SURVIVAL OF CERVICAL CANCER PATIENTS AT A REFERRAL HOSPITAL IN SOUTHERN SUMATRA, INDONESIA Ketahanan Hidup Pasien Kanker Serviks di Rumah Sakit Rujukan Sumatera Bagian Selatan, Indonesia

by Rico Januar

SURVIVAL OF CERVICAL CANCER PATIENTS AT A REFERRAL HOSPITAL IN SOUTHERN SUMATRA, INDONESIA

Ketahanan Hidup Pasien Kanker Serviks di Rumah Sakit Rujukan Sumatera Bagian Selatan, Indonesia

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ABSTRACT

Background: Cervical cancer is the second most common cancer and the third leading cause of death in Indonesia. **Purpose:** This study aims to identify the survival rate of cervical cancer patients and the prognostic factors that influence in a referral hospital in Southern Sumatra Indonesia. **Methods:** Cohort retrospective study using secondary data from medical records of cervical cancer patients from January 2014 until December 2016. Data of each patient was evaluated during 36-month period since the patients were firstly diagnosed with cervical cancer. Kaplan Meier curve was used to determine the survival rate and identify the proportional hazard asumpstion. Survival analysis was used by cox regression model to determine the survival rate and Hazard Ratio (HR). **Results:** There were 274 of 799 cervical cancer patients met the inclusion criteria. The 3-years survival rate for cervical cancer patients at survival rate was around 65%, and prognostic factors related to survival of cervical cancer patients with p value < 0.05 i.e. age (HR 0.50; 95%CI: 0.29-0.90), metastasis (HR 2.43; 95%CI: 1.28-4.61), and completeness of treatment (HR 7.23; 95%CI: 3.82-13.71. Complication was confounding factor in relation metastasis and survival rate. **Conclusion:** The 3-years survival rate for cervical cancer patients at Mohammad Hoesin Hospital Palembang (RSMH) was 65%. The prognostic factors for the survival rate were age, metastasis, and completeness treatment. It was very important for to adhere the therapy program recommended by doctors to increase the survival rate of cervical cancer patients.

ABSTRAK

Latar Belakang: *Kanker serviks merupakan penyakit kanker kedua terbanyak dan urutan ketiga penyebab kematian akibat kanker di Indonesia.* ***Tujuan:*** *Penelitian ini bertujuan untuk mengidentifikasi survival rate pasien kanker serviks dan faktor prognostik yang mempengaruhinya di rumah sakit rujukan wilayah Sumatra Bagian Selatan di Indonesia.* ***Metode:*** *Penelitian kohortretrospektf dengan*

data sekunder dari catatan rekam medis pasien diagnosa kanker serviks periode Januari 2014-Desember 2016. Data setiap pasien dievaluasi selama periode 36 bulan sejak pasien didiagnosis menderita kanker serviks. Digunakan analisis survival untuk mengetahui survival rate dan Hazard Ratio (HR) masing- masing variabel yang diteliti. **Hasil:** *Sebanyak 274 dari 799 pasien kanker serviks memenuhi kriteria inklusi. Survival rate 3 tahun adalah sekitar 65%, dan faktor prognostik yang berhubungan dengan ketahanan hidup pasien kanker serviks yang memiliki p value< 0.05 adalah usia (HR 0.50; 95% CI : 0.29-0.90), metastasis (HR2.43; 95% CI : 1.28-4.61), dan kelengkapan pengobatan (HR 7.23; 95% CI : 3.82-13.71).* **Kesimpulan:** *Survival rate 3 tahun bagi pasien kanker serviks di Rumah Sakit Mohammad Hoesin Palembang (RSMH) adalah 65%. Faktor-faktor prognostik yang mempengaruhi adalah usia, metastasis, dan kelengkapan pengobatan. Sangat penting bagi pasien kanker serviks untuk mematuhi semua program pengobatan yang dianjurkan dokter untuk meningkatkan survival rate.*

INTRODUCTION

The most common malignancy cancer associated with the Human Papillomavirus (HPV) Cervical was cervical cancer (Majidi et al., 2016), which was leading to high mortality in advanced stage (Li, Wu, & Cheng, 2016). One woman with cervical cancer died every 2 minutes, adding up to over 270.000 deaths globally per year (Siegel, Miller, & Jemal, 2018). The mortality and incidence rate of cervical cancer was higher in developing countries than developed countries (Cecilia, N.C. et al., 2017).

Cervical cancer was the fourth most types of cancer after breast cancer, colorectal cancer, and lung cancer, and the fourth cause of death in the world based on Global Burden Cancer (Globocan) in 2018 (Bray et al., 2018). Basic Health Research (Riskesdas) stated the prevalence of cancer in Indonesia increased (1.40 per 1000 population in 2013 to 1.79 in 2018), meanwhile the prevalence of cancer in South Sumatra was 1.54 per 1000 population (Kementerian Kesehatan RI, 2018). The 55% of non-communicable diseases existed in the population in South Sumatra was about cervical cancer (Sumsel, 2016).

Knowing the survival rate and the prognostic factors of cervical cancer could have an impact to improve the quality of life of cervical cancer in the consideration of primary efforts must be done by the community and secondary prevention efforts must be available in treatment program of cervical cancer patients in hospital. Studies about cervical cancer were mostly focused on predisposing factors while those related to survival of cervical cancer patients were still limited. A survival analysis was used to identify the probability survival by doing modeling factors that influenced the survival rate of cervical cancer patients (Afifah & Purnami, 2016). This study aimed to identify the prognostic factors and analyze the 3-year survival rate of cervical cancer patients at Mohammad Hoesin Hospital Palembang (RSMH) as a referral hospital in Southern Sumatra of Indonesia.

METHODS

This study was retrospective cohort study. The inclusion criteria were the patient with the main diagnosis based on ICD-10 was C53.9, the patient had complete medical records and no part of the study was lost. The number of samples successfully collected were 274 of 799 patients diagnosed with cervical cancer during January 2014-December 2016 period at Mohammad Hoesin Hospital Palembang, Southern Sumatra. This study was approved by the Health Research Ethics Committee of the Faculty of Public Health, Sriwijaya University (No: 290/ UN9.1.10/ KKE/2019) and the consent was waived due to the nature of the retrospective study.

The data in this study were collected by examining the contents of the medical record, and then fulfilling the instrument of data collecting modified by author about the variables studied in

terms of demographics (age and education), frequency of labor (parity), disease (histopathological type, metastasis, complication, and completeness of therapy), survival time (which was calculated since the patient first diagnosed as cervical cancer until the end of observation, calculated in units of months), and survival status. It was categorized as event if the patient died during the observation period, and categorized as sensor if the patient was still alive, loss to follow, or died without cervical cancer disease during the observation period.

Statistical Analysis

Data were analyzed with SPSS 16 program by using survival analysis. The Kaplan Meier curve could identify the survival time, median survival, and decide whether they met the Proportional Hazard (PH) assumption. If they met the PH assumptions, bivariate analysis with cox regression could be done to identify the relationship between the independent variable and the patient's survival based on Hazard Ratio (HR) and Confidence Interval (CI) of each independent variable. P value <0.05 was used to state the significance of statistical relationship. All variables that had p value <0.25 in the bivariate analysis would be included in the multivariate analysis. In addition, if variables did not meet the assumptions, but theoretically important they would be included in the multivariate analysis. Multivariate analysis was performed using Time Independent Cox Regression.

Statistically, the predictor variables included in the cox regression modeling analysis were those had statistically significant relationship with cervical cancer survival (p value <0.05). The changes of Hazard Ratio (HR) were determined by multivariate analysis. It was considered as a confounding factor if there was the difference of HR >10%.

RESULTS

The results of this study showed there were 52 patients (18.98%) died (stated as event cases), and 222 patients (81.02%) as sensor cases. Sensor cases in this study included 47 patients (17.15%) alive and 175 patients (63.85%) loss to follow.

Table 1 illustrated characteristics of patients based on socio-demographic and clinical factors, number of death events and survival rate of each independent variable. Patients who visited Mohammad Hoesin Palembang mostly came from outside Palembang city where the hospital is located (63.90%), 53.60% of patients were ≥49 years old, the level of education was mostly under or equal to Junior High School (53.60%), and 59.10% of patients was at the stage III of cervical cancer. Median survival in this study was not obtained because the overall survival rate of cervical cancer patients was around 65%. It meant that during the 36 months observation period, 65% of cervical cancer patients did not experience a death event. The high value of survival rate must be considered by reason 81.02% of cervical cancer patients were sensors. The lowest survival rate was influenced by cervical cancer patients with incomplete therapy, around 35% (Table 1).

Figures 1-4 showed that survival rate were lower for patients with age under to 49-years old, patients with education lower or equal to Junior High School, patients with complications, and patients with incomplete therapy. The median survival for stage IV metastasis, complication and incomplete therapy patients were around 25 months, 30 months and 22 months respectively. Commonly, there was the decreased of survival rate by increasing time.

The result of bivariate and multivariate analysis using the cox model was described in Table 2. The results of bivariate analysis showed that age was a protective factor (HR 0.50; 95% CI: 0.29-0.87), and there was no statistically significant relationship between education level and survival of cervical cancer patients (p value 0.07) (Table 2).

The stage of cancer was added in multivariate analysis because its importance in survival of cervical cancer patients. However, the final model showed the variables related to survival rate of cervical cancer patients were age, metastasis, and completeness of therapy (Table 2) and complication was confounding variable for the relationship between metastasis and survival rate of cervical cancer.

Table 1.
Socio-demographic and Clinical Characteristics of Cervical Cancer- RSMH 2014-2016

| Characteristic	Amount of Samples		Amount of Event		Survival Rate (%)
	n	%	n	%	
Age (years)					
≥49	147	53.60	21	14.30	75
<49	127	46.40	31	24.40	55
Education					
≤ Junior High School	147	53.60	32	11.80	60
≥ Junior High School	127	46.40	20	15.70	70
Recidence					
Out Palembang	175	63.90	39	22.30	60
In Palembang	99	36.10	13	13.10	80
Parity					
Grandepara	64	23.40	10	15.60	70
Multipara	188	68.60	38	20.20	65
Nullipara	22	8.00	4	18.20	75
Stage					
Stage IV	10	3.70	3	30.00	40
Stage III	162	59.10	32	19.80	60
Stage II	63	23.00	11	17.50	70
Stage I	39	14.20	6	15.40	80
Type of Histopatology					
Squamosa cell carcinoma	226	82.50	39	17.30	65
Adeno carcinoma	33	12.00	8	24.20	60
Other type	15	5.50	5	33.30	62
Metastasis					
Yes	69	25.20	20	29.00	50
No	205	74.80	32	15.60	70
Complication					
Yes	140	51.10	37	16.40	50
No	134	48.90	15	11.20	85
Completeness of therapy					
Incomplete	131	47.80	37	28.20	35
Complete	143	52.20	15	10.50	80
Total	**N samples = 174**	**100%**	**N event =52**	**100%**	
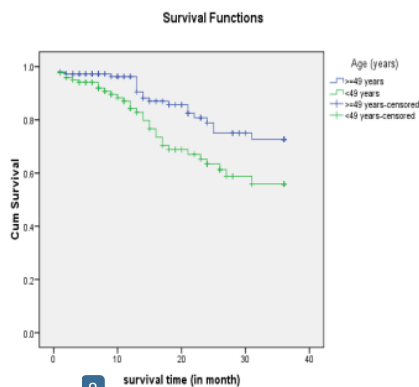
Figure 1. Kaplan-Meier survival curves for cervical cancer patients according to age
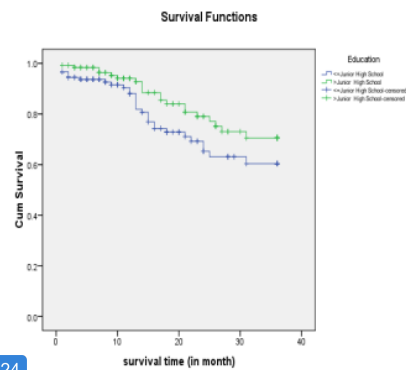
Figure 2. Kaplan-Meier survival curves for cervical cancer patients according to education

Survival Functions
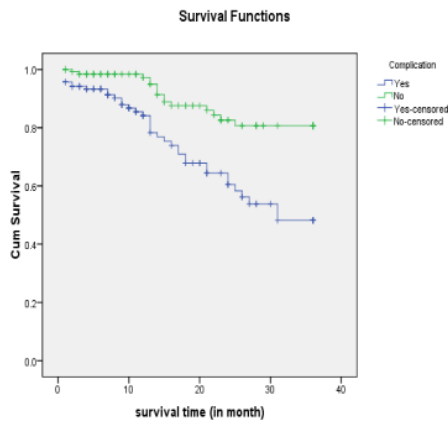
Figure 3. Kaplan-Meier survival curves for cervical cancer patients according to complication

Survival Functions
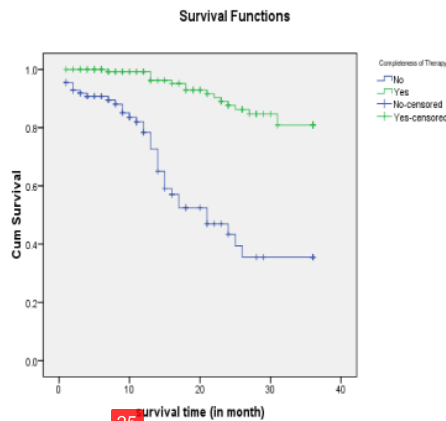
Figure 4. Kaplan-Meier survival curves for cervical cancer patients according to completeness of therapy

DISCUSSION

The results of this study indicated the survival rate of cervical cancer patients was about 65% and the prognostic factors influenced the survival of cervical cancer patients were age, metastasis, and completeness of therapy. The survival rate in this study was higher than other developing countries such as India (60,5%) (Jayant et al., 2016), but it was lower than developed countries such as Brazil 84% (Carneiro et al., 2017). This high survival rate must be observed because most of the samples in this study were loss to follow cases (63.85%) in which the patients might be lived or died.

The survival rate based on age showed the <49-years- cervical cancer patients had the lower survival rate than the ≥49-years cervical cancer patients, with p value 0.02 (HR 0.51; 95% CI: 0.29-0.90). It was contradicted with a studies in India, where it found the ≤ 50 years-cervical cancer patients had a higher survival rate compared to the >50 years-cervical cancer patients (79.20 and 77.10%, respectively) (Balasubramaniam et al., 2020). It showed that cervical cancer mortality rates increased with age. Even though, the period effect may be the key factor affecting cervical cancer mortality trends, so it was needed the immediate implementation of screening and effective treatment (Wang, Bai, Gao, Zhang, & Zhang, 2021). The time recommended to start the cervical cancer screening was the age of 30 with a repetition of every five years and continuing until the age of 69 (Khodakarami, Farzaneh, Yavari, & Akbari, 2016). Cervical cancer was one type of cancer that could be prevented by safe, simple, and inexpensive methods (Cecilia, N.C. et al., 2017) by giving a vaccine against HPV virus (Majidi et al., 2016).

The low survival rate of <49 years- cervical cancer patients compared to ≥49 years-cervical cancer patients may be caused those ≥49 years-cervical cancer patients, who were non-productive age, were not to go to seek regular medical treatment to hospitals or health facilities for various reasons based on the result of this study, including living far from hospital, low education level, advanced cancer stage (stage III and IV), having many complications with low hope of recovery. These reasons made the high of loss to follow up cases and provided an overview of most deaths patients occurred in the age <49 years (31 of 52 patients).

The factors influencing the prognosis of cervical cancer were not only aging as one of sociodemografic characteristics, but also clinical condition, such as stages at diagnosis, and clinical treatment information (Xie et al., 2020). The favourable prognosis was dued to the detection of early stage cancer by screening combined with adequate treatment, in which the 5- years survival of stage IA patients was 95,10% and stage IV patients was 5.30%; the HR of death for stage I and IA and IV disease were 1.00 and 28.60 (95% CI : 13.70-59.80) (Jayant et al., 2016).

Table 2
Bivariate and Multivariate Analysis using the Cox Model

Variables	Bivariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)						
<49	0.50	0.29-0.87	0.01	0.51	0.29-0.90	0.02
≥49						
Education						
≤ Junior High School	0.60	0.34-1.05	0.07			
>Junior High School						
Metastasis						
Yes	0.39	0.22-0.69	0.00	2.43	1.28-4.61	0.00
No						
Complication						
Yes	3.21	1.76-5.86	0.00	1.83	0.93-3.57	0.07
No						
Completeness of therapy						
Incomplete	6.67	3.60-12.36	0.00	7.23	3.82-13.71	0.00
Complete						

The majority stage of cervical cancer patients was advanced stage (63.80%), in which the highest proportion was stage III (59.10%). Patients could presented complication as the disease progress, include pain, ureteric obstruction causing renal failure, hemorrhage, lymphedema, and fistulae (Bhatla, Aoki, Sharma, & Sankaranarayanan, 2018). In this study, the cervical cancer patients with complication were 51.10%. Cervical cancer was a cancer that had a high level of success dued to down-staging, early detection, and improved compliance for completion of treatment and follow up (Balasubramaniam et al., 2020). This data showed the possibility of low awareness of patients to early check up and to seek treatment regularly.

The median survival for stage IV was 25 months, based on the stage of cervical cancer. This study showed the level of stage was inversely proportional to the survival rate. It was in line with other studies (Jayant et al., 2016; Balasubramaniam et al., 2020;   Nuranna & Fahrudin, 2019; Melan et al., 2017).

Patients with metastasis in this study were 25.20% and the median survival for metastasis was 25 months.   The multivariate analysis found that complication was confounding factor for the relationship between metastasis and survival of cervical cancer patients. There were 2-types of metastasis related to the choice of therapy and survival rate, namely hematogenous metastasis and lympatic metastasis (Li, Wu, et al., 2016). The survival rate of cervical cancer patients without metastasis is much higher than the patients with metastasis (81.50%) and there was a relationship between metastasis and survival of cervical cancer patients (Carneiro et al., 2017). The cervical cancer was a disease having worse or becoming metastatic, both hamatogenous metastasis and lympatic metastasis, however   it could be prevented by giving a vaccine (Li, Wu, et al., 2016).

A striking difference in the survival rate of cervical cancer patients with complete and incomplete therapy could be seen in Kaplan Meier curve, in which patients with complete therapy had a   80%-survival rate, while patients with incomplete had 30%- survival rate. The incomplete therapy patients had   22-months median survival. The multivariate analysis showed cervical cancer patients with incomplete therapy had 7.23 times more likely to die than them with complete therapy. The therapy program for cervical cancer   patient was   determined individually based on the stage, risk factors, anatomic pathology result, and the general condition of the patient (Kementerian Kesehatan RI, 2016). Some experts continuously evaluated therapy options for cervical patients. There were many therapies for cervical cancer, such as surgery,   radiotherapy,   chemotherapy,   a combination of radiotherapy and chemotherapy, palliative care, and supportive care, but there was no term of the superior therapy to other. (Li, Wu, et al., 2016).

Chemotherapy   was   well-tolerated   and efficient therapy for lymphatic metastases. Combination chemotherapy and/ or surgery was an

option for distant metastases, such as resistant lung metastases. Chemoradiotherapy was the optimal option for stage IVB. Chemotherapy and bone irradiation were an option for bone metastases Surgery and in combination with radiotherapy were for brain metastases (Li, W, & Cheng, 2016). Another study at an advanced stage found that chemotherapy with cisplatin and paclitagxel regimens was still the main choice, but with the addition of bevacizumab it could increase patient survival rates (Fuentes & Garcia, 2016). It can be said suppress the development of cancer and for better survival, multimodal therapy was needed, according to the patient's symptoms and health conditions, and patient compliance in carrying out treatment actions according to the doctor's program.

The effect of residence on survival was most likely related to access for cancer screening and treatment program (Melan et al., 2017). In this study, it showed the majority of cervical cancer patients did not live in Palembang city (63.9%). Further studies were needed to investigate the relations between location of residence and survival of cervical cancer patients.

CONCLUSION

The 3-years survival rate for cervical cancer patients at a referral hospital Mohammad Hoesin Hospital Palembang (RSMH) was 65%. The prognostic factors for the survival rate were age, metastasis, and completeness treatment. Complication was confounding factor for the relationship between metastasis and survival of cervical cancer patients It was very important for to adhere the therapy program recommended by doctors to increase the survival rate of cervical cancer patients.

CONFLICT OF INTEREST

The authors affirm no conflict of interest in this study

AUTHOR CONTRIBUTION

ZZ : Designed the study, collected data, analyzed and interpreted data, wrote draft and revised manuscript

RJ : Designed the study, reviewed the methodology, participated to draft the article and suggest important intelectual content

RF : Designed the study, reviewed the methodology, participated to draft the article and suggest important intelectual content

All authors gave final approval of the version published.

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27 Chen, Chao-Yu, Chyong-Huey Lai, Kuan-Der Lee, Shih-Hao Huang, Yen-Mei Dai, and Min-Chi Chen. "Risk of second primary malignancies in women with cervical cancer: A population-based study in Taiwan over a 30-year period", Gynecologic Oncology, 2012.
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