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Survival analysis of cervical cancer patients at Wangaya Hospital, Bali Province, Indonesia

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ABSTRACT

Background and purpose: In Indonesia, cervical cancer has the second-highest prevalence of cancer cases after breast cancer. This study aims to determine the survival rate and to explore factors that affect the survival of cervical cancer patients at Wangaya Hospital, Denpasar, Bali.

Methods: This was a retrospective cohort study. The samples were 165 cervical cancer patients who started therapy at Wangaya Hospital between 2016 – 2021 and met the research criteria. The variables retrieved from medical record were age, employment status, marital status, education level, parity, stage of cancer, type of treatment, comorbidities and time to event of death. Data were analyzed using Kaplan Meier, Log-rank test, and Cox Proportional Hazard.

Results: The result shows the cervical cancer survival rate during the period of study is 67.27% with the average of follow up time was 38.4 months and a mortality rate was 7.2/1000 person months (IR=0.007). From a total of 165 patients who were sampled, 54 patients died (32.73%). Based on the results of the Cox Proportional Hazard model, it was found that the factors significantly affected the death of cervical cancer patients at Wangaya Denpasar Hospital were older age (HR=1.06; 95%CI: 1.03–1.08; p<0.001), patients who were employed (HR=2.32; 95%CI: 1.24–4.33; p=0.008), at stage 1 cancer (HR=3.94; 95%CI: 1.07–14.49; p=0.039), stage 2 (HR=5.86; 95%CI: 1.50–22.78; p=0.011), stage 3 (HR=11.73; 95%CI: 3.15-43.56; p<0.001), stage 4 (HR=18.95; 95%CI: 4.33-82.91; p<0.001) and had comorbidities (HR=2.11; 95%CI: 1.12-3.99; p=0.021).

Conclusion: The survival of cervical cancer patients at Wangaya Hospital is quite good and needs to be improved. To increase patient survival, appropriate treatment is needed, especially in patients who have comorbidities and older age. Screening efforts also need to be improved to find cases at earlier stages.

Keywords: survival analysis, cervical cancer, cox proportional hazard

INTRODUCTION

Cervical cancer is a cancerous growth that appears in the cervix, the area of the uterus closest to the vagina. This cancer usually affects women aged 35-55 years because this age is the peak reproductive age in women.[1] This cancer is the fourth most common cancer in women in the world. In 2020 an estimated 604,000 women worldwide will be diagnosed with cervical cancer and 341,000 of them will die.[2] In Indonesia, cervical cancer is a cancer with the second-highest prevalence of cases after breast cancer. According to Globocan 2020, the number of new cervical cancer cases in Indonesia was about 36,633 people (17.2%) with a mortality of 21,003 (9.0%).[2] In Bali Province, cervical cancer is one of non-communicable diseases which the incidence rate tends to increase. The 2018 Basic Health Research (*Riskesdas*) stated that the prevalence of cervical cancer in Bali was 2.3 per mile, this figure increased compared to Riskesdas 2013 which was 2.0 per mile. In Denpasar, the capital city of Bali, out of a total of 5,255 women who took the visual inspection with acetic acid (VIA) test, 81 (1.5%) of them had positive results.[3]

The ratio of patients who survive to the total number of patients after receiving therapy for a predetermined amount of time is one of the factors that may be used to measure the effectiveness of cervical cancer treatment. A study conducted in Yogyakarta found the five-years survival rate for patients after treatment was 69.4%.[4] The survival of cancer patients is affected by factors, such as age, education, marital status, type of treatment, stage, and complication.[5-8] In addition, there is a strong correlation between the quality of life of cervical cancer patients and family support since this population may experience emotions of hopelessness while receiving treatment and will thus require family support to alleviate their discomfort, lack of confidence, stress, and anxiety.[9] The anxiety of cancer patients affects how their treatments are administered and has a detrimental influence on their chances of survival.[10]

Research related to the survival of cervical cancer patients has been carried out in Indonesia, such as a study conducted at dr. Sutomo Surabaya Hospital. A study by Riyandianci in 2017 with Stratified Cox Regression analysis found that the factors that influence cancer survival is complicated.[7] Meanwhile, Afifah (2016) with the Cox Extended Regression analysis found that factors which influence the survival of cervical cancer patients are the stage of cancer, type of treatment, and complications.[5] Then Khoiri's research in 2018 with Survival Least Square-SVM analysis found age, stage of cancer, complications, and type of treatment affected the survival of cervical cancer patients.[11] Even with the same research setting, differences in research result are assumed to occur due to differences in data result and data analysis performed.

Wangaya Hospital is one of the cervical cancer referral hospitals in Bali Province. Based on data obtained from the Wangaya Hospital, there were 90 new cervical cancer patients being treated at this hospital in 2021. This number has increased compared to 2016, where there were a total of 59 new patients. Research related to the survival of patients with cervical cancer has never been conducted in this hospital. This research aims to determine the factors that impact the survival of patients with cervical cancer at Wangaya Hospital. The result of this study can be used by hospitals and cancer therapy services as a reference in improving services and treatment of cervical cancer patients so that patients survival increases.

METHODS

This is a retrospective cohort study conducted in cervical cancer patients at Wangaya Hospital, in Bali Province, Indonesia. The population in this study were all cervical cancer patients who were treated at Wangaya

Hospital. The sample consisted of patients diagnosed with cervical cancer at Wangaya Hospital between 2016 and 2021 who met the research criteria. The inclusion criteria for this research were cervical cancer patients who had initial therapy between 1 January 2016 - 31 January 2021, while the exclusion criteria were patients having more than 50% incomplete medical information. Based on medical record data, there were 248 patients treated and 165 of them met the research criteria. The sampling method used is total population sampling and observation of the samples were conducted until 31 January 2022.

The data used in this study are secondary data obtained from extraction of the medical records of cervical cancer patients at Wangaya Hospital which includes age, employment status, marital status, education level, parity, stage of cancer, type of treatment, comorbidities, time of diagnosis and time of death. Education variable was categorized into high (above junior high school) and low education (≤junior high school), marital status was categorized into married and not married, employment status was also divided into working and not working, parity was categorized into nullipara, primipara, multipara and grand multipara. The cancer stages were categorized into stages 0, 1, 2, 3 and 4, then the therapy types were categorized into targeted therapy, PRC transfusion and surgery, while the comorbidities were categorized into none and with comorbidities. The time variable was measured starting from being diagnosed with cervical cancer until death or censoring occurs in months of observation. Censor status was seen from no event until the end of observation, lost to follow up (dropped out of treatment and moved for treatment to another hospital). From these data, there were no lost to follow up data.

The data analysis was including descriptive analysis, Kaplan Meier, Log-rank test and Cox Proportional Hazard Regression. The Kaplan Meier test was performed to see the survival rate of patients while Log-rank test was performed to see the difference of survival for each variable. Factors that affect the survival of cervical cancer patients at Wangaya Hospital were analyzed by Cox Proportional Hazard with backward method selection. Variables with a p-value <0.25 would proceed to multivariable analysis.[12]

This research was approved and declared ethically feasible by the Ethics Commission at Wangaya Denpasar Hospital with grant number 066/V.6/KEP/RSW/2022 issued on June 6, 2022.

RESULT

Characteristics of the samples

The results of the descriptive analysis of cervical cancer patients in Table 1 show that the average age of the sample was 49 years. Most of the samples in this study had a high level of education (81.21%), more than half of the samples (67.88%) were married, 52.72% were employed, and 56.97% of the samples had multipara parity status. From a total of 165 patients who initially treated at Wangaya Hospital between 1 January 2016 - 31 January 2021 and met the research criteria, 54 patients (32.73%) died during the 72 months observation period (1 January 2016 - 31 January 2022).

A total of 40 patients (24.24%) were diagnosed with stage 3 at the start of treatment. The most common type of treatment given to cervical cancer patients is targeted therapy (66.67%). Targeted therapy is a type of treatment by administering drugs or substances that can attack cancer cells. From a total of 165 patients who were sampled in this study, 54 patients (32.73%) had comorbidities other than cervical cancer. Some other comorbidities are pneumonia, hypertension, diabetes mellitus, and sepsis.

Table 1. Sosiodemographic, clinical characteristics and death among cervical cancer patients

Variable	Frequency	Percentage (%)
Age (Mean (± SD))	49 (±12.23)	
≤35	18	10.91
36–49	64	38.79
50–65	65	39.39
>65	18	10.91
Education Level		
High	134	81.21
Low	22	13.33
Unfilled	9	5.46
Marital status		
Married	112	67.88
Not Married	39	23.63
Unfilled	14	8.49
Employment status		
Yes	87	52.72
No	73	44.24
Unfilled	5	3.04
Parity		
Nullipara	17	10.30
Primipara	19	11.51
Multipara	90	54.54
Grand multipara	28	16.96
Unfilled	11	6.69
Stage		
Stage 0	30	18.18
Stage 1	37	22.42
Stage 2	39	23.64
Stage 3	40	24.24
Stage 4	19	11.52
Treatment type		
Targeted therapy	110	66.67
PRC transfusion*	45	27.27
Surgery	10	6.06
Comordibities		
Yes	54	32.73
No	111	67.27
Status		
Survive	111	67.27
Died	54	32.73

Survival Analysis of cervical cancer patients

Based on the result of the Kaplan Meier analysis, it was found that more than 50% of cervical cancer patients survived until the end of the observation on 31 January 2022 (Figure 1). Summary of the survival analysis showed the average of follow up time of cancer patients in this study was 38.4 months with a mortality rate of 7.2/1000 person months (IR = 0.007).

Based on the result of Log-rank test of the 8 variables analysed, there were two variables which have no

significant differences in survival, namely education level (p=0.79) and marital status (p=0.16). Other variables, namely age, employment status, parity, stage of cancer, type of treatment and comorbidities, had significant differences in survival rates between the groups (p<0.05).

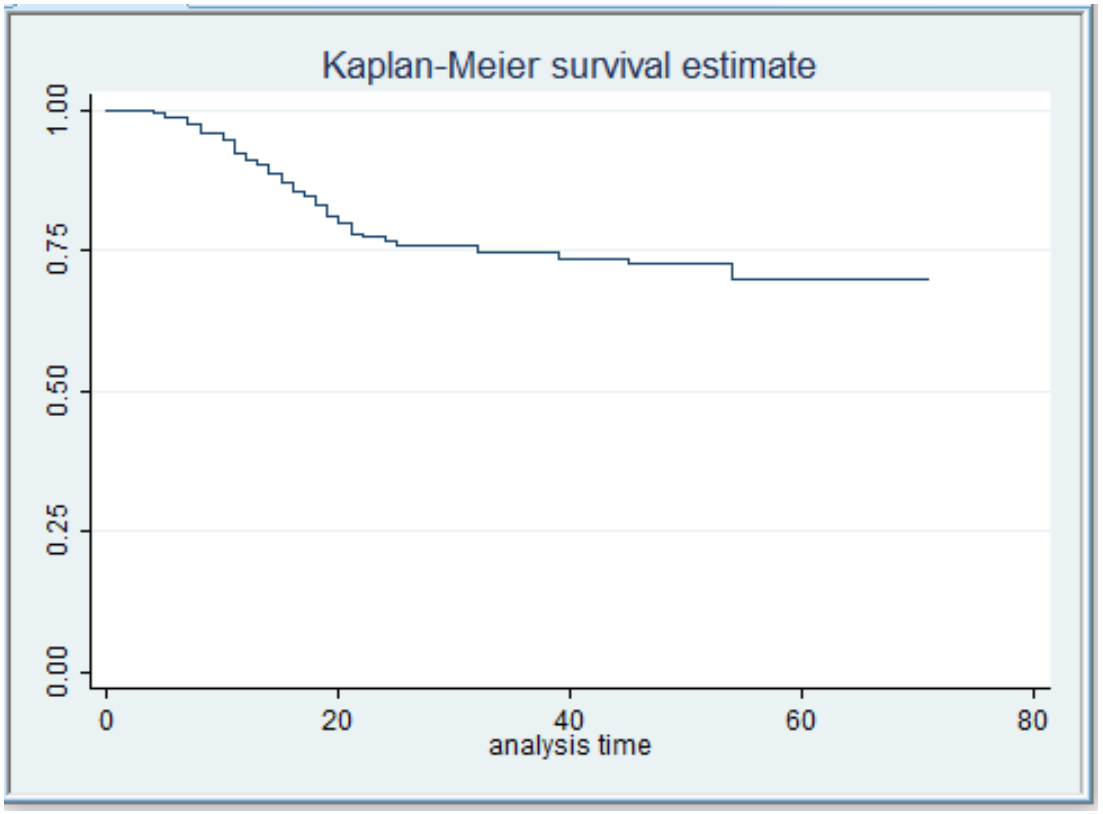

Figure 1. Survival of cervical cancer patients at Wangaya Hospital

Analysis of factors associated with survival of cervical cancer patients

The results of the bivariable analysis of the factors that affect the survival of cervical cancer patients are presented in Table 2. Factors associated with survival were age, employment status, parity, stage of cancer, and comorbidities which showed a statistically significant effect on the survival of cervical cancer patients (p<0.05). However, the other variables, namely marital status and treatment type, were continued to the multivariate analysis since they met the inclusion cut off (p<0.25), and only educational level was not included in the multivariate model.

Based on the results of the analysis in Table 3, of the eight variables included in the initial model, four variables were significantly associated with survival in the final model which were age, employment status, stage of cancer, and comorbidities (p<0.05). With every year increase in the patient's age at baseline the risk of death increased by 1.06 times. Patients who do not work have a risk of death 2.32 times higher than patients who work. Based on the stage of cancer, patients who are diagnosed with stage 4 at the start of treatment have a risk of dying 18.95 times compared to those with stage 0. Patients with comorbidities have a risk of death 2.11 times higher than patients who do not have comorbidities.

Table 2. Crude association between each factor and survival of cervical cancer patients in Wangaya Hospital

Factors	HR	95%CI HR	p-value
Age	1.06	1.45 – 1.09	<0.001
Education level			0.694
Low	Ref		
High	1.18	0.50 – 2.77	0.701
Marital status			0.202
Married	Ref		
Not Married	1.46	0.82 – 2.58	0.192
Employment status			<0.001
Yes	Ref		
No	3.76	2.06 – 6.84	<0.001
Parity			0.022
Nullipara	Ref		
Primipara	1.58	0.44 – 5.60	0.478
Multipara	1.92	0.68 – 5.50	0.219
Grand multipara	4.10	1.37 – 12.31	0.012
Stage			<0.001
Stage 0	Ref		
Stage 1	3.19	0.90 – 11.33	0.072
Stage 2	3.92	1.09 – 14.19	0.037
Stage 3	8.99	2.65 – 30.49	<0.001
Stage 4	14.19	3.64 – 55.32	<0.001
Treatment type			0.071
Targeted therapy	Ref		
PRC transfusion	1.49	0.82 – 2.70	0.198
Surgery	2.87	1.19 – 6.93	0.015
Comorbidities			0.005
No	Ref		
Yes	1.62	0.94 – 2.80	0.081

Ref=reference group

DISCUSSION

The survival of cervical cancer patients in this study was relatively good, since until the end of the observation on 31 January 2022, more than half (67.3%) of the samples were still alive. The result from the American Cancer Society states that the probability of survival for cervical cancer patients for 5 years is 66%.[13] A study conducted in Malaysia, also found that the survival of cervical cancer patients for 5 years was 71.1%.[13] In this study, however, the particular year survival rate of the cervical cancer patients cannot be calculated because the length of follow up time for each sample was not the same. Samples who survived until the end of observation time (31 January 2022) were those who just started the therapy on 31 January 2021 (only 1 year follow up) or before 31 January 2022 (more than 1 year follow up).

Although the survival rate in Wangaya Hospital is quite good, but it still needs to be improved by adding treatment facilities in accordance with the standard treatment of international cervical cancer guidelines. International guidelines for cervical cancer recommend radiation therapy and chemotherapy as standard of care for advanced cervical cancer.[14] These treatment facilities, however, remain unavailable at Wangaya Hospital.

Table 3. Results of multivariable analysis of factors affecting survival of cervical cancer patients at Wangaya Hospital

Factor	Initial Model			Final Model		
	aHR	95%CI	p-value	aHR	95%CI	p-value
Age	1.07	1.04 – 1.10	<0.001	1.06	1.03 – 1.08	<0.001
Marital status						
Married	Ref					
Not Married	1.01	0.44 – 2.58	0.995	-	-	-
Occupational status						
Yes	Ref			Ref		
No	2.74	1.39 – 5.43	0.004	2.32	1.24 – 4.33	0.008
Parity						
Nullipara	Ref					
Primipara	0.76	0.18 – 3.15	0.701	-	-	-
Multipara	0.50	0.14 – 1.72	0.272	-	-	-
Grand multipara	0.46	0.12 – 1.75	0.257	-	-	-
Stage						
Stage 0	Ref			Ref		
Stage 1	3.69	0.95 – 14.27	0.058	3.94	1.07 – 14.49	0.039
Stage 2	5.51	1.39 – 22.15	0.015	5.86	1.50 – 22.78	0.011
Stage 3	12.67	3.32 – 48.34	< 0.001	11.73	3.15 – 43.56	<0.001
Stage 4	16.9	3.52 – 80.96	< 0.001	18.95	4.33 – 82.91	<0.001
Treatment type						
Targeted therapy	Ref					
PRC transfusion	1.76	0.88 – 3.51	0.106	-	-	-
Operation	2.36	0.91 – 6.19	0.079	-	-	-
Comorbidities						
No	Ref			Ref		
Yes	2.25	1.17 – 4.33	0.014	2.11	1.12 – 3.99	0.021

Ref =reference group

After 72 months of observation period in the cohort of cervical cancer patients, the average patient survival time was 38.4 months. This result is higher when compared to the results of a study in Brazil which found the average survival of cervical cancer patients was 29.8 months.[15] However, these results were lower than the results of a study in India which obtained an average survival rate of 45.6 months.[16]

In this study, age has a significant effect on the survival of cervical cancer patients. Vishma's research stated that older age at initial treatment can increase the risk of death for cervical cancer patients. Younger patients who started treatment had a higher survival than older patients.[17] In line with a study in Malaysia which stated that the survival rate of cervical cancer patients who were treated at age >65 years was only 30.9%.[18] Patients who are diagnosed with cervical cancer at an old age tend to experience delays in carrying out treatment. The survival of cervical cancer patients undergoing treatment worsens with age.[19] In this study, patients aged under 50 years reached 50%, where 10% of them were aged less than 35 years. Early detection of cervical cancer in women of childbearing age is very important. Cervical cancer screening coverage is still very low in

Denpasar City. It is known that the cervical and breast cancer screening rate in women aged 30 to 50 years was only 2.5% in 2021.[20] Effective coverage for reducing cervical cancer mordibity and mortality is 85%.[21] By knowing the status of cervical cancer earlier, the survival of cervical cancer patients can be improved.

We found the stage of cancer is an important predictor of survival of cervical cancer patients. In line with the study in Nigeria who found that stage of cancer affects patient survival. Patients with stage 4 increase the risk of death by 9.17 times compared to stage 1.[22] These results are also supported by research conducted by Gashu, it is stated that stage of cancer has a significant association with survival time in outpatients with cervical cancer. Lower survival rates in cervical cancer patients are clearly associated with advanced stages. The study also showed that outpatients with advanced cervical cancer had a 28% shorter life expectancy compared to those with early stage cancer.[23] The high possibility of complications and the wide spread in the final stage causes more complex treatment measures. This can lead to a low probability of patients surviving.[24]

Early detection efforts are needed to be able to see the presence or absence of cancer cells in a person's body in earlier stage. WHO recommends early detection by carrying out an HPV DNA test (the sensitivity level reaches 94%). However, this test is only recommended for ages 30 and over, for women under 30 years of age it is recommended to do a pap smear or IVA. If the presence of the HPV virus or cancer cells is detected, treatment should be carried out immediately to reduce the risk of death from cervical cancer.

In addition, we found comorbidities also influence survival of cervical cancer patients. The results of this study are in line with previous research which stated that patients who have other diseases have a 1.58 times higher risk of dying than those who do not have other diseases.[18] The presence of comorbidities in cervical cancer patients can affect the quality of the treatment given. The more comorbidities in the patient means the lower patient's chance to survive.[25]

The employment status also showed significant effect on the survival of cervical cancer patients. In line with research conducted by Thulaseeedharan, it was found that employment status affects the survival of cervical cancer sufferers.[26] Work has a close relationship with person’s economic condition. Economic status is related to certain variables that affect survival, such as nutrition, psychosocial well-being, access to healthcare and stage of diagnosis.[27] In addition, patients with good economics affect patient adherence in undergoing treatment. In this study, economic status is only seen from employment status. In future studies, it is advisible to examine the variables of income and insurance ownership on the survival of cervical cancer patients.

From our analysis, we were unable to prove the association between type of treatment, parity, level of education and marital status. This could be due to interrelationship with other variables in the model or the demographic characteristics of the samples or different treatment availability in the hospital.[28,29] However, we found those with grande multiparas have a greater risk of dying than those who don't have children. Studies and research discussing the effect of parity and survival of cervical cancer patients are very limited. High parity is associated with the higher risk of cervical cancer.[30,31]

This study used secondary data from medical records of cervical cancer patients at Wangaya Hospital. The consequence of using this secondary data is the limited variables available, so that other factors that might affect survival of cervical cancer patients could not be researched because the required data were not available, such as income, insurance ownership, quality of marriage and spousal support. Another limitation in this study was during the collection and extraction of medical record data. There are several medical records where the data is incomplete. With a larger sample, it is hoped that the resulting data will better reflect the actual condition of cervical cancer patients at Wangaya Hospital.

CONCLUSION

From a total of 165 patients who were the study sample, the average of follow up time of cancer patients in this study was 38.4 months with a mortality rate of 7.2/1000 person months (IR = 0.007). Based on the analysis, it was found that 4 variables significantly affected the survival of cervical cancer patients at Wangaya Hospital were age, employment status, stage of cancer, and comorbidities.

Based on the results of this study, it is recommended that doctors who treat cervical cancer patients at Wangaya Hospital to provide more attention in the treatment for patients with comorbidities, older age, and advanced stages. In addition, it is also expected to add treatment facilities that are in accordance with international guidelines for cervical cancer, namely chemotherapy and radiation therapy for treatment of patients with advanced stages. For future researchers, it is better to extend the duration of the observation to represent the actual survival time of the patient and add other variables, namely income, insurance, ownership, qualty of marriage, and spousal support. The duration of follow up for each sample should also be the same in order to be able to calculate the particular year of survival rate for all samples (e.g. 5 year survival rate).

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AUTHOR CONTRIBUTION

AARI designed the research, collected data, analysed data, and drafted the manuscript. PCDY was involved in analysing the data, providing feedback on the manuscript, and editing the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing of interests.

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