy and Renal Cell Carcinoma (RCC) is around 85% of all renal malignancy.[3,4] Highest incidence on age group 60-70 years old and men twice more often than women.[5]

Metastatic RCC (mRCC) are found in 20-30% of all patients. Moreover, 20-50% of patients that underwent nephrectomy will have recurrence and develop into mRCC. Prognosis will become poor after the disease develops into mRCC, with survival rate around 0-20%.[6,7]

Lack of effective systemic therapy and the many variations of RCC course of disease causing poor survival of mRCC patients emphasize the importance to define patients' factor and disease relating to survival rate, recurrence, and progression. Reliable identification system and validated prognostic model on the outcome of mRCC patients will be an important device that can be used to help optimizing patients' choice of specific treatment strategy and help interpret how far the therapy affects the course of disease.

OBJECTIVE

Few approaches had been suggested to help predict course of disease of renal cancer and to differentiate between patients with well and poor risks. In this study, we observed existing prognostic factors and compared them with available prognostic models.

MATERIAL & METHODS

This study is a cross sectional descriptive-analytic study to find out prognostic factors of renal cancer at Haji Adam Malik General Hospital Medan on patients diagnosed with renal cancer in year 2011-2015. Data was analyzed using SPSS version 23 and presented in the form of table and narration.

RESULTS

From year 2011 until 2015 there were 38 patients with renal cancer diagnosis. According to sex, 24 patients were male, while 14 patients were female. Mean age of patients was 48.26 ± 14.68 years old, with the youngest being 22 years old and the oldest 77 years old. With 50 years old as the limit, there were 22 patients aged ≤ 50 years old and 16 patients aged >50 years old. Performance status was scored using Karnofsky Performance Status (KPS) when patient first came for treatment. With KPS limit 80, there were 26 patients with KPS score <80 and 12 patients with KPS ≥ 80. Weight loss was experienced by 14 patients.

Tumor size was measured using abdominal CT Scan and based on post-nephrectomy size. Mean size of renal cancer was 15.45 ± 2.42 cm, with the largest measured 21 cm and the smallest 7 cm. With 10 cm as the limit for size, there was only one patient with tumor size ≤ 10 cm and 37 patients with tumor size >10 cm. On renal cancer patients, 18 patients underwent nephrectomy, 3 patients had biopsy, and 17 patients had no treatment.

Regional lymph node involvement was found on 14 patients and remote metastasis on 12 patients. There were 7 patients with single metastasis and 4 patients with multiple metastasis. Location of metastasis included were; lungs metastasis on 7 patients, bone metastasis on 3 patients, liver metastasis on 6 patients, and brain metastasis on 1 patient. These data are shown in table 1.

Laboratory parameter examined in this study included hemoglobin, thrombocyte, neutrophil, ESR, ALP, LDH, and Corrected Ca. Each laboratory parameter was measured using normal value range accepted by Department of Clinical Pathology Haji Adam Malik General Hospital Medan. Reference value for each parameter was; Hb < lower limit of normal value, thrombocyte ≥ 400.000/μL, neutrophil>upper limit of normal value, ESR ≥ 100 mm/hour, ALP > 100 IU/L, LDH > 1.5 x upper limit of normal value, Corrected Ca > 10 mg/dL. Corrected Ca was counted using the formula Corrected Ca=Ca – 0.707 (Albumin-3.4). Median value and range of each laboratory parameter is presented in table 2. Patients' distribution according to referred value for each laboratory parameter is presented in table 3.

Outcome considered to evaluate prognosis from factors above is mortality. Mortality of renal

Table 1. Characteristics of patients with renal cancer.

Variable	Total (%)
Sex	
Male	24 (63.16)
Female	14 (36.84)
KPS	24 (63.16)
<80	26 (68.4)
≥80	12 (31.6)
Weight Loss	
Ya	14 (38.6)
Tidak	24 (63.2)
Tumor Size	
Mean	15.45 ± 2.42
≤10cm	1 (2.6)
>10cm	37 (97.4)
Nefrectomy	
Yes	18 (47.7)
No	20 (52.6)
Regional Lymph Node	
Yes	14 (36.8)
No	24 (63.2)
Metastasis	
Yes	12 (31.6)
No	26 (68.4)
Number of Metastasis	
≤1	8 (66.7)
>1	4 (33.3)
Metastasis Location	
Lung Metastasis	
Yes	7 (18.4)
No	31 (81.6)
Bone Metastasis	
Yes	3 (7.9)
No	35 (92.1)
Liver Metastasis	
Yes	6 (15.8)
No	32 (84.2)
Brain Metastasis	
Yes	1 (2.6)
No	37 (97.4)

Table 2. Characteristics of laboratory parameter.

Parameter	Median	Range
Hb		
Male	10.05	5.5–13.3
Female	10.70	2.9–15.5
Thrombocyte	359.000	120.000–608.000
Neutrophil	10.6	2.86–36.81 x 10^3
ESR		
Male	46	13–155
Female	46	10–96
ALP	103.5	33–232
LDH	628.5	222–6570
Corrected Ca	9.51	7.66–16.36

Table 3. Laboratory parameter of patients with renal cancer.

Variable	Total (%)
Hb (gr/dL)	
Normal	6 (15.8)
<Normal	32 (84.2)
Thrombocyte (µL)	
<400.000	24 (63.2)
≥400.000	14 (36.8)
Neutrophil (µL)	
>6.5 x 103	24 (63.2)
≤6.5 x 103	14 (36.8)
ESR (mm/hour)	
<100	37 (97.4)
≥100	1 (2.6)
ALP (IU/L)	
≤100	18 (47.4)
>100	20 (52.6)
LDH (U/L)	
≤330	8 (21.1)
>330	30 (78.9)
Corrected Ca (mg/dL)	
≤10.0	28 (73.7)
>10.0	10 (26.3)

cancer is 81.6%. Factors are divided into two, demographic and clinical factors, as well as laboratory parameter. Table 4 shows the relationship between demographic and clinical factors and mortality rate of patients with renal cancer. Demographic and clinical factors that shows significant relationship towards mortality rate were KPS, weight loss, and nephrectomy.

From table 5 can be seen the relationship between laboratory parameter results and mortality rate of patients with renal cancer. There was no significant relationship between laboratory parameter and mortality rate.

In this study, we identified potential factors as prognostic factors of renal cancer, they were KPS, weight loss, tumor size, nephrectomy, and remote

Table 4. Relationship between demographic and clinical factors and mortality rate.

Variable	Mortality (%)	p
Age		
≤50 years old	19 (86.4)	0.425
>50 years old	12 (75.0)	
Sex		
Male	21 (87.5)	0.387
Female	10 (71.4)	
KPS		
<80	24 (92.3)	0.022
≥80	7 (58.3)	
Weight Loss		
Yes	14 (100)	0.033
No	17 (70.8)	
Tumor Size		
≤10 cm	0 (0.0)	0.184
>10 cm	31 (83.8)	
Nephrectomy		
Yes	12 (66.7)	0.038
No	19 (95.0)	
Regional Lymph Node		
Yes	13 (92.9)	0.227
No	18 (75.0)	
Metastasis		
Yes	12 (100)	0.074
No	19 (73.1)	
Number of Metastasis		
≤1	8 (100)	1.000
>1	4 (100)	
Metastasis Location		
Lung Metastasis		
Yes	7 (100)	0.309
No	24 (77.4)	
Bone Metastasis		
Yes	3 (100)	1.000
No	28 (80.0)	
Liver Metastasis		
Yes	6 (100)	0.569
No	25 (78.1)	
Brain Metastasis		
Yes	1 (100)	1.000
No	30 (81.1)	

Table 5. Relationship between laboratory parameter and mortality rate.

Variable	Mortality (%)	p
Hb (gr/dL)		
Normal	4 (66.7)	0.302
<Normal	27 (84.4)	
<400.000	20 (83.3)	1.000
≥400.000	11 (78.6)	
Neutrophil (µL)		
>6.5 x 103	20 (83.3)	1.000
≤6.5 x 103	11 (78.6)	
ESR (mm/hour)		
<100	30 (81.1)	1.000
≥100	1 (100)	
ALP (IU/L)		
≤100	14 (77.8)	0.687
>100	17 (85.0)	
LDH (U/L)		
≤330	8 (100)	0.37
>330	23 (76.7)	
Corrected Ca (mg/dL)		
≤10.0	22 (78.6)	0.650
>10.0	9 (90.0)	

metastasis. From multivariate analysis results, nephrectomy was identified as the sole prognostic factor of renal cancer. Prevalence ratio of mortality of patients with renal cancer that underwent nephrectomy was 0.056 times lower than patients with renal cancer that did not undergo nephrectomy. This is shown in table 6.

DISCUSSION

Old age was the predictor of increasing renal cell carcinoma-specific mortality (RCC-SM). Age influence by the time diagnosis RCC was assigned shows that patients aged 50-75 years old have moderate risks for RCC-SM. Meanwhile, RCC-SM risks

Table 6. Multivariate analysis results.

	Parameter Estimate	SE	p	Prevalence Ratio	95% CI
KPS	2.271	1.510	0.133	9.692	0.502-187.111
Weight Loss	-20.079	8766.763	0.998	0.000	0.000
Tumor Size	19.147	40192.970	1.000	206824883.8	0.000
Nephrectomy	-2.890	1.354	**0.033**	0.056	0.004-0.789
Metastasis	15.980	8610.441	0.999	8707569.707	0.000

on patients aged >75 years old increased to 7.4 times higher. Patients aged <50 years old have lowest risks of RCC-SM, that is 87% lower from patients aged 50-75 years old.[8] This result is not consistent with the result of this study, in which mortality rate of patients aged ≤ 50 years old was higher than patients aged > 50 years old, which is 86.4–75.0%.

Sex plays a role in increasing disease-specific survival (DSS) and OS on female rather than male patients. Female RCC patients shows a decrease of 25% of disease-specific mortality risks compared to male patients (Hazard Ratio (HR) 0.75).[9] This is in accordance with the result of this study, in which mortality rate on female patients was lower than the male patients, which is 71.4–87.5%.

KPS was the prognostic factor that plays a role in deciding the survival rate of RCC patients. Patients with lower KPS (< 80) had Risk Ratio (RR) 1.53x higher towards mortality than patients with KPS ≥ 80.[10] This is suitable with the result of this study, in which mortality rate in patients with KPS < 80 was higher than patients with KPS ≥ 80, that is 92.3–58.3%.

Patients that experienced weight loss was categorized as patients having constitutional symptoms. RCC patients with constitutional symptoms were associated with HR 1.9x higher towards mortality rate.[11] Weight loss ≥ 10% was also connected to faster progression (RR 2.028).[12] This is consistent with the result of this study, in which mortality rate of patients experiencing weight loss was higher than patients that did not lose their weight, that is 100–70.8%.

In this study, there was only one patient whose tumor was ≤ 10 cm and 37 patients whose tumor >10 cm. Mortality rate was higher on patients whose tumor >10 cm compared to patient whose tumor was ≤ 10 cm, that is 83.8–0%. Increase in tumor size was related to higher probability of metastasis and poorer OS. There was a significantly higher survival rate on patients with smaller tumors. DSS in 5 years was 86% for tumor <4 cm, 72% for tumor between 4-7 cm, 53% for tumor between 7-11 cm, and 32% for tumor >11 cm.[13]

Patients that did not undergo nephrectomy had RR 1.35 higher towards mortality than patients that underwent nephrectomy.[10] This is in accordance with the result of this study, in which mortality rate on patients than did not have nephrectomy was higher than patients who underwent nephrectomy, 95.0–66.7%. The advantage of nephrectomy was shown on patients with metastatic-RCC (mRCC), whose median OS was longer for patients that had nephrectomy, followed by interferon-α (IFN-α), compared to patients who were given only IFN-α (Flanigan et al, 2001: 11.1 months compared to 8.1 months; Mickisch et al, 2001: 17 months compared to 7 months).[14,15] However, the most effective and suitable immunotherapy post nephrectomy still could not be specified. The 5-year survival rate was reported to be 19.6% on interleukin-2 (IL-2) and 10% on IFN-α as adjuvant therapy post nephrectomy.[5]

Regional lymph node involvement was associated with increased mortality rate of RCC (Leibovich et al, 2003: 1.4x higher; Zisman et al, 2002: Relative Risk 2.1).[11,16] Patients with mRCC without involvement of regional lymph node had OS longer than patients having regional lymph node involvement (14.7 months compared to 8.5 months).[17] This is suitable with the result of this study, in which mortality rate of patients with regional lymph node involvement was higher than patients without, 92.9–75.0%.

Metastasis affected the CSS and OS of patients with RCC. Mortality rate was found higher on patients with metastasis compared to patients without (CSS HR 33.23 and OS HR 10.74).[18] This is consistent with the result of this study, in which mortality rate of patients with metastasis was higher than patients without, 100–73.1%.

The number of metastasis was related to OS and PFS. RR OS for patients with metastasis >1 compared to patients with 1 metastasis was 1.243.[19] Other similar studies showed poorer median and PFS on patients with metastasis >1 (HR 1.51).[20] This is not suitable with the result of this study, in which mortality rate of patients with metastasis > 1 was similar with patients whose metastasis ≤1.

A number of literatures reported that the location of the metastasis plays a bigger role in deciding the prognosis of mRCC; however, other studies reported that the number of metastasis has more prognostic value. Lung or bone metastasis only has HR 2.0 towards the mortality rate, compared to metastasis on other locations or multiple metastasis in patients with mRCC post nephrectomy and IL-2.[11] Median of survival rate on patients with mRCC and lung metastasis was shorter than patients with mRCC without lung metastasis,that is, 14.1 months compared to 16.1 months.[21] In this study, the

mortality rate of patients with lung metastasis was higher than patients without 100–77.4%.

OS on patients with bone metastasis was shorter than patients without (Négrier et al, 2002: RR 1.304; Atzpodien et al, 2003: HR 1.5; Donskov et al, 2005: HR 2.1).[19,22,23] In this study, the mortality rate of patients with bone metastasis was higher than patients without, 100–80%.

Patient with liver metastasis had poorer OS and PFS (RR 1.343 and RR 2.809).[19] Other literatures mentioned that the median OS was also shorter, that is 16.6 months compared to 7.5 months.[21] In this study, the mortality rate of patients with liver metastasis was higher than patients without, 100–78.1%.

Brain metastasis affected OS due to the possibility of spontaneous bleeding and widespread peritumoral edema, that needs surgery for decompression.[24] In this study, mortality rate of patients with brain metastasis was higher than patients without, 100–81.1%.

Some studies found that anemic patients had higher mortality rate (Motzer et al, 1999: RR 1.76; Négrier et al, 2002: OS RR 1.400, PFS RR 1.506; Donskov et al, 2005: HR 1.8; Heng et al, 2009: HR 1.744).[10,19,23,25] This is consistent with the result of this study, in which patients with anemia had higher mortality rate, 84.4–66.7%.

Prognostic potential of thrombocytosis had been reported in a number of studies. mRCC patients that underwent nephrectomy and adjuvant therapy with normal thrombocyte value had OS 64% better than patients with thrombocytosis.[26] Other studies found that mRCC patients with thrombocytosis had higher HR towards mortality rate (Suppiah et al, 2006: HR 1.65; Heng et al, 2009: HR 1.524)[25,27] This is suitable with the result of this study, in which patients with thrombocytosis had higher mortality rate than patients without, 83.3–78.6%.

In some studies, neutrophilia was related with higher mortality rate (Atzpodien et al, 2003: HR 1.9; Donskov et al, 2005: HR 2.0; Négrier et al, 2002: RR 1.403, PFS RR 2.132).[19,22,23] This is consistent with the result of this study, in which patients with neutrophillia had higher mortality rate than patients without, 83.3–78.6%.

Négrier et al, 2002, reported that increased ESR was associated with higher mortality rate (OS RR 1.694, PFS RR 1.671).[19] This is consistent with the result of this study, in which patients with ESR ≥ 100 had higher mortality rate than patients whose ESR was lower than 100, that is 100–81.1%.

According to a number of studies, ALP increase was connected with higher mortality rate (Négrier et al, 2002: RR 1.297; Escudier et al, 2007: HR 1.671).[19,20] This is suitable with the result of this study, in which patients with increased ALP had higher mortality rate than the patients without, that is 85.0–77.8%.

Previous studies mentioned that increase in LDH was associated with higher mortality rate (Motzer et al, 1999: RR 2.52; Mekhail et al, 2005: Median survival 3.4 compared to 15.8 months; Donskov et al, 2005: HR 5.4; Escudier et al, 2007: HR 1.681).[10,20,21,23] This is not consistent with the result of this study, in which patients with increase in LDH value had lower mortality rate than patients without, 76.7–100%.

Corrected kalsium was used to examine total serum calcium that binds with protein, where 80% bindswith albumin. A number of studies suggested that hypercalcemia was linked with higher mortality rate (Motzer et al, 1999: RR 1.7; Mekhail et al, 2005: Median survival 5.4 compared to 15.8 months; Escudier et al, 2007: HR 3.046; Heng et al, 2009: HR 1.893).[10,20,21,25] This is consistent with the result of this study, in which patients with hypercalcemia had higher mortality rate than patients without hypercalcemia, that is 90–78.6%.

Demographic and clinical factors that have significant relationship with mortality rate of renal cancer were KPS, weight loss, and nephrectomy. Meanwhile, there was no significant relationship between laboratory parameter and mortality rate. This study found that nephrectomy was the sole prognostic factor of renal cancer. Mortality rate was 0.056x lower on patients that underwent nephrectomy than on patients that did not have nephrectomy.

CONCLUSION

According to results and discussion in this study, we can conclude that demographic and clinical factors that have significant relationship with mortality rate of renal cancer were KPS, weight loss, and nephrectomy. Meanwhile, there was no significant relationship between laboratory parameter and mortality rate. Multivariate analysis conclude that nephrectomy was the sole prognostic factor of renal cancer. Mortality rate was 0.056x lower on patients that underwent nephrectomy than on patients that did not have nephrectomy.

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