Jurnal Aisyah: Jurnal Ilmu Kesehatan

Volume 7, Issue S1, 2022, p. 233–242
ISSN 2502-4825 (print), ISSN 2502-9495 (online)

Survival Analysis of Clinicopathology Profile, Risk Factor, and Prognostic Factor in Cervical Carcinomas with Chemoradiation

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ARTICLE INFO

Article history:

Received 11 March 2021
Accepted 21 June 2022
Published 10 July 2022

Keyword:

Survival Analysis
Cervical Carcinoma
Clinicopathological Profile
Risk Factors
Prognostic Factors

A B S T R A C T

Cervical carcinoma causes several problems like pain, and suffering at least death. However, it is the most preventable, curable, and high survival type of cancer. This study aims to analyze the survival of cervical cancer patients based on factors that are considered influential, such as clinicopathological profiles, risk factors, and prognostic factors to order the effectiveness of therapy, and improving the quality of life in patients receiving chemoradiation. In an analytical observational retrospective cohort design study, using secondary data, samples contain all patients diagnosed with cervical cancer who received chemoradiation therapy from January to December 2017 which is 151 patients. This study revealed that the 5year survival rate is 57.6%. The lowest Person Time is 3 months and the longest is 60 months, average 45.80 months, standard deviation 18.179 months. There was a significant influence on the clinicopathological profile including Age (0.002), Histopathology (0.012), and Stage (0.000). Risk factors: parity (0.000), Education (0.007), Number of Marriages (0.025), Menstrual Disorders (0.021), Contraception (0.004), Cancer History (0.000), Body Mass Index (0.022), Area of residence (0.009). Prognostic factors: chemoradiation type (0.002), chemotherapy type (0.000), radiation type (0.001), radiation technique (0.007). The results indicate that the survival rate of cervical cancer patients with chemoradiation still has tobe concerned.

Kata kunci:

Analisis Kesintasan
Karsinoma Serviks
Profil Klinikopatologi
Faktor Risiko
Faktor Prognostik

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DOI: 10.30604/jika.v7iS1.1187

A B S T R A K

Karsinoma serviks menyebabkan masalah kesakitan, penderitaan dan menjadi penyebab kematian. Akan tetapi, juga merupakan jenis kanker yang paling dapat dicegah, disembuhkan dan memiliki kesintasan hidup tinggi. Penelitian ini bertujuan untuk menganalisa kesintasan hidup pasien karsinoma serviks berdasarkan faktor yang dinilai berpengaruh yaitu profil klinikopatologi, faktor risiko, dan faktor prognostik guna menilai efektivitas terapi demi peningkatan kualitas hidup pada pasien yang menerima kemoradiasi. Penelitian ini merupakan studi analisis observasional dengan desainretrospective cohort, menggunakan data sekunder, sampel dalam penelitian ini mencakup semua pasien dengan diagnosa karsinoma serviks yang menerima terapi kemoradiasi dari bulan Januari hingga Desember 2017 sejumlah 151 pasien. Pada penelitian ini didapatkan data 5 tahun kesintasan sebesar 57.6%. Person Time terendah 3 bulan dan terlama 60 bulan dengan nilai rata-rata 45,80 bulan, standar deviasi 18,179 bulan. Terdapat pengaruh signifikan Profil Klinikopatologi meliputi kategori Usia (0.002), Histopatologi (0.012), Stadium (0.000). Faktor Risiko meliputi kategori paritas (0.000), Pendidikan (0.007), Jumlah Pernikahan (0.025),

Gangguan Menstruasi (0.021), Kontrasepsi (0.004), Riwayat Kanker (0.000), Indeks Masa Tubuh (0.022), Daerah tinggal (0.009). Faktor Prognostik meliputi Jenis Kemoradiasi (0.002), Jenis Kemoterapi (0.000), Jenis Radiasi (0.001), Teknik Radiasi (0.007). Hasil ini menunjukan bahwa kesintasan hidup pada pasien karsinoma serviks yang mendapat terapi kemoradiasi masih membutuhkan perhatian.

INTRODUCTION

Cervical carcinoma is thirds of the most cancer cases in the world, with a prevalence of 500,000, being the biggest cause of death in developing countries. In Indonesia, the incidence got 136.2/100,000 of the population. East Java is one of the provinces that have the highest estimated number of cervical carcinoma cases compared to other provinces (Ministry of Health RI, 2020). Malang City is the second the largest city in East Java Province, based on data in 2020, it is known to have increased by 5 cases of cervical carcinoma (Malang Health Office, 2020). A study in Malang City in 2014, have shown that the one-year survival rate of patients with advanced cervical carcinoma was localized at RSUD dr. Saiful Anwar Malang is 72% (Sherly, 2014). The survival of cervical cancer patients plays an important role in assessing the effectiveness of therapy and predicting the chances of quality of life for cancer patients. Improved survival is the cornerstone, a benchmark for the expected clinical benefits as well as a reference for therapeutic recommendations (Singh et al., 2018).

The latest diagnosis and treatment in the field of oncology are expected to improve patient survival. The choice of cervical cancer therapy depends on the clinical stage, this is considered to affect the survival and the possibility of recurrence of cervical carcinoma (Adhisty, 2018). Radiations are the main choice in advanced patients based on the propagation of cancer cells that have reached the parametrium so that surgical therapy cannot be performed. However, in some circumstances, radiation therapy is considered unsatisfactory, for example, if the size of the cancer is large (bulky), it is necessary to give a chemotherapy agent as a radiosensitizer to increase the effectiveness of therapy (Chemoradiation). Concurrent use of chemotherapy and radiation can provide a better effect than single therapy and performed a significant increase in the survival rate (Yoshida et al., 2020).

Based on research data, the survival of cervical cancer patients is influenced by several factors, including the clinicopathological profile, risk factors, and prognostic factors. Considering RSUD dr. Saiful Anwar Malang is the largest hospital as well as a referral hospital for the East Java region, and also in previous studies in Malang City only used 1-year of survival. Therefore, is necessary to carry out further and recent research with 5-year survival based on the influence of the clinicopathological profile, risk factors, and prognostic factors of cervical cancer patients with chemoradiation therapy in RSUD dr. Saiful Anwar Malang to be the basis for consideration in the selection of therapy to improve patient survival.

METHOD

Participant characteristics and research design

There is a similarity in the characteristics of patients in this study, where the population of this study was all patients with cervical carcinoma who had been diagnosed by clinicians in the obstetrics and gynecology section of RSUD dr. Saiful Anwar Malang, confirmed by histopathological examination results, and received chemoradiation therapy from January 1, 2017, to December 31, 2017. This study is an analytical observational study using a retrospective cohort design. The sampling method in this study was saturation sampling, involving all patients.

Sample size, power, precision, and Measures

Based on the medical record data obtained from 225 patients with cervical carcinoma underwent chemoradiation in 2017. After all medical record data were searched based on inclusion, exclusion, and follow-up criteria, the remaining 151 patient samples met the criteria. The instrument of this study was a questionnaire form which was used to collect data from the medical record status of patients suffering from a cervical carcinoma and undergoing chemoradiation. By using the form that has been created, data collection will be carried out, for further data analysis.

Data analysis

Survival analysis was conducted to assess the effect of the independent variables (clinicopathological profile, risk factors, and prognostic factors) and the dependent variable (survival assessed by patient status and *person time*). This study uses the *Kaplan Meier test*, to determine the significance of each independent variable on the probability of survival using a *log-rank test so* that it can be seen which factors have a significant effect, and the *Hazard Ratio Test* (HR) to determine the level of significance of the variable. Cox Regression analysis was conducted to see the effect of all independent variables on the dependent variable, with the assumption of proportional hazard testing as one of the prerequisites before conducting the Cox Regression analysis.

RESULTS AND DISCUSSION

Univariate analysis in this study was carried out to test one by one the research variables assessed in this study. The variables assessed include each part of the clinic opathological profile, risk factors, and prognostic factors. This univariate analysis was carried out using a descriptive test based on a frequency distribution test with results as the following distribution of the respondents characteristics.

Table 1
Distribution of the Respondents Characteristics

No	Characteristics	Amount	Percent
	Age		
1	31-40 years old	14	9.3
2	41-50 years old	50	33.1
3	51-60 years old	63	41.7
4	61-70 years old	24	15.9
	Histopathology		
1	*Adenocarcinoma*	22	14.6
2	*Squamous Cell Carcinoma*	113	74.8
3	*Adenosqamous Carcinoma*	12	7.9
4	*Adenosarcoma*	3	2.0
5	*Carcinosarcoma*	1	0.7
	Degree of Differentiation		
1	Grade I (Well differentiated)	110	72.8
2	Grade II (Moderately differentiated)	20	13.2
3	Grade III (Poorly differentiated)	13	8.6
4	No data found	8	5.3
	Lymphovascular Invasion		
1	There's Invasion	3	2.0
2	No invasion	2	1.3
3	No data found	146	96.7
	KGB metastases		
1	There are metastases	12	7.9
2	No metastases	130	86.1
3	No data found	9	6.0
	Stadium		
1	II B	13	8.6
2	III A	6	4.0
3	III B	127	84.1
4	IV A	4	2.6
5	IV B	1	0.7
	Parity		
1	<3 times (Primiparous)	60	39.7
2	3 times (Multipara)	91	60.3
	Education		
1	SD	38	25.2
2	junior high school	36	23.8
3	high school	67	44.4
4	College	10	6.6
	Employment		
1	IRT/Not working	43	28.5
2	Self-employed	44	29.1
3	civil servant	11	7.3
4	Private	16	10.6
5	farmer	37	24.5
	Number of Marriages		
1	Not married yet	1	0.7
2	Married 1 time	114	75.5
3	Married 2 times	36	23.8
	Menstrual Disorder		
1	*Amenorrhea*	19	12.6
2	*Metrorrhagia*	13	8.6
3	*Menorrhagia*	51	33.8
4	*Menometrorrhagia*	48	31.8
5	No disturbance	20	13.2

No	Characteristics	Amount	Percent
	Contraception		
1	Hormonal	67	44.4
2	Non-Hormonal	20	13.2
3	No KB	64	42.4
	Cancer History		
1	There's History	15	9.9
2	No history	136	90.1
	Body Mass Index (BMI)		
1	Underweight	26	17.2
2	Normal	111	73.5
3	Overweight	8	5.3
4	Obesity	6	4.0
	Living Area		
1	Poor	49	32.5
2	Out of town	102	67.5
	Types of Chemoradiation		
1	1 week	13	8.6
2	3 weeks	138	91.4
	Types of Chemotherapy		
1	*Adjuvant chemotherapy*	145	96.0
2	*Palliative chemotherapy*	6	4.0
	Chemotherapy Regimen		
1	Carboplatin+Fancopage	94	62.3
2	Carboplatin+Paclitaxel	41	27.2
3	Carboplatin+Paxus	3	2.0
4	Carboplatin	13	8.6
	Radiation Type		
1	Definitive curative	145	96.0
2	palliative	6	4.0
	Radiation Engineering		
1	*External Beam Radiation Therapy*	66	43.7
2	*Brachytherapy*	1	0.7
3	*EBRT and Brachytherapy*	84	55.6
	Survival status		
1	Yes	87	57.6
2	No	64	42.4
	Total	151	100.0

Based on the analysis of the data in the table, it is known that 151 respondents in this study, showed that most of the respondents were 51-60 years old, lived outside the city of Malang, had a high school education, worked as an entrepreneur and householder, married 1 time, parity 3 times. (multipara), using hormonal contraception, having menstrual disorders in the menometrorrhagia category, no history of cancer, having a BMI in the normal category, receiving 3-week chemotherapy, receiving adjuvant chemotherapy, receiving carboplatin + fancopage chemotherapy regimen, receiving definitive curative radiation, receiving the EBRT radiation technique combine with brachy therapy, had histopathology in the *adenosquamous carcinoma* category, had a grade I (well differentiated) degree, no lymphovascular invasion, no lymph node metastases, already in stage iii b, and survive.

The results obtained were 87 people which is 57.6% were survive and 64 people or 42.4% did not survived. This is lower than the previous study by Sherly in 2014, with a survival rate of 72%. This is possible because in this study only one-year of survival was performed for patients with locally advanced cervical carcinoma (LAAC) with limited coverage of patients only receiving external radiation therapy without brachy therapy. This is also following previous studies at stage IIB having a survival rate of 60 to 65%. In Stage III the survival rate is 30-50%, and in stage IV it is 20-30%. (P faendler et al., 2018). Where in this study, the stage characteristics of cervical carcinoma patients who underwent chemoradiation in RSUD dr. Saiful Anwar Malang is stage IIB, III A, IIIB, IVA, IVB.

The lowest *person time* of chemoradiation patients in RSUD dr. Saiful Anwar Malang is 3 months and the longest is 60 months. The average value of *person time* for chemoradiation patients at RSUD dr. Saiful Anwar Malang is 45.8013 months with 18.17948 months for standard deviation. The standard deviation value which is smaller than the average indicates that the variation in *person time* between respondents tends to be small. Following the theory that an individual *person time* of cervical carcinoma will be influenced by many factors, including the clinicopathological profile, risk factors, and prognostic factors. Chemotherapy treatment combined with radiotherapy at the same time, is intended to increase the effectiveness of treatment to maximalize patient survival as indicated by an increase in *person time* which is considered a measure of the expected clinical benefit as a risk and analysis to performed the

effectiveness obtained from clinical care. This is illustrated by the longest person time of 60 months which indicates the patient is still surviving.

Table 2
Description of Person Time

Variable	N	Minimum	Maximum	mean	Std. Dev
Person Time	151	3	60	45.80	18.179

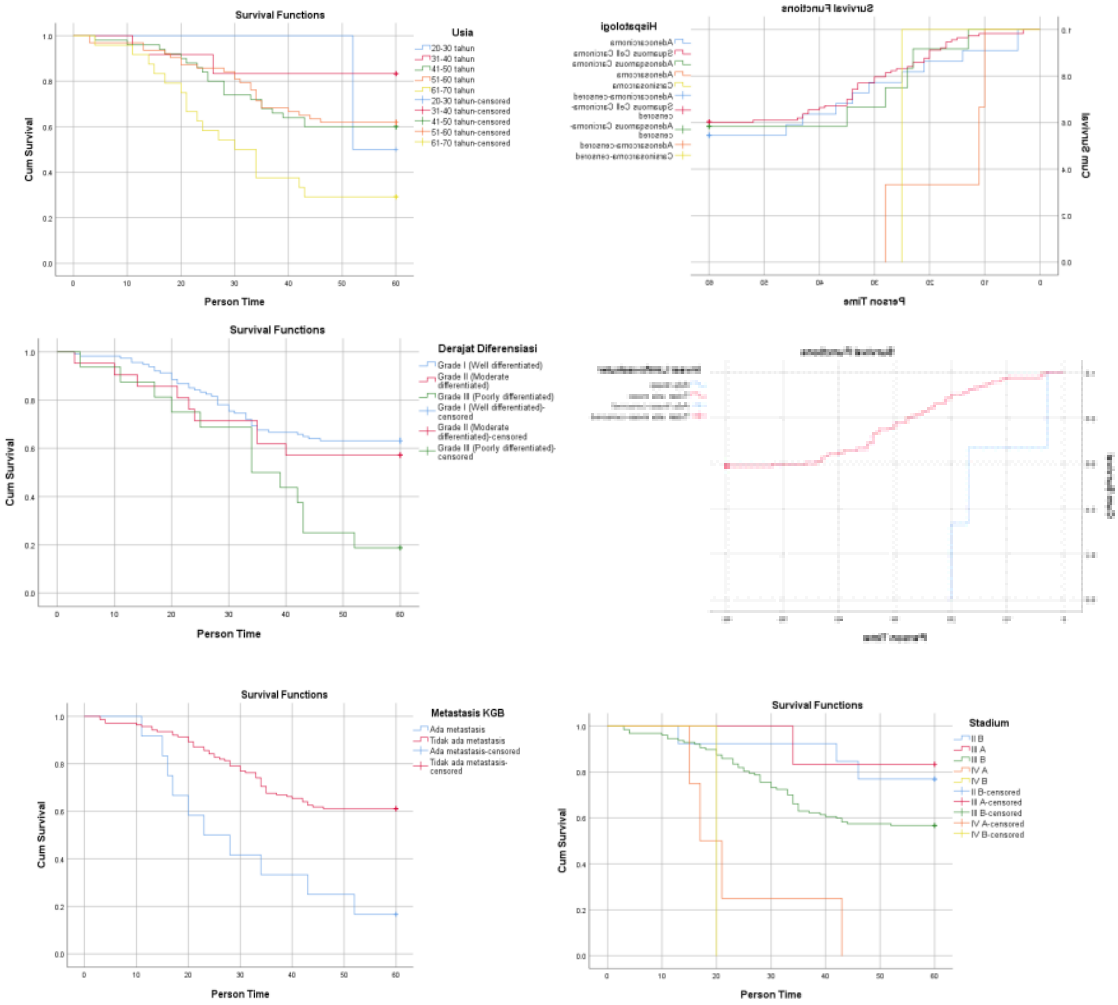

Figure 1. Kaplan Meier Curve of Clinicopathological Profile: Age, Histopathological Classification, Grade of Differentiation, Lymphovascular Invasion (LVSI), Lymph node Metastasis, Stage.

Based on the data, the results showed that there were significant differences between categories.: age, histopathology classification, and stage of the survival. This is analogous to the theory that women aged 71 – 80 years have physical susceptibility and decreased immunity, also an age who have fewer activities and workloads that increase stressors and tend to need the help of others to get treatment (Scatchard et al., 2012). This is following previous studies which suggested that adenocarcinoma had a worse prognosis and response to treatment when compared to other histopathology types (Karadag Arli et al., 2019). Accordance with research conducted by P faendler et al., 2018 stage IIA has a 5-year survival of 70-90%, for stage IIB has a survival of 60 to 65%. In Stage III the survival rate is 30-50%, and in stage IV it is 20-30%. Based on the data, the results showed that there were no significant differences in the variables Grade of Differentiation, Lymphovascular Invasion (LVSI), and Lymph node Metastasis. This is because some of the data are not completed by the examination, where as in fact this examination is important to support the diagnosis and accuracy of therapy.

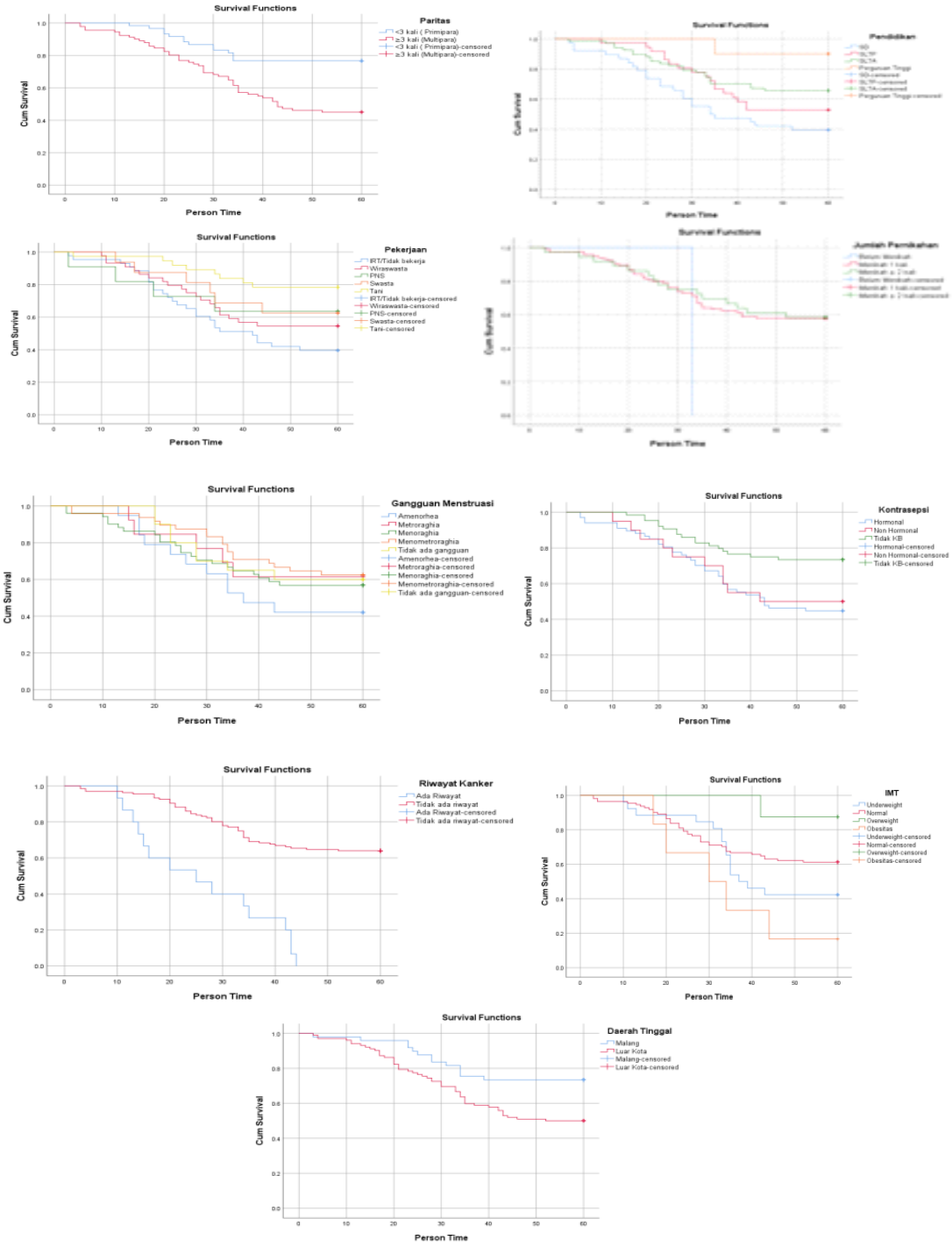

Figure 2. Kaplan Meier Curve of Risk Factors: Parity, Education, Employment, Number of Marriages, Menstrual Disorders, Contraception, Cancer History, Body Mass Index (BMI), Area of Residence.

Based on the results of the study, there was a significant effect on the variables Parity, Education, Number of Marriages, Menstrual Disorders, Contraception, Cancer History, Body Mass Index, and Area of residence. This can be explained from the existing literature, that women who have more than 3 parity numbers have a 5.5 greater risk (Aballéa et al., 2020). Low education is at risk for cervical carcinoma because the level of education is related to knowledge and awareness of health (Momenimovahed & Salehiniya, 2017). The number of marriages is related to sexual activity and the number of sexual partners. The younger the woman who is sexually active and often changes partners, have greater the risk (Ryan et al., 2019). Menstrual disorders are important indicators of reproductive system dysfunction that can be associated with an increased risk of cervical carcinoma (Nkfusai et al., 2019). The risk of non-invasive and invasive

cervical carcinoma is associated with the long-term use of contraception (Putri et al., 2019). It is known that patients without a history of cancer have a higher survival rate than patients with a history of cancer. Women with a family history of cervical carcinoma, have a risk of cervical cancer as much as 2 times. This is related to the occurrence of DNA damage that carries the characteristics of cancer cells (Wright & Ronnett, 2018). Normal BMI results are a better spread of clinical response, with a more variable distribution even though the progressive response is dominant (Madli et al., 2019). Area of residence, including the distance of residence and availability of health service facilities are related to a person's perception of obtaining health services (American Cancer Society, 2021). While the work variable was not found to be significant, this is possible because in general when someone is sick, a person will not work anymore, and focuses on therapy.

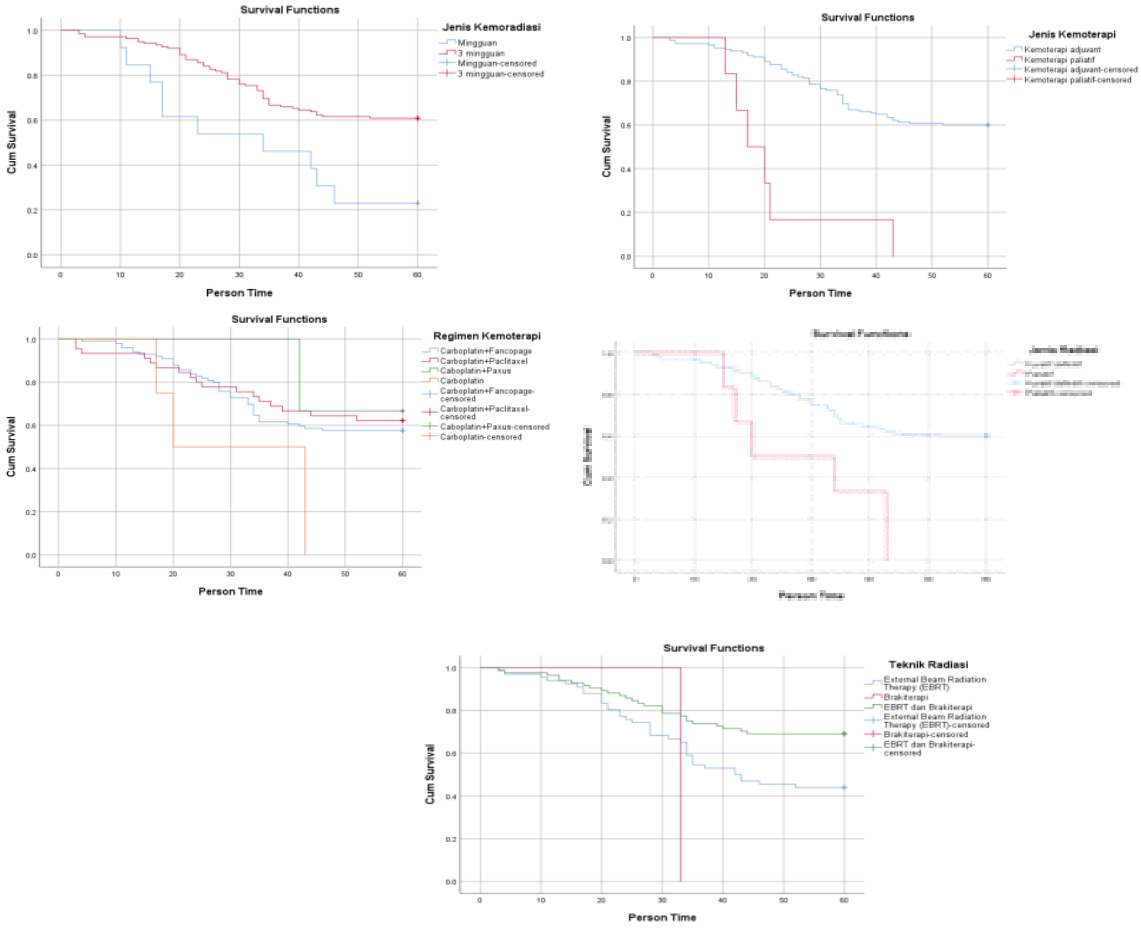

Figure 3. Kaplan Meier Curve of Prognostic Factors: Type of Chemoradiation, Type of Chemotherapy, Type of Chemotherapy Regimen, Type of Radiation, Radiation Technique

There was a significant effect of prognostic factors on the survival of cervical carcinoma patients in the categories of Chemoradiation Type, Chemotherapy Type, Radiation Type, and Radiation Technique. This can be explained as follows, from various studies it seems that 3-week therapy has a higher total response rate, disease progression-free survival, and overall survival compared to weekly, but with higher toxicity (Ovodenko et al., 2021). Adjuvant chemotherapy is usually given for newly diagnosed stage IB2 or higher, which tends to have a better prognosis, whereas palliative chemotherapy has a worse prognosis (Ovodenko et al., 2021). Based on the results of the *Kaplan Meier* curve, it was found that patients with carboplatin + paclitaxel chemotherapy regimens had the highest survival, while patients with carboplatin chemotherapy regimens alone had the lowest survival but no significance was found because the diversity of variable categories could lead to data be lack in the bivariate test.

The results of the significance test showed to examine the effect on the survival of cervical carcinoma patients undergoing chemoradiation at dr. Saiful Anwar Malang hospital, using the Cox regression test has found that there was a significant effect between age, employment, history of cancer, BMI, type of chemoradiation, type of radiation, radiation technique, histopathological classification, lymphovascular invasion, lymph node metastasis, stage. There was no significant effect on the variables of residence, education, number of marriages, parity, contraception, menstrual disorders, type of chemoradiation, chemotherapy regimen, or grade of differentiation. This relates to the Cox regression analysis model; here is a selected analysis conducted to see the effect of the independent variable on

the dependent variable of the best model after the backward method based on the value of the Wald test.

Table 3
Cox . Regression Analysis

No	Coefficient	B	SE	Wald	df	Sig.	Exp (B)
1	Age	0.512	0.177	8,401	1	0.004*	1,669
2	Living Area	-0.422	0.389	1.180	1	0.277	0.656
3	Education	-0.316	0.183	2,962	1	0.085	0.729
4	Work			6,817	4	0.146	
	Job (1)	1.034	0.455	5.164	1	0.023*	2.812
	Job (2)	0.936	0.529	3.134	1	0.077	2,549
	Job (3)	1.555	0.830	3.509	1	0.061	4.734
	Job (4)	1,208	0.658	3.376	1	0.066	3.348
5	Number of Marriages	0.082	0.376	0.047	1	0.829	1.085
6	parity	0.882	0.436	4.085	1	0.043*	2.416
7	Contraception			1.118	2	0.572	
	Contraception (1)	0.400	0.384	1.083	1	0.298	1,491
	Contraception (2)	0.168	0.475	0.125	1	0.724	1.183
8	Menstrual Disorder			5,931	4	0.204	
	Menstrual Disorder (1)	-0.184	0.619	0.088	1	0.767	0.832
	Menstrual Disorder (2)	-1,797	0.932	3,719	1	0.054	0.166
	Menstrual Disorder (3)	-0.434	0.489	0.789	1	0.375	0.648
	Menstrual Disorders (4)	-0.779	0.523	2.221	1	0.136	0.459
9	Cancer History	-1.255	0.580	4.686	1	0.030*	0.285
10	Body mass index	-0.548	0.232	5.574	1	0.018*	0.578
11	Types of Chemoradiation	-1.625	0.805	4.074	1	0.044*	0.197
12	Types of Chemotherapy	-3.141	0.916	11.751	1	0.001*	0.043
13	Chemotherapy regimen			5.544	3	0.136	
	Chemotherapy Regimen (1)	2.416	1.377	3.079	1	0.079	11.202
	Chemotherapy Regimen (2)	1,622	1.353	1.439	1	0.230	5.065
	Chemotherapy Regimen (3)	1.668	1,761	0.897	1	0.344	5.302
14	Radiation Type	3.556	1,571	5.121	1	0.024*	35,026
15	Radiation Engineering			8,476	2	0.014*	
	Radiation Engineering (1)	0.730	0.319	5,223	1	0.022*	2.075
	Radiation Engineering (2)	3.521	1.546	5.184	1	0.023*	33,806
16	histopathology			15,143	4	0.004*	
	Histopathology (1)	-4.064	1.325	9.412	1	0.002*	0.017
	Histopathology (2)	-4.434	1,295	11,727	1	0.001*	0.012
	Histopathology (3)	-3.464	1.458	5,643	1	0.018*	0.031
	Histopathology (4)	-4.784	1.825	6.869	1	0.009*	0.008
17	Degree of Differentiation	0.196	0.264	0.549	1	0.459	1.216
18	Lymphovascular Invasion	-1,248	1.218	1.049	1	0.306	0.287
19	KGB metastases	-2.028	0.652	9,659	1	0.002*	0.132
20	Stadium	1,211	0.523	5.351	1	0.021*	3.356

Notes. The value of the chi-square table at degrees of freedom (db) 1 at a significance level of 5% is 3.841

LIMITATION OF THE STUDY

The retrospective design tends to have potential confounders, in this case there is limited data on the variables of lymphovascular invasion, degree of differentiation, and lymph node metastasis because not all of them were examined.

CONCLUSIONS AND SUGGESTIONS

The 5-year survival rate of cervical carcinoma patients undergoing chemoradiation at dr. Saiful Anwar Malang is 57.6%. There is a significant influence on clinicopathological profile, risk factors, and prognostic factors. This study was found that there was some lack in the data that led to a decrease in the level of significance, to improve the quality of therapy and to improve survival, examination of lymphovascular invasion, grade of differentiation, and lymph node metastasis must do at all cervical carcinoma patients.

Acknowledgment

Gratefully acknowledged to dr. Yahya Irwanto Sp.OG (K), who has given permission and support to conduct this research, thanks to Diklit, Medical Record staff of RSUD dr. Saiful Anwar Malang who has provided to support us, so this research can be carried out properly as expected.

ETHICAL CONSIDERATIONS

Approved by the Ethics committee of general hospital dr. Saiful Anwar Malang, with regards to the protection of human rights and welfare in medical research, has carefully reviewed the research protocol entitled with number of registration 400/007/K.3/302/2022.

Conflict of Interest Statement

There is no conflict of interest statement.

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 ISSN 2502-4825 (print), ISSN 2502-9495 (online)