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ORIGINAL RESEARCH

THE THREE-YEAR SURVIVAL RATE OF CERVICAL CANCER PATIENTS AT REFERRAL HOSPITAL IN SOUTHERN SUMATRA, INDONESIA

Tingkat Kelangsungan Hidup Tiga Tahun Pasien Kanker Serviks di Rumah Sakit Rujukan, Sumatera 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 3-year survival rate of cervical cancer patients and its prognostic factors 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 for 36 months since the patients were firstly diagnosed with cervical cancer. Kaplan Meier curve was used to determine the survival rate and identify the proportional hazard assumption. The Cox regression model was utilized to determine the survival rate and Hazard Ratio (HR). Results: There were 274 of 799 cervical cancer patients who met the inclusion criteria. The 3-year survival rate for cervical cancer patients at survival rate was around 65%, and prognostic factors related to the survival of cervical cancer patients with p-value <0.05, i.e. age (HR=0.51; 95%CI=0.29-0.90), metastasis (HR=2.43; 95%CI=1.28-4.61), and completeness of therapy (HR=7.23; 95%CI=3.82-13.71. The complication was a confounding factor with metastasis and survival rate. Conclusion: The 3-year 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 therapy. It was essential for cervical cancer patients to adhere to the therapy program

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recommended by doctors to increase the survival rate.

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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 tingkat kelangsungan hidup (survival rate) 3 tahun pasien kanker serviks dan faktor prognostiknya di rumah sakit rujukan wilayah Sumatra Bagian Selatan di Indonesia. Metode: Penelitian kohort retrospektf 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. Kaplan Meier 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=0.51; 95% CI=0.29-0.90), metastasis (HR=2.43; 95% CI =1.28-4.61), dan kelengkapan pengobatan (HR=7.23; 95%CI=3.82-13.71). Kesimpulan: Tingkat kelangsungan hidup (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 vang dianjurkan dokter untuk meningkatkan ketahanan hidupnya.

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INTRODUCTION

The most common malignancy cancer associated with the Human Papillomavirus (HPV) was cervical cancer (Majidi et al., 2016), which leads to a high mortality rate in the advanced stage (Li, Wu, & Cheng, 2016). One woman with cervical cancerdies every 2 minutes, increasing 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 in developed countries (Cecilia, Rosliza, & Suriani, 2021).

Cervical cancer was the fourth most type 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). Ministry of Health RI (2018) stated the prevalence of cancer in Indonesia increased (from 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. The 55% of non-communicable diseases that existed in the population in South Sumatra was cervical cancer (South Sumatera Health Office, 2016).

Knowing the survival rate and prognostic factors of cervical cancer can have an impact on improving the quality of life of cervical cancer. This can be considered with the community's primary efforts, and secondary prevention efforts must be available in the treatment program of cervical cancer patients in hospitals. Studies about cervical cancer mainly were focused on predisposing factors, while those related to the survival of cervical cancer patients were still limited. Survival analysis was used to identify the probability of survival by modelling factors that influenced the survival rate of cervical cancer patients (Afifah & Purnami, 2016). This study

aimed to determine 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 South Sumatra, Indonesia.

METHODS

This study was a retrospective cohort study. The inclusion criteria were the patient with the primary diagnosis based on ICD-10 was C53.9, the patient had complete medical records, and no part of the study was lost. The samples successfully collected were 274 of 799 patients diagnosed with cervical cancer during January 2014-December 2016 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). The consent was waived due to the nature of the retrospective study.

In this study, the data were collected by examining the contents of the medical record and then completing the data collection instrument modified by the researcher regarding the variables. The variables themselves include age (≥ 49 years and <49 years), education (the formal education of the patient), parity (the number of times the patient gave birth to a baby), histology type (based on the result of the anatomical pathology examination), metastasis (spread of cancer from the initial site to other places in the body), complication (worsening condition due to cervical cancer), completeness of therapy (compliance of the patient to carry out all her cervical cancer treatment programs), 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 an event if the patient died during the observation period. It was categorized as a sensor during the observation period if the patient was still alive, lost to follow, or died without cervical cancer disease.

Parity was the number of times the patients have given birth to a baby. It was categorized into three groups, namely grand multipara (given birth more or equal to 5 times), multipara (given birth 2-4 times), and primipara/ nullipara (for the patients gave birth once or never). The staging classification in this study adapted the FIGO (The International Federation of Gynaecology and Obstetrics) system, which is divided into four levels broadly. The higher the stage, the wider the spread of cancer. There was much histology of cervical malignancy. The predominant ones were squamous cell carcinoma and adenocarcinomas. The other histologies, such as small cell carcinoma, melanoma, and lymphoma, were included as different histology types. Each patient had a cervical cancer treatment program according to the patient's condition and disease. This study categorized the completeness of therapy if the patient underwent and adhered to the treatment program, which can be surgery, radiation therapy, and/ or chemotherapy.

Statistical Analysis

Data were analyzed by using survival analysis. The Kaplan Meier curve could identify the survival time and median survival and decide whether they met the Proportional Hazard (PH) assumption. If they met the PH assumptions, the next step was continued by Cox regression to identify the relationship between the dependent variables and the patient's survival based on the Hazard Ratio (HR) and Confidence Interval (CI) of each independent variable. P-value <0.05 was used to state the significance of the statistical relationship. All variables with p-value <0.25 would be included in the final modelling analysis. In addition, if variables did not meet the assumptions but are theoretically important, they also would be included in the last modelling statistics by using Time Independent Cox Regression. The Hazard Ratio (HR) change>10% was considered a confounding factor.

RESULTS

The results of this study showed there were 52 patients (18.98%) who died, 48 patients (17.52%) alive and 174 patients (63,50%) lost to follow up. Table 1 s patients' characteristics based on sociodemographic and clinical characteristics the number of death events, and the survival rate of each independent variable. Most patients who visited Mohammad Hoesin Palembang came from outside Palembang city, where the hospital is located (63.87%). Then, 53.60% of patients were \geq 49 years old, the level of education was mostly under or equal to Junior High School (53.65%), and 59.13% of patients were at 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%. During the 36 months observation period, 65% of cervical cancer patients did not experience a death event. The high-value survival rate must be considered because 81.02% of cervical cancer patients were sensor. The lowest survival rate was influenced by

cervical cancer patients with incomplete therapy, around 35% (Table 1).

Figures 1-4 showed that survival rates were lower for patients 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 insufficient therapy patients were around 25 months, 30 months, and 22 months. Commonly, there was a decrease in the survival rate by increasing time.

Table 2 shows the relation between the dependent and independent variables and the cox model analysis. The results 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 1.

Socio-demographic and Clinical Characteristics of Cervical Cancer- RSMH 20)14-2016
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	Amount						Total		Commission
Characteristic	Died		Ali	Alive		Loss to follow up		Jiai	Survival $\mathbf{D}_{oto}(0)$
	n	%	n	%	n	%	Ν	%	Rate (%)
Age (years)									
≥49	21	14.29	31	21.09	95	64.62	147	53.65	75.00
<49	31	24.41	17	13.39	79	62.20	127	46.35	55.00
Education									
\leq Junior High School	32	21.77	21	14.29	94	63.94	147	53.65	60.00
> Junior High School	20	15.75	27	21.26	80	62.99	127	46.35	70.00
Residence									
Out Palembang	39	22.29	24	13.71	112	64.00	175	63.87	60.00
In Palembang	13	13.13	24	24.24	62	62.63	99	36.13	80.00
Parity									
Grand Multipara	10	15.63	12	18.75	42	65.62	64	23.36	70.00
Multipara	38	20.21	33	17.55	117	62.24	188	68.61	65.00
Primipara/ Nullipara	4	18.18	3	13.64	15	68.18	22	8.03	75.00
Stage									
Stage IV	3	30.00	1	10.00	6	60.00	10	3.65	40.00
Stage III	32	19.75	20	12.35	110	67.90	162	59.13	60.00
Stage II	11	17.46	15	23.81	37	58.73	63	22.99	70.00
Stage I	6	15.38	12	30,77	21	53.85	39	14.23	80.00
Type of Histology									
Squamosa cell	39	17.26	36	15.93	151	66.81	226	82.48	65.00
carcinoma									
Adeno carcinoma	8	24.24	7	21.21	18	54.55	33	12.04	60.00
Other type	5	33.33	5	33.33	5	33.33	15	5.48	62.00
Metastasis									
Yes	20	28.98	7	10.15	42	60.87	69	25.18	50.00
No	32	15.61	41	20.00	132	64.39	205	74.82	70.00
Complication									
Yes	37	26.43	16	11.43	87	62.14	140	51.09	50.00
No	15	11.19	32	23.88	87	64.93	134	48.91	85.00
Completeness of therapy									
Incomplete	37	28.25	7	5.34	87	66.41	131	47.81	35.00
Complete	15	10.49	41	28.67	87	60.84	143	52.19	80.00
Total	52	18.98	48	17.52	174	63.50	274	100.00	

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

DISCUSSION

This study indicated that the survival rate of cervical cancer patients was about 65%. The prognostic factors influencing the survival of cervical cancer patients were age, metastasis, and completeness of therapy. The survival rate in this study was higher than in other developing countries such as India (60.50%) (Jayant et al., 2016). Still, 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 the current study were lost to follow-up cases (63.5%) in which the patients might have lived or died.

The survival rate based on age showed that <49-years- of cervical cancer patients had a lower survival rate than those >49-years of cervical cancer patients, with a p-value of 0.02 (HR 0.51; 95% CI: 0.29-0.90). It was contradicted by a study in India, which found that ≤ 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 critical factor affecting cervical cancer mortality trends, it was needed the immediate implementation of screening and effective treatment (Wang, Bai, Gao, Zhang, & Wang, 2021). The time recommended for starting the cervical cancer screening was 30 with a repetition of every five years and continuing until 69 (Khodakarami, Farzaneh, Yavari, & Akbari, 2016). Cervical cancer is one type that could be prevented by safe, simple, and inexpensive methods by giving a vaccine against the HPV virus (Cecilia et al., 2021; 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 nonproductive age, were not go to seek regular medical treatment to hospitals or health facilities for various reasons based on the result of this study. It includes living far from the hospital lived outside Palembang), a low (63.87%) education level (53.65% ≤Junior High School), and an advanced cancer stage (59.13% of patients were stage III), 51.09% of patients having complications due to cervical cancer. These reasons made the high loss follow up cases and provided an overview of most deaths patients occurred in the age <49 years (31 of 52 patients).



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



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



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

The factors influencing the prognosis of cervical cancer were ageing as one of the sociodemographic characteristics, clinical characteristics, such as stages at diagnosis, and clinical treatment information (Xie et al., 2020). The favorable prognosis was due 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 were 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).

The majority stage of cervical cancer patients was the advanced stage (62.78%), in the highest proportion was stage III (59.13%). Patients could be presented with complications as the disease progresses, including pain, ureteric obstruction causing renal failure, hemorrhage, lymphedema, fistulae (Bhatla, Aoki. Sharma. and & Sankaranarayanan, 2018). In this study, the cervical cancer patients with complications were 51.09%. Cervical cancer was highly successful due to down-staging, early detection, and improved compliance for completion of treatment and followed up (Balasubramaniam et al., 2020). This data showed the possibility of low awareness of patients to early check-ups and seeking treatment regularly.

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

Patients with metastasis in this study were 25.18%, and the median survival for metastasis was 25 months. The cox model analysis found that complication was a confounding factor in the relationship between metastasis and survival of cervical cancer patients. There were 2-types that were related to the choice of therapy and survival namely hematogenous and lymphatic rate. metastasis (Li et al., 2016). The most common metastatic site was the lungs, which had a similar prognosis to other single metastatic sites (Zhou & Peng, 2020). The survival rate of cervical cancer patients without metastasis is much higher than that of patients with metastasis (81.50%). There was a relationship between metastasis and survival of cervical cancer patients (Carneiro et al., 2017). The cervical cancer is a disease having worse or becomes metastatic, both hematogenous metastasis and lymphatic metastasis, however, it could be prevented by giving a vaccine (Li et al., 2016).

A striking difference in the survival rate of cervical cancer patients with complete and incomplete therapy could be seen in the Kaplan Meier curve. Patients with full therapy had an 80%-survival rate, while patients with incomplete had 30%-survival rate. The incomplete therapy patients had a 22-months median survival. The cox model analysis showed that cervical cancer patients with incomplete therapy were 7.23 times more likely to die than complete therapy. The therapy program for cervical cancer patients was determined individually based on the stage, risk factors, anatomic pathology result, and the patient's general condition (Komite penanggulangan kanker nasional, 2015).

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. Still, there was no term of the superior therapy to others. 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. Chemo-radiotherapy 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 et al., 2016).

Table 2

Variables	The relation Indep	between Deper bendent Variab	ndent and le	The Final Analysis		
	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						
\leq 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						

Another study at an advanced stage found that chemotherapy with cisplatin and paclitaxel regimens was still the primary choice, but the addition of bevacizumab could increase patient survival rates (Fuentes & Garcia, 2016). It can be said to suppress the development of cancer. 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 to cancer screening and treatment programs (Melan et al., 2017). This study showed that most cervical cancer patients did not live in Palembang city (63.987%). Further studies were needed to investigate the relationship between residence location and cervical cancer patients' survival.

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 of therapy. Complication was a confounding factor in the relationship between metastasis and survival of cervical cancer patients. It was imperative to adhere to 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 CONTRIBUTIONS

ZZ: Designed the study, collected data, analyzed and interpreted data, and wrote a draft and revised manuscript. RJ: Designed the study, reviewed the methodology, participated in drafting the article and suggested important intellectual content. RF: Designed the study, reviewed the methodology, participated to prepare the article and suggested important intellectual content. All authors gave final approval of the version published.

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