Research Article

The Age as a Risk Factor for Advanced Stage in Cervical Cancer Patients: A Retrospective Multivariate Study

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Abstract

Objectives: To evaluate the relationship between age and the occurrence of advanced-stage cervical cancer in a national referral hospital setting as a step towards effective prevention, early detection, and management.

Methods: This research adopts a retrospective study design based on the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital focusing on cervical cancer patients from 2019 to 2022. Multivariate analysis was conducted with age as the primary independent variable, considering parity and employment status in the analysis. The FIGO classification of cervical cancer stages was used to categorize patients into early and advanced stages.

Results: Out of 512 cervical cancer cases, 492 were included in this study. The distribution of cervical cancer stages shows Ninety-one subjects (18.4%) were classified as having early-stage cervical cancer, while 401 other subjects (81.6%) were classified as having advanced-stage cervical cancer. The age distribution of patients is 273 cases (55.4%) in the 18-54 years old group and 219 cases (44.6%) in the >54 years old group. The multivariate analysis of the relationship between cervical cancer stage and age shows an increased risk towards the occurrence of higher cervical cancer stages, and is statistically significant ($p<0.05$) with an odds ratio of 2.13, particularly in individuals aged >54 years.

Conclusion: Age over 54 years is a significant risk factor for advanced-stage cervical cancer. Although there is no significant association with parity and employment history, these findings support preventive and early detection efforts in the older population. Increased screening programs and education are expected to reduce cases of advanced-stage cervical cancer in the future.

Keywords: age, cervical cancer, FIGO staging, multivariate analysis, risk factor.

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INTRODUCTION

In 2020, cervical cancer ranked as the fourth most common cancer in women globally, with an incidence of 604,000 cases. In Indonesia, cervical cancer holds the second position among the most prevalent cancers in women, with a total of 36,663 cases and 21,003 deaths, accounting for 19.1%; this information is based on the health profile data (2021) of all cancer-related deaths.[1] Approximately 70% of cervical cancer cases in Indonesia are diagnosed at an advanced stage.[2] Known risk factors contributing to cervical cancer include age, histological findings, smoking habits, race, and the initial cancer stage at diagnosis.[3] Several studies conclude that old age is an independent risk factor for the increased occurrence of advanced-stage cervical cancer cases.[3] Cervical cancer is known to be predominantly caused by persistent Human Papilloma Virus (HPV) infections. Among 200 different HPV serotypes, 12 have been deemed carcinogenic, and two of which, HPV-16 and HPV-18 are known as high risk serotypes which accounts for 50% and 10% of cervical cancer cases, respectively.[4] It is known that an infection of the two strains increases risk of cervical cancer by 435-fold and 248-fold respectively.[5] Persistent cervical infections of high-risk HPV serotypes are known to be detected among 99.7% of cervical cancer patients globally, and it is estimated that

roughly 80% of women would be infected by HPV through sexual contact by the age of 45.[5-7] HPV infection that occurs during early adulthood or adolescence, are known to remain asymptomatic for the next 10-15 years, however such infection are known to cause micro damage of the cervical epithelium, allowing pathogens and other HPV serotypes to inflict multiple infections. It has been demonstrated that increasing age is a risk factor for developing multiple HPV infection, which is speculated to be the result of decreased immunity, and the longer duration of time which allowed for the infection to manifest into symptoms of cervical cancer.[8] According to the National Cancer Institute (2013-207), there is a surge in the incidence of advanced-stage cancer cases in the population aged >=55 years compared to those <55 years.[9] Therefore, exploring the connection between age and cervical cancer becomes crucial for prevention, early detection, and effective management. This study aims to investigate the relationship between old age and the occurrence of advanced-stage cervical cancer in cervical cancer patients at Dr. Cipto Mangunkusumo General Hospital from 2019 to 2022.

METHODS

The research design employed in this study is a retrospective study based on the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital for cervical cancer patients from 2019 to 2022. Ethical approval for this study was obtained from the Health Research Ethics Committee of FKUI-RSCM with the approval number KET-1291/UN2.F1/ETIK/PPM.00.02/2023 on October 2, 2023. We conducted multivariate analysis with age as the primary independent variable, considering parity and employment status as other variables in the analysis. Age was categorized into two groups: 18-54 years and >54 years. Parity was divided into two groups: parity history 0-2 and >2. Employment history was also divided into two groups: employed and unemployed. The classification of cervical cancer stages by the Fédération Internationale de Gynecologie et d'Obstetrique (FIGO) was used, where stages IA1-IIA were classified as early-stage, and stages IIB-IVB were classified as advanced-stage. The inclusion criteria for this study were cervical cancer patients registered in the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital from 2019 to 2022 with complete clinical and demographic data, while patients with missing data (e.g., age, parity, employment status, or cancer stage) were excluded. Employment status was classified as "employed" for patients with a recorded profession or job and "unemployed" for those listed as homemakers, retirees, or without employment. Age was categorized into 18-54 years and >54 years, based on evidence from the National Cancer Institute (2013-2017) showing a significant increase in advanced-stage cancer incidence in individuals aged ≥55 years compared to those <55 years.[9] Variables with a P-value <0.25 in bivariate analysis were included in the multivariate logistic regression to analyze associations between age (primary variable), parity, employment status, and cervical cancer stages. The results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals, considering a P-value <0.05 as statistically significant.

RESULTS

Based on medical records, the total number of cervical cancer cases at Dr. Cipto Mangunkusumo from 2019 to 2022 was 512; however, due to data incompleteness, the total cases used in this study amounted to 492. Out of 512 cervical cancer cases recorded at Dr. Cipto Mangunkusumo from 2019 to 2022, 20 cases were excluded due to incomplete sociodemographic data: 8 patients lacked parity information, 7 were missing age data, and 5 did not have employment status recorded. This resulted in a total of 492 cases included in the analysis.

The distribution of age, parity, occupation and cervical cancer stages among patients can be observed in Table 1. Ninety-one subjects were classified as having early-stage cervical cancer, while 401 other subjects were classified as having advanced-stage cervical cancer. The relationship between cervical cancer stage and sociodemographic factors can be seen in Table 2.

The table presents the sociodemographic profile and stages of cervical cancer. In terms of age, there were 273 cases in the 18-54 years old group and 219 cases in the >54 years old group, with a significant association ($p<0.05$) and an adjusted odds ratio (aOR) of 2.13 (95% CI: 1.28-3.53). Regarding parity, 262 cases were in the 0-2 parity group and 230 cases were in the >2 parity group, with no significant association ($p=0.59$) and an aOR of 1.13 (95% CI: 0.70-1.84). Regarding occupation, there were 69 cases among the employed and 423 cases among the unemployed, with no significant association ($p=0.58$) and an aOR of 1.20 (95% CI: 0.61-2.38).

The non-significant findings for parity and employment status may reflect the complex interplay of sociodemographic and clinical factors that were not fully captured in this study, such as broader socioeconomic conditions or health-seeking behaviors. Study limitations include the retrospective design, reliance on secondary data prone to missing information, and the inability to explore other potential confounders not recorded in the dataset, which may influence the associations observed.

DISCUSSION

According to data from the Indonesian Ministry of Health, the incidence of cervical cancer cases in Indonesia continues to increase each year, with the discovery of 40,000 new cases annually and approximately 7,000 deaths each year.[2] About 70% of new cases are diagnosed at an advanced stage.[2] In this study, approximately 81.5% of cervical cancer cases were found at an advanced stage (IIB-IVB). Similar findings were obtained in another study, where 64.1% of cases were diagnosed at an advanced stage (IIIB), with the highest incidence in the age group of 51–60 years.[3] In Table 2, an increase in advanced-stage cases was observed in the age group of 18-54 by twofold, while in the age group >54 years, advanced-stage cases increased sevenfold. Another study states that 63% of advanced-stage cervical cancer cases were found in patients aged ≥65 years.[10] Several factors that may support this include a decline in the immune system function in elderly patients, affecting the growth and spread of cancer cells.2 Other factors may be influenced by a lack of early detection or screening coverage, leading to most cases being diagnosed at an advanced stage.[11] Age itself can affect cervical tissue changes; long-term exposure to estrogen and progesterone hormones can lead to changes in the transformation zone of the cervix, increasing the risk of pre-cancerous lesions and cervical cancer itself.[11] The possibility of infection by certain HPV types also has the potential to progress to an advanced stage in patients. In this study, old age was found to be statistically significant ($p<0.05$).[11]

In examining the correlation between age and the increased risk of advanced-stage cervical cancer in individuals aged above 54, an intriguing aspect emerges, suggesting a potential link between the progression of the disease and the historical lack of screening practices, particularly during the early stages of adulthood or before the age of 30. The discussion revolves around the assumption that individuals in this older age group may not have undergone comprehensive screening measures during their formative years, a critical period for the early detection of cervical abnormalities.[12] Currently, various methods are available for cervical cancer screening. Screening for high-risk HPV (hr-HPV) is now considered the gold standard for preventing cervical cancer and other HPV-related diseases. In high-resource countries, current screening strategies include cytological evaluation (Pap smear), nucleic acid HPV testing, or a combination of both. Visual inspection with acetic acid (VIA) is another method commonly performed in developing countries, aiming to detect pre-cancer and early cancer lesions in apparently normal and asymptomatic women. Additionally, urine-based HPV-DNA testing using CerviScan has been studied in Indonesia and has demonstrated reliability in detecting high-risk HPV subtypes. This test could serve as an alternative method for HPV-DNA testing to expand cervical cancer screening programs.[13] This assumption draws attention to the possibility that, without

regular screenings and proactive healthcare initiatives at a younger age, there might be missed opportunities for identifying precancerous lesions or early-stage cervical cancer. Consequently, the disease may evolve unnoticed, gaining momentum and reaching advanced stages before clinical intervention. While this hypothesis underscores the importance of early and consistent screening practices, it's essential to emphasize that it is speculative in nature and warrants empirical investigation to substantiate the claim definitively. Addressing this assumption through further research could shed light on the effectiveness of current screening programs and potentially inform the development of targeted interventions for specific age groups, ultimately contributing to more tailored and impactful cervical cancer prevention strategies. Implementing a mandatory HPV vaccination program for elementary school children by the Indonesian government could be a key strategy for cervical cancer prevention in Indonesia. This program has the potential to protect both younger and older individuals in the future from HPV infections, including high-risk types, thereby reducing the likelihood of developing cervical cancer.[14]

Cases of advanced-stage cervical cancer were also found to be higher in populations with parity history 0-2 (79.3%) and in populations with parity history >2 (83.9%). My previous study also compared parity with cervical cancer stages. The results showed no significant difference in cervical cancer stages at diagnosis between the parity groups ($p = 0.058$).[15] Another meta-analysis states a similar finding. This can be explained by the high levels of estrogen and progesterone hormones during pregnancy, especially in the late stages.[16] In the third trimester, metaplasia of the transformation zone also significantly increases, contributing to the occurrence of uterine cancer.[16] However, in this study, no significant statistical difference was found between the two groups ($p=0.59$).

A total of 81.3% of advanced-stage cases were found in patients who were unemployed. Another study links employment status to cervical cancer incidence, where 39.4% of cervical cancer cases are unemployed patients. Employment status is indirectly related to cervical cancer incidence. Employment status, especially in the unemployed population, correlates with low socioeconomic status. In this study, socioeconomic status is said to affect patient knowledge. The population with stable employment is likely to have better access to education and information about cervical cancer, while the population with low socioeconomic status is assumed to have less awareness of cervical cancer and its prevention methods, leading to less effective screening and advanced gynecological examinations.[17] However, no significant statistical relationship was found in this study ($p=0.58$).

CONCLUSIONS

Based on the results of this study, it can be concluded that age is a significant risk factor for the occurrence of advanced-stage cervical cancer in patients with cervical cancer at Dr. Cipto Mangunkusumo General Hospital during the period 2019-2022. Age over 54 years has a statistically significant relationship with an increased risk of advanced-stage cases. Although there is no significant relationship between the patients' parity history and employment status with cervical cancer stage, these findings provide important insights into efforts for prevention, early detection, and effective management of cervical cancer, especially in the elderly population. These findings can ultimately be applied as soon as possible through rigorous screening for elderly women by not only gynecologists, but as early as possible from general practitioners, and emphasizing the need for national-scale programs for cervical cancer screening in the elderly. Besides that, future research can be directed to see whether any additional modifiable and unmodifiable risk factors add to the prevalence of advanced stage cervical cancers, and see whether added effects from the risk factors increase the likelihood of said cancers.

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CONFLICT of INTEREST

None.

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Tabel 1. Profile of Patient Characteristics in Cervical Cancer Patients at Dr. Cipto Mangunkusumo General Hospital in the Years 2019–2022 (n=492)

Category	N	%
Age (y o)		
18-54	273	55.50
>54	219	44.50
Parity		
0-2	262	53.20
>2	230	46.80
Occupation		
Employed	69	14.00
Unemployed	423	86.00
Cervical Cancer Stage		
Early	91	18.50
Late	401	81.50

Table 2. Relationship between Cervical Cancer Stage and Demographic Factors in Cervical Cancer patients at Dr. Cipto Mangunkusumo General Hospital in the Years 2019–2022 (n=492)

Sociodemographic	Cervical Cancer Stages			*P-value*	aOR
Age (y o)	**Early**	**Late**	**Total**		**95% CI**
18-54	64	209	273	<0.05	2.13 (1.28-3.53)
>54	27	192	219		
Parity					
0-2	54	208	262	00.59	1.13 (0.70-1.84)
>2	37	193	230		
Occupation					
Employed	12	57	69	00.58	1.20 (0.61-2.38)
Unemployed	79	344	423		