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ORIGINAL ARTICLE

Survival Analysis of Clinicopathology Profile and Risk Factor in Cervical Cancer with Surgery

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ABSTRACT

Introduction: Cervical cancer is one of the most preventable types of cancer compared to all cancer cases , but it is also deadly. Objective: This study aimed to determine the five year survival rate of surgical cervical cancer at Saiful Anwar Hospital Malang and to know the effect of clinicopathological profile and risk factors on survival rate.

Methods: Our method is analytic observational with a retrospective cohort type using medical records of surgical cancer cervix from January until December 2017. Theanalysis used the Log-rank test, Kaplan Meier, and Cox regression.

Results: The total of the 144 study samples, found 92 alive and 52 dead. This research of clinicophatology profile showed significant affect in stage (p .001), histopathology (p .006), degree of differentiation (p .000), and lymph node metastases (p .000). While the research of risk factor showed significant affect in age (p- value 0.000), total of parity (p .000), marital history (p .000), occupation (p .003), menstrual history (p .003), and type of contraception (p 0.000), type of therapy (p .001). And then, it was found no significant affect in BMI (p .471) area of residence (p .475).

Conclusion:. The survival rate of cervical cancer patients in five years with surgery is 90 %. Based on the clinicopathological profile, it was found that that stage variable, histopathology, degree of differentiation, and lymph node metastases significantly affectthe survival rate. In the characteristics of risk factors, The variables of age, parity, marital history, occupation, menstrual history, contraception, type of therapy, and placeof residence) have a significant effect on survival.

Keywords: Cervival Cancer; Clinicopathological Profile; Survival Analysis

INTRODUCTION

Cervical cancer is one of the most preventable and curable types of cancer compared to all cancer cases, but it is also deadly (1). Factors including age at diagnosis, condition status, stage and duration of treatment are prognostic factors for cervical cancer. In addition, research classifications, including location, size of tumour, lymphovascular invasion, lymph node invansion, and treatment, are significantly correlated with survival (2). In this case, the stage of cervical cancer is related to the potential for invasion and metastasis. In addition, the clinicopathological characteristics of cervical cancer are strongly associated with treatment (therapy) and prognosis (3).

Various risk factors influence the occurrence of cancer especially the cervix, sociodemographic, unhealthy sexual behaviour, and uncircumcised sexual partners. In addition, low of immunity, number of births, poor hygiene, active or passive smoker, family history, and cervix trauma (4). Delay in diagnosis at an advanced stage, weak general condition, low socioeconomic status, limited resources, limited infrastructure, type of histopathology and degree of education affect the prognosis of people with cervical cancer (1,4).

Cervical cancer tends to increase yearly, and there are five additional cases of cervical cancer to 77 cases in 2020 in Malang City (5). In Saiful Anwar Hospital Malang, every month new cases are found. Happened because Saiful Anwar Hospital is a type A hospital that is a reference for malignancy cases in Malang. A large number of cases of cervical malignancy has made researchers interested in examining these cases at RSUD dr. Saiful Anwar Malang.

Cancer survival patients with surgery in Malang has never been studied. That information is an actual problem because Malang is one of the areas with the second-most cases of cervical cancer in East Java (5). The survival rate is essential to study because it can Estimates the percentage five years after being diagnosed with cancer of the same type and stage also still alive. In addition, the authors attempted to assess the influence of clinicopathology and risk factors on survival that had not been studied.

METHODS

This research was carried out at Saiful Anwar Hospital Malang from March to April 2022 using analytical observational (retrospective cohort type) through medical record data. Inclusion criteria: cervical cancer patients diagnosed by clinicians the Obstetrics and Gynecology section and confirmed by histopathological examination, cervical cancer patients who underwent surgery from January 1, 2017, to December 31, 2017. Exclusion criteria: patients with other malignancies. Then selecting a sample of medical record data that matched the inclusion criteria, and those that did not were excluded, only 144 patient samples met the requirements. In this study, the independent variables were clinicopathological characteristics (stage, histopathology, lymph node status, degree of differentiation) and risk factors (age, parity, area of residence, education, employment, contraceptive use, menstrual history, marital history, BMI). The dependent variable is the survival rate. Data analysis using Log-rank test, Kaplan Meier, and Cox regression.

RESULTS

The samples studied were 144 medical records (92 people were alive, and 52 died). The following are the clinicopathological characteristics and risk factors of the study sample. From the tab.1, it showed a significant affect in the staging and majorityat stage IIB, dead and living. Furthermore, based on the histopathological type, the most common type was Keratinizing Squamous Cell Carcinoma in living patients. Likewise, there are more Grade II patients who died. Based on lymph node metastases, it was found that most patients had no lymph node invasion in living patients.

The characteristics of cervical cancer risk factors (Table.2), the research sampleshowed significant affect ($p<0.05$) in ages, parity, marital history, employment, menstrual history, type of

family planning (contraception), type of therapy, and area of residence. Tab.2 known that patients with more death status at the age of 71-80, therewere 28 (19%) patients. Meanwhile, there were 34 (24%) patients with living situationsat the age of 51-60.

Table 1: The Characteristics of Clinicopathological Profile

Clinicopathological Profile	Survival Status				P-Value
	Death		Living		
Stage					
IA	6	(4.2%)	6	(4.17%)	0.000
IB	8	(5.6%)	1	(0.69%)	
IIA	2	(1.4%)	2	(1.39%)	
IIB	36	(25.0%)	83	(57.6%)	
Histopathology					
Non Keratinizing Squamous Cell Carcinoma	8	(5.6%)	10	(6.9%)	0.002
Keratinizing Squamous Cell Carcinoma	16	(11.1%)	63	(43.8%)	
Adenocarcinoma	9	(6.3%)	7	(4.9%)	
Other types	19	(13.2%)	12	(8.3%)	
Degree of_Differentiation					
Grade I (derajat baik)	16	(11.1%)	58	(40.3%)	0.000
Grade II (derajat sedang)	24	(16.7%)	31	(21.5%)	
Grade III (derajat buruk)	12	(8.3%)	3	(2.1%)	
Lymph node Metastasis					
Invasion	31	(21.5%)	32	(22.2%)	0.004
no invasion	21	(14.6%)	60	(41.7%)	

Regarding parity characteristics (Table.2), More patients who lived were found than the number of births with more than three. In Tab.2, it was found that most surviving patients were married for more than 18 years (38%) and on the job description with private employees (45%). Of the living patients who mainly used hormonal contraception (44%) and (46%) were without menstrual disorders. Regarding the type of therapy and place of residence (Table.2), patients who lived were more found in patients with pure surgical therapy and living in the city, namely 31 (22%) and 52 (36%).

Table 2: The Characteristics of Risk Factors

Risk Factor	Survival Status				p- value
	Death		Living		
Age					
31 -40 y	3	2%	10	7%	0.041
41 -50 y	4	3%	4	3%	
51 -60 y	16	11%	34	24%	
61 -70 y	1	1%	22	15%	
71 -80 y	28	19%	22	15%	
Parity					
> 3 times	6	4%	38		0.000
≤ 3 times	46	32%	54		
Education					
Elementary school	8	6%	8	6%	0.987
Junior high School	9	6%	7	5%	
Senior high School	16	11%	65	45%	
College	19	13%	12	8%	
Marital (the age of first married)					
≤18	8	6%	37	26%	0.002
>18	44	31%	55	38%	
Employment					
IRT/Not working	7	5%	8	6%	0.001
Private	16	11%	65	45%	
Civil servant	9	6%	6	4%	
Self-employed	20	14%	13	9%	
Menstrual history					
Disorder	40	28%	26	18%	0.000
No disorder	12	8%	66	46%	

Table 3:

Contraception					
Hormonal	16	11%	63	44%	0.000
Non Hormonal	36	25%	29	20%	
BMI					
Underweight	8	6%	20	14%	0.947
Normal	19	13%	12	8%	
Overweight	16	11%	53	37%	
Obesity	9	6%	7	5%	
Therapy					
Surgery	31	22%	83	58%	0.000
Surgery dan Neoadjuvant Chemoteraphy	21	15%	9	6%	
Residence					
Rural	0	0%	22	15%	0.000
Urban	52	36%	70	49%	

Table 4: The Analisys Kaplan Meier Survival rate

Variabel	Median Survival Time	Log Rankp value
Stage		
IA	67	0.001
IB	59	
IIA	58	
IIB	56	
Histopathology		
Non Keratinizing squamous cell ca	55	0.006
Keratinizing Squamous cell ca	56	
Adenocarcinoma	55	
Other types	59	
Degree of Differentiation		
Grade I	67	0.000
Grade II	59	
Grade III	55	
Lymph nodes metastases		
No invasion	59	0.000*
Invasion	55	
Age		
31-40 years old	60	0.000
41-50 years old	59	
51-60 years old	55	
61-70 years old	55	
71-80 years old	54	
Employment		
IRT/Not working	55	0.003
Private	56	
Civil servant	55	
Wiraswasta	59	
Parity		
> 3 times	54	0.000
< 3 times	58	
Education		
Elementary school	55	0.000
Junior high School	55	
Senior high School	56	
College	59	

Table 5:

Variabel	Median Survival Time	Log Rankp value
Marital		
< 18 years old	54	0.000
> 18 years old	57	
Therapy		
Surgery	56	0.001
Surgery dan Neoadjuvant Chemoteraphy	59	
Menstrual history		
No Disorder	60	0.003
Disorder	55	
Contraception		
Non Hormonal	55	0.000
Hormonal	59	
BMI		
Underweight	54	0.471
Normal	59	
Overweight	56	
Obesity	55	
Residence		
Rural	56	0.475
Urban	56	

* Berpengaruh signifikan berdasarkan hasil uji Log Rank pada taraf α = 0.05

From table 3, it is shown that of all the variables, several variables are significant. The variables were a stage, histopathology, degree of differentiation, lymph node metastases, age, employment, parity, education, marital history, type of surgery, menstrual history, and contraceptive use. At the same time, the variables of BMI and area of residence (p> 0.05), It is known not found to be significant to survival.

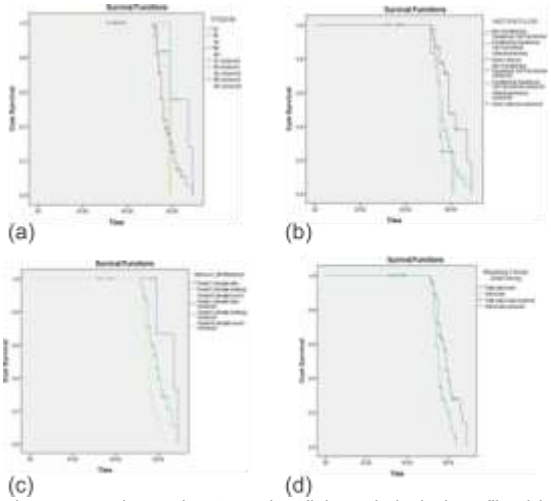

Figure 1: Kaplan Meier Curve in Clinicopathological Profile: (a) stage, (b) histopathology, (c) degree of differentiation, (d) lymph node metastases

Fig.1, shown that the proportional hazard assumption was not fulfill in histopathology, stage, and degree of differentiation, as well as lymph node metastases, which showed that there was only 1 line on the survival graph, so the proportional hazard assumption was also.

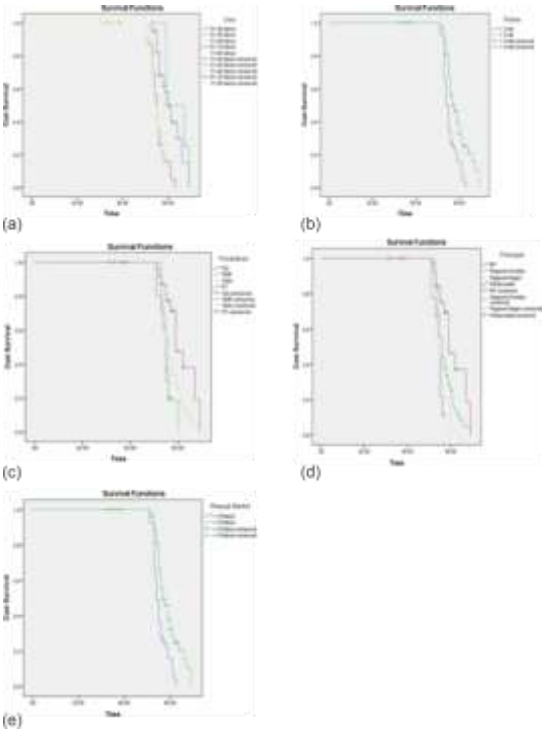

Figure 2: Kaplan Meier curve on risk factors: (a) age, (b) parity, (c) education, (d)employment, (e) marital history

Fig 2, On the survival graph, it is found that the lines that intersect. The proportional hazard assumptions for age, parity, education, employment, and marital history were not met.

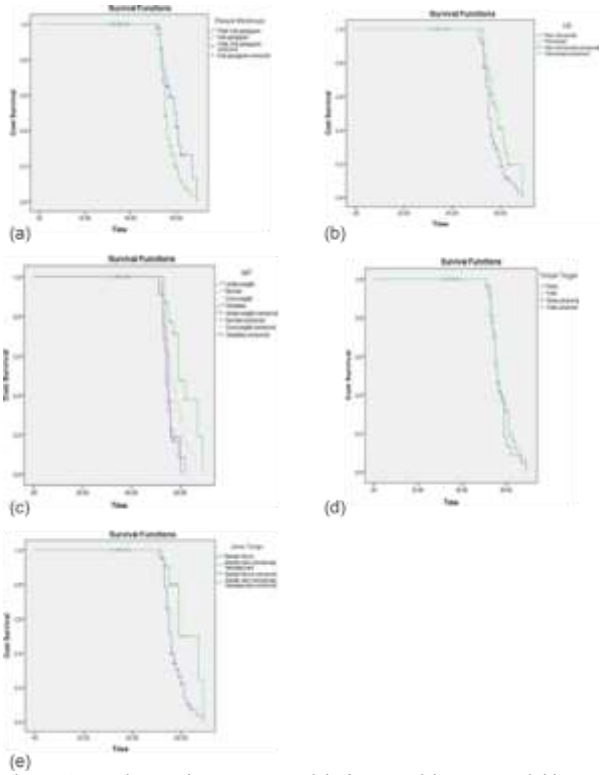

Figure 3: Kaplan Meier curve on risk factors: (a) menstrual history, (b) contraception, (c) BMI, (d) residence (e) therapy

Based on Figure 3, it is shown that there is an intersection of the lines on the survival graph. This test showed that the proportional hazard assumptions on menstrual history, contraceptive use, BMI, place of residence, and the type of therapy were not met.

Table 3: Multivariate Analysis Results with Cox Regression

	B	Hr	Sig.	Exp(B)
Stage	.015	.006	.937	1.016
Histopathology	.733	2.008	.156	2.081
Degree of Differentiation	-1.461	5.907	.015	.232
Lymph node metastases	-1.034	2.612	.106	.356
Age	-.330	6.872	.009	.719
Parity	.348	.101	.750	1.417
Education	-.475	4.672	.031	.622
Marital	-.465	.194	.660	.628
Contraception	-.445	3.627	.057	.641
Menstrual history	.437	3.103	.078	1.547
Therapy	-.580	.809	.369	.560
Employment	-.444	.885	.347	.641

Based on Table.3, Multivariate analysis with cox regression showed the degree of differentiation, age and education obtained p-value = 0.015 (p<0.05), while histopathological, lymph node metastasis, parity, marital history, contraception,menstrual history, type of therapy and employment had no effect multivariate on the survival (p>0.05).

DISCUSSION

The stage of the disease is the most vital determinant or determinant of survival (6). Patients with stage one and two cervical cancer live longer than stage three and four. (7). Histology and degree of differentiation are better predictors of

survival and recurrence (8). Tumour differentiation is a prognostic factor in women with squamous cervical cancer. Higher tumour grade with worse life (9).

Our findings were based on the histopathological type; keratinizing squamous cell carcinoma is the most common type in living patients. Histopathology is an important prognostic factor among patients with cervical cancer (10). SCC (cervical squamous cell carcinoma) is known to have better survival than the one associated with worst survival, i.e. ADC (adenocarcinoma) (11).

Our findings were based on lymph node metastases, and it was found that most patients had no lymph node invasion in living patients, with a significant affect in lymph node metastases. Our findings are in line with other research. For example, univariate analysis in the study of Stanca and Căpîlna (2021) showed that the prognosis of survival rate was directly affected by lymph nodes metastases. Furthermore, lymph node metastases prognostic factors may affect survival (12).

Our findings are in line with other research. Based on the study's results, Tshewang et al., (2021) revealed that patients diagnosed at old age were significantly associated with a decreased survival rate. Tshewang et al., imply that The younger age group has a higher survival rate and decreases with age (13). However, a period over 45 years is known to have an increased risk factor for patient mortality compared to the younger age group (≤45 years) (13).

Based on the study's results, parity was affected, so it can be seen that patients who gave birth > three times had a lower survival rate than patients who gave birth more than three. The number of parity more than three has a significantly five times more risk for cervical cancer than parity less than three (14). Dangerous parity is to have more than two children, or the delivery distance is too close. That can trigger changes in abnormal cells in the cervix and can develop into malignancy (15). In addition, women with high parity have a relationship with eversion of cervical columnar epithelium during pregnancy which can result in the displacement of new immature metaplastic

epithelium resulting in an increased risk of -cell changes, making it easier to become infected with HPV (16).

Risk factors significantly affect prognosis (8,17). In the study results, education is one of the risk factors that influence the survival rate, so it can be concluded that education can affect the prognosis. In the other studies, namely, the level of education related to behavior, health, or the ease of receiving knowledge and resources has a direct and indirect impact on the survival of cervical cancer patients (17).

A marital history of good relations with one's culture and society. Marriage has a good impact on American and European women, namely protection. Marriage statistically significantly affects shelter for women with high social status and vice versa for women with low social levels. (18). The type of work can be seen that most patients live in the private sector compared to other occupations in our study. Based on other studies, statistically, work can reduce the risk of death significantly. In addition to work, medical factors are also associated with survival. Therefore, work can provide good survival (19).

One of the factors that influence survival in our study is menstrual history. According to another study, patients diagnosed with menstrual irregularities had a statistically probable effect on survival. Then another survey on Thai women using a case-control method found that women with a history of irregular menstruation in number and frequency had twice the susceptibility to cervical cancer compared to women on average, so the menstrual history also indirectly affected survival (20).

Based on the study results, the type of contraception is a risk factor that can affect the survival rate. The use of hormonal contraceptives has been shown to reduce survival. However, in our study, most patients lived on hormonal contraception. Hormonal contraception (injections and pills) is the leading choice of contraception for most women in Indonesia (21). Based on the research of Iversen et al., hormonal use the possibility or risk of cervical cancer with squamous histopathology and adenocarcinoma. In addition, using hormonal contraception by cervical cancer patients can affect survival (22).

Our research found there was no effect of BMI on survival rate. However, it is known that underweight has a lower survival rate than other BMI statuses, so it can be concluded that this study is in line with other studies in the analysis of underweight

BMI compared with normal BMI, was associated with decreased survival (23). Underweight cervical cancer patients (BMI <18.5 kg/m^2) have potential for complications greater than normal BMI and obesity and reduced survival (23). This study is also in line with other studies, namely that obese and underweight patients have a much higher metastatic potential than patients with a normal BMI and potentially reduce survival. (24).

Other studies have shown that administering NACT before radical surgery has the advantage that it can reduce the level of difficulty of the operation, reduce the risk of surgery, and provide optimal therapy for advanced cervical cancer without lowering the story of life (25). In addition, compared with revolutionary treatment alone, cervical patients who received neoadjuvant chemotherapy (NACT) radical surgery at stage IB2- IIB were shown to significantly improve survival and reduce recurrence rates and lymphnode metastases (26).

From our research, it is known that the place of residence of the deceased patient is found in patients who live in the city, so it can be concluded that the area of residence is one of the risk factors for survival rate that does not have a significant result. Most studies investigating the relationship between the area of residence and cervical cancer survival rate were conducted in developed countries, but the findings were inconsistent (27).

CONCLUSION

Patients of cervical cancer with surgery at Saiful Anwar Hospital Malang have a five- year survival rate of 90%. It was found that the clinicopathological profile affected the patient's survival rate on the stage variables, histopathology, degree of differentiation, and lymph node metastasis. In addition, it was found that there was an influence of risk factors on the survival rate on the variables of parity, age, marital history status, education, type of work, menstrual history, type of contraception, and type of therapy. Based on multivariate analysis with Cox regression shows significant results on the survival rate to the variable degrees of difference, age, and education.

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