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Comparison of ADC and K^{trans} values with mitotic rate and histopathological subtypes of endometrial cancer

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Abstract

Endometrial cancer is the most common gynecological cancer in women, after breast, colon, and lung cancer. This study aims to analyze the comparison between ADC values and Ktrans values in patients with high and low risk subtypes of endometrial cancer and the mitotic rate of endometrial cancer. This study used a diagnostic test with a retrospective design. The sample population consisted of endometrial cancer patients who underwent pelvic MRI and hysterectomy or biopsy at Dr. Soetomo Regional General Hospital. The study population consisted of 65 patients. In this study, 47 low-risk endometrial cancer samples and 18 high-risk samples were obtained. The range of endometrial cancer Ktrans values was between 0.23-1.33 min-1, while the range of ADC values was between 0.50-1.27 x 10-3 mm2/s. The average Ktrans value was 0.58 min-1 with 34 samples with values below the average and 31 samples above the average. The average ADC value was 0.72 x 10-3 mm2/s with 38 samples below the average. Based on these figures, a diagnostic test using the Mann Whitney test was carried out, showing a relationship between ADC and histopathological subtypes of endometrial cancer, showing a p-value >0.05 (95% CI), which means that statistically there is no significant relationship between ADC and histopathological subtypes of endometrial cancer. A diagnostic test using a t-test revealed no statistically significant association between Ktrans and histopathological subtypes of endometrial cancer. Analysis of the relationship between ADC and the mitotic rate of endometrial cancer using the Spearman's rho correlation test revealed a statistically significant association between ADC and the mitotic rate of endometrial cancer, with a correlation coefficient of -0.34, indicating a weak negative correlation between the two variables. However, the analysis of the relationship between Ktrans and the mitotic rate of endometrial cancer was not significant. Based on diagnostic tests, the association between ADC and Ktrans with endometrial cancer histopathological subtypes and the association between Ktrans and the endometrial cancer mitotic rate was insignificant. Meanwhile, the association between ADC and the endometrial cancer mitotic rate was significant, with a weak negative correlation between the two variables.

Keywords: Endometrial cancer, ADC, Ktrans, MRI, Histopathological subtypes.

Introduction

Endometrial cancer is a gynecological cancer that frequently occurs in women after breast, colon, and lung cancer.[1] In developed countries, endometrial cancer patients are generally 60 years old, whereas in Indonesia, this cancer is found at a younger age, with 63.9% at age ≤50 years and 12.5% at age ≤40 years. The incidence of endometrial cancer per year reaches 9.99 per 100,000 populations worldwide. Mortality rates have increased from 1997 to 2018.[1] Endometrial cancer that has passed more than 50% of myometrial thickness is very aggressive, easily invades lymphovascular spaces, metastasizes to lymph nodes, facilitates tumor recurrence, and worsens prognosis.[2] Histopathological type also affects mortality; more than 16% of endometrial cancer deaths are caused by high-risk histopathological types, which is a large number considering that high-risk histopathological types only comprise 10-20% of endometrial cancers.[3] Another significant prognostic index in endometrial cancer is mitotic rate. Mitotic rate is related to cancer proliferation, where high proliferation means faster cancer growth, resulting in worse prognosis.[4]

MRI is considered the most precise method for assessing the extent of endometrial cancer within the body due to its exceptional ability to distinguish between soft tissues.[5] Preoperative MRI examination for determining treatment is very significant because surgical technique depends on local stage and two histopathological types of endometrial cancer, namely low-risk and high-risk.[6] Therefore, to boost the accuracy of diagnosis and prognosis in endometrial cancer, advanced MRI methods are being merged with conventional MRI. These emerging techniques, including DCE-MRI, DWI, and ADC mapping, are tailored to correspond with specific histopathological subtypes[5].

The DWI technique provides insight into tissue microstructure by tracking the diffusion of water protons. A key quantitative metric derived from DWI is the ADC value. Clinically, a reduced ADC value often

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points to increased cellularity within a mass[5]. In Bharwani et al.'s study, it was found that ADC values showed a tendency to be lower in relation to grades 1, 2, and 3 endometrioid carcinoma, although statistically not significant.[7] In further research, it was found that there was a significant difference in decreased ADC value in high-risk endometrioid grade 3 (0.680×10^{-3} mm^2/sec) compared to low-risk grade 1 (0.829×10^{-3} mm^2/sec) and 2 (0.786×10^{-3} mm^2/sec).[8] Quantitative parameters obtained from DCE-MRI are flux rate constant (Kep), volume transfer constant (K^{trans}), and extracellular volume (Ve). Volume transfer constant (K^{trans}) acts as a functional parameter in relation to the appropriate pharmacokinetic model and has the ability to highlight the rate of contrast agent transport from blood plasma to the extravascular-extracellular space, which can be used when evaluating low-risk or high-risk endometrial cancer because K^{trans} in high-risk endometrial cancer (0.04-0.05 min^{-1}) shows significantly lower values compared to low-risk (0.09-0.12 min^{-1}).[9]

Currently, there is no research comparing ADC values and K^{trans} values with mitotic rate and histopathological subtypes of endometrial cancer. To investigate imaging biomarkers for aggressiveness, this study at Dr. Soetomo Hospital performed a comparative analysis of ADC and K^{trans} values in patients, stratifying by endometrial cancer risk subtype and correlating findings with mitotic rate. It is hoped that through these results, radiologists can estimate histopathological subtypes of endometrial cancer on advanced MRI examination and can facilitate gynecologists in evaluating endometrial cancer, thereby increasing the accuracy of endometrial cancer diagnosis for surgical technique purposes.

Based on this background, this study aims to analyze the comparison between ADC values and K^{trans} values in patients with high-risk and low-risk endometrial cancer subtypes and mitotic rate of endometrial cancer.

Materials and Methods

This study is a comparative analytical study with retrospective design. The target population in this study is endometrial cancer patients who underwent pelvic MRI examination using ADC sequence and DCE-MRI on 3 Tesla MRI and had not received surgery, chemotherapy, or radiotherapy at the Radiology Installation of Dr. Soetomo Regional Hospital. The accessible population includes endometrial cancer patients who met these criteria and underwent MRI examination in the period from January 2022 to December 2024. Research samples were taken using total sampling method, namely all accessible populations that met the inclusion criteria were made research samples.

Patients were included in this study if they had a clinical diagnosis of endometrial cancer, underwent advanced MRI between January 2022 and December 2024, and proceeded to definitive surgical resection or biopsy post-MRI. Complete and accessible medical records were also required for inclusion. Exclusion criteria include patients with a history of other cancers, patients who had artifacts on MRI examination, and patients with endometrial cancer lesion sizes too small to be detected by MRI, namely less than 15 mm^2.

This study was conducted at the Radiology Installation of Dr. Soetomo Regional Hospital Surabaya in the period from January 2025 to March 2025. Research instruments used include 3 Tesla MRI brand Siemens Magnetom Skyra with sequences T1WI TSE, T2 FSE FatSat, and T1WI TSE FatSat with contrast on axial, coronal, and sagittal slices, as well as DWI sequence. The intravenous contrast agent used was Dotarem (Gadoteric acid) with a concentration of 0.5 mmol/ml. In addition, patient medical records were used to obtain demographic data and anatomical pathology examination results.

Under the supervision of two expert consultant radiologists with more than two decades of experience in female imaging, an advanced Radiology resident performed all data collection and measurements. The MRI data were then organized and entered into dedicated case report forms. Subsequently, data including DWI sequence, ADC value, Time Intensity Curve (TIC) type, and histopathological results were arranged in table form to analyze frequency and distribution.

Statistical analysis was conducted with SPSS software (version 25.0). A descriptive analysis was employed to categorize data by age and study variables, evaluating their frequency and distribution.

Quantitative analysis was performed through comparison tests to compare ADC and K^{trans} values in high-risk and low-risk endometrial cancer subtype patients and based on mitotic rate. In addition, comparative analysis was performed between measurements by first and second observers for ADC and K^{trans} values using Cohen's Kappa interrater reliability test and Interclass Correlation Coefficient (ICC). Kappa values are interpreted as slight at range 0.01–0.20, fair at 0.21–0.40, moderate at 0.41–0.60, good at 0.61–0.80, and very good to almost perfect at 0.81–1.00. Meanwhile, ICC values less than 0.5 indicate poor reliability, 0.5–0.75 moderate reliability, 0.75–0.9 good reliability, and above 0.9 very good reliability.

Before performing bivariate analysis, data normality test was first performed. To evaluate data normality, the Shapiro-Wilk test was applied to samples of n < 50, and the Kolmogorov-Smirnov test to samples of n < 100. For normally distributed data, the independent t-test was used for analysis; for non-normally distributed data, the Mann-Whitney U test was applied. Correlations were assessed using Spearman's rho. A p-value of less than 0.05 (95% confidence level) was considered statistically significant, and results are presented in tabular format. The study was conducted after obtaining approval from the UNAIR Medical Research Ethics Commission submitted before study implementation, and respondents were not charged for data collection related to this study.

Results

Samples used were from the period January 2022 to December 2024. The number of samples obtained was 65 samples. Researchers assessed the comparison of ADC values and K^{trans} values with mitotic rate and histopathological subtypes of endometrial cancer. Researchers also correlated the relationship between ADC and histopathological subtypes of endometrial cancer and mitotic rate, as well as between K^{trans} and histopathological subtypes of endometrial cancer and mitotic rate. Re-measurement of ADC and K^{trans} values of pelvic MRI in patients with endometrial cancer was performed by two radiologists who did not know the histopathological analysis results of endometrial cancer, and readings were performed separately. All data were recorded on data collection sheets. Research data in the period from January 2022 to December 2024 with a diagnosis of endometrial cancer who underwent pelvic MRI totaled 98 samples. Samples that met inclusion and exclusion criteria totaled 65 samples.

Research sample distribution: Research samples with a total of 65 patients with distribution based on age and histopathological subtypes of endometrial cancer according to table 1.

Table 1. Research sample distribution

Age	Low Risk (n = 47)	High Risk (n = 18)	Total Sample (n = 65)
21 - 30 years	4	3	7 (10,8 %)
31 - 40 years	10	2	12 (18,5 %)
41 - 50 years	12	3	15 (23,1 %)
51 - 60 years	14	8	22 (33,8 %)
61 - 70 years	6	2	8 (12,3 %)
71 and above	1	0	1 (1,5 %)

In this research sample, there were no cases of endometrial cancer at age below 20 years, and the oldest sample age obtained was 73 years. Based on table 5.1, it can be seen that the age distribution of samples was most common at age 51 to 60 years (33.8%) and second most common at age distribution 41 to 50 years at 23.1% of total samples. Samples with low risk (72.3%) were more numerous than samples with high risk (27.7%). Both low-risk and high-risk samples showed the most common distribution at age 51 to 60 years.

Distribution of ADC and K^{trans} data from 65 samples is presented in table 2.

Table 2. Distribution of ADC and K^{trans} in patients with endometrial cancer at Dr. soetomo regional hospital from January 2022 to December 2024

	K^{trans}	ADC
Minimum	0.23	0.50
Maximum	1.33	1.27
Median	0.55	0.70
Mean	0.58	0.72
Standar deviasi	0.23	15.8

In this study, it was found that the range of K^{trans} values for endometrial cancer was between 0.23-1.33 min^{-1}, while the range of ADC values was between 0.50-1.27 x 10^{-3} mm^2/s. The mean K^{trans} value obtained was 0.58 min-1 with the number of samples with values below the mean being 34 samples and above the mean being 31 samples. The mean ADC value obtained was 0.72 x 10^{-3} mm^2/s with the number of samples below the mean being 38 samples.

Research sample characteristics

Research sample characteristics were assessed based on histopathological subtypes of endometrial cancer, ADC, and K^{trans}. Of 65 samples, 47 were low-risk endometrial cancer samples and 18 were high-risk samples.

Table 3. Sample distribution based on PA and K^{trans}

PA Result	K^{trans}					
	Number	Minimum	Maximum	Median	Mean	Std. Deviation
Low Risk	47	0.23	1.33	0.55	0.57	0.24
High Risk	18	0.33	1.05	0.61	0.62	0.18
Total	65	0.23	1.33	0.55	0.58	0.23

Based on cross-tabulation between histopathological subtypes of endometrial cancer and K^{trans}, it was found that the minimum K^{trans} value for low risk was 0.23 min^{-1} and the highest value was 1.33 min^{-1}, while the minimum K^{trans} value for high risk was 0.33 min^{-1} and the highest value was 1.05 min^{-1}. The average K^{trans} value for low risk was 0.57 min^{-1} and for high risk was 0.62 min^{-1}.

Table 4. Sample distribution based on PA and ADC

PA Result	ADC					
	Jumlah	Minimum	Maximum	Median	Mean	Std. Deviation
Low Risk	47	0.52	1.06	0.69	0.72	0.13
High Risk	18	0.50	1.27	0.71	0.73	0.20
Total	65	0.50	1.27	0.70	0.72	0.15

Based on cross-tabulation between histopathological subtypes of endometrial cancer and ADC, it was found that the minimum ADC value for low risk was 0.52 x 10^{-3} mm^2/s and the highest value was 1.06 x 10^{-3} mm^2/s, while the minimum ADC value for high risk was 0.50 x 10^{-3} mm^2/s and the highest value was 1.27 x 10^{-3} mm^2/s. The average ADC value for low risk was 0.72 x 10^{-3} mm^2/s while for high risk was 0.73 x 10^{-3} mm^2/s. The number of low-risk histopathological subtype endometrial cancer patients with ADC values below the mean value (27 patients) and those above (20 patients) the mean were almost the same. The maximum ADC value in high-risk subtype endometrial cancer was higher than low-risk subtype, but only 2 patients out of 18 patients had ADC higher than the maximum ADC limit of low-risk endometrial cancer patients in this study.

Inter-Observer reliability: To assess reliability between observers using Interclass Correlation Coefficient (ICC) and 95% Confidence Interval (CI), which can show agreement between two or more observers for continuous variables and with Cohen's Kappa for categorical data. The Cohen's Kappa value analyzes the agreement of two observers. The value ranges from -1 to 1, with a value of 1 being perfect agreement while a value of 0 indicates no agreement. Under the condition of not obtaining agreement, data analysis cannot be continued.

Table 5. Cohen's kappa range values

Cohen's kappa	Interpretation
<- 0·2	Poor agreement
0·21-0·4	Fair agreement
0·41-0·6	Moderate agreement
0·61-0·8	Good agreement
0·81-1·0	Very Good agreement

In the statistical results, the Cohen's Kappa value between two observers for ADC was 0.72 (95% CI) with p value <0.05, which means there was good

agreement from both observers, while Cohen's Kappa for K^{trans} was 0.87 (95% CI) with p value <0.05, which means there was very good agreement from both observers. With these results, the statistical data presented can be further analyzed, and the research data used for statistical calculations are the average values from both observers.

Normality test of ADC, K^{trans}, and mitotic rate values

Normality test was performed on ratio-type data, namely ADC, K^{trans}, and mitotic rate data. There were 65 samples in this study, so the Kolmogorov-Smirnov test was used. In the statistical results, mitotic rate and ADC data had p value <0.05 and K^{trans} data had p value > 0.05. It can therefore be concluded that ADC data is normally distributed, so bivariate analysis will use the Mann-Whitney test, while K^{trans} data is not normally distributed, so bivariate analysis will use t-test. Meanwhile, the relationship of mitotic rate with ADC and K^{trans} will be analyzed using Spearman's rho, as will the relationship between ADC and K^{trans} in this study.

Analysis of the relationship between ADC and histopathological subtypes of endometrial cancer

Data analysis was performed using Mann-Whitney test comparison. The relationship between ADC and histopathological subtypes of endometrial cancer showed p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between ADC and histopathological subtypes of endometrial cancer. Although not statistically significant, 13 out of 18 high-risk subtype endometrial cancer patients had ADC values lower than the mean value, which means that high-risk subtype endometrial cancer tends to have low ADC.

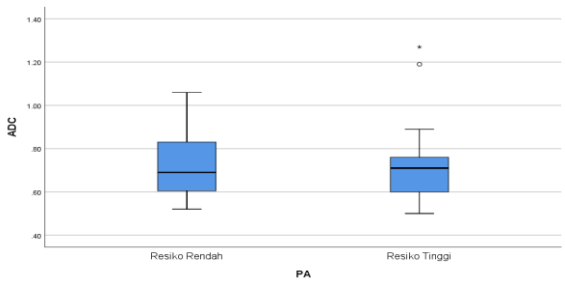

Figure 1. Boxplot diagram of ADC distribution values and histopathological subtypes of endometrial cancer

Analysis of the relationship between K^{trans} and histopathological subtypes of endometrial cancer

Data analysis was performed using t-test comparison. The relationship between K^{trans} and histopathological subtypes of endometrial cancer showed p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between K^{trans} and histopathological subtypes of endometrial cancer. Nevertheless, it was found that the maximum K^{trans} value in high-risk histopathological subtype endometrial cancer patients in this study was lower than the maximum K^{trans} value in low-risk histopathological subtype endometrial cancer patients.

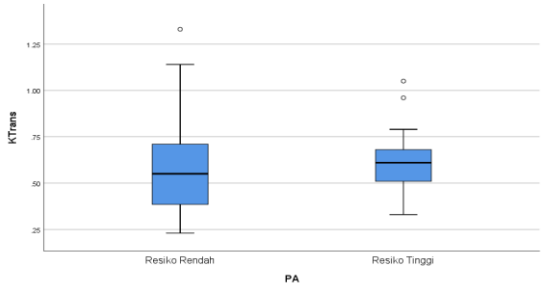

Figure 2. Boxplot diagram of K^{trans} distribution values and histopathological subtypes of endometrial cancer

Analysis of the relationship between ADC and mitotic rate of endometrial cancer

A Spearman's rho correlation analysis revealed a statistically significant, inverse relationship between ADC values and the mitotic rate of endometrial cancer ($\rho = -0.34$, $p < 0.05$, 95% CI). This indicates a weak negative correlation, suggesting that lower ADC values are associated with higher mitotic activity.

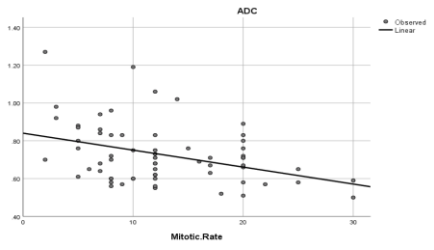

Figure 3. Scatter plot diagram of ADC distribution values and mitoti c rate of endometrial cancer

Analysis of the relationship between K^{trans} and mitotic rate of endometrial cancer

Data analysis was performed using Spearman's rho correlation test. The relationship between K^{trans} and mitotic rate of endometrial cancer showed p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between K^{trans} and mitotic rate of endometrial cancer, although the correlation coefficient shows a value of -0.05.

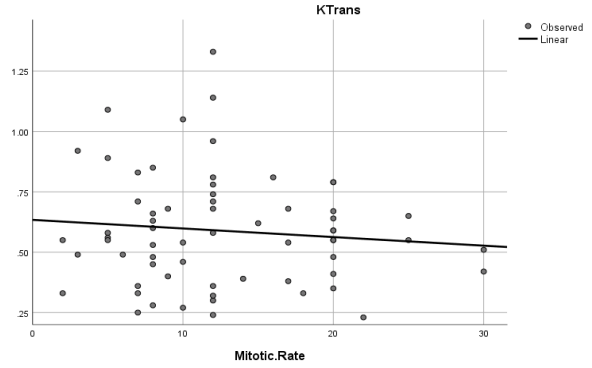

Figure 5. Scatter plot diagram of K^{trans} distribution values and mitotic rate of endometrial cancer

Analysis of the relationship between ADC and K^{trans} in endometrial cancer patients

A Spearman's rho correlation test was performed to assess the relationship between ADC and K^{trans}. The analysis revealed a negligible and statistically non-significant correlation ($\rho = 0.08$, $p > 0.05$), indicating no meaningful association between these two parameters in our cohort.

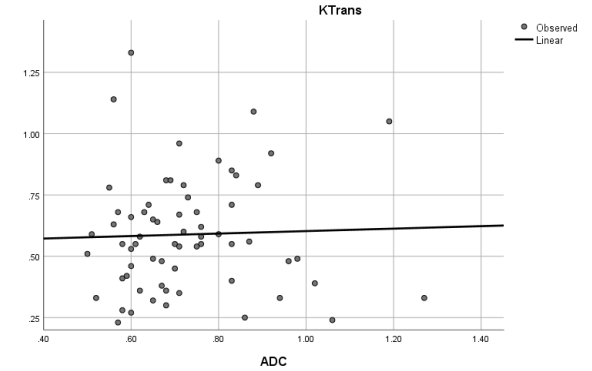

Figure 6. Scatter plot diagram of ADC distribution values with K^{trans} in endometrial cancer patients

Discussion

Analysis of demographics and sample characteristics

The distribution of patient demographics and sample characteristics in this study provides important insights regarding the epidemiology of endometrial cancer, particularly the patient population at Dr. Soetomo Regional Hospital. Of the 65 samples that met the inclusion criteria, the majority of patients were in the age range of 51 to 60 years, namely 22 patients, with a total of patients aged below 60 years being 56 patients out of 65 samples (86.15%), and those aged above 60 years were 9 samples. These results are consistent with Tulumang et al.'s study, which stated that in Indonesia, endometrial cancer patients are most commonly found at age above 50 years, which is younger compared to endometrial cancer cases in developed countries found at age above 60 years.[1] This is related to the average age of Indonesians entering menopause being at age 50 years. In this post-menopausal phase, decreased estrogen and progesterone hormones are found, causing imbalance in endometrial growth, making it prone to endometrial cancer.[10,11]

Based on histopathological subtypes of endometrial cancer, the distribution of samples was most common in low risk, namely 47 samples (72.3%), while high risk was 18 samples (27.7%). This is consistent with the theory that low-risk endometrial cancer / type I is the most frequently occurring subtype.[12]

Validity and Inter-Observer reliability

Validity, reliability, and agreement between two observers are key words for the effectiveness of a study evaluating ratio data. This study was conducted with statistical analysis using two observers. The results of this study showed Cohen's Kappa values for ADC and K^{trans} had intraobserver agreement values with good agreement and very good agreement values, p value < 0.05, which means there is quite high agreement between the two observers. The measurement results from both observers can be said to be consistent and quite reliable, so statistical data analysis can be continued.

Apparent Diffusion Coefficient (ADC) value in low-risk subtype endometrial cancer at Dr. Soetomo Hospital

The number of low-risk endometrial cancer patient samples in this study was 47 patients. ADC values in low-risk subtype endometrial cancer can be seen in table 4, where the minimum value was 0.52 x 10^{-3} mm^2/s and the maximum value was 1.06 x 10^{-3} mm^2/s, with a mean value of 0.72 x 10^{-3} mm^2/s. The number of patients with ADC values below the mean value and above the mean in low-risk subtype endometrial cancer patients was almost the same. In Bharwani et al.'s study, the minimum ADC value in endometrioid carcinoma grade I was 0.74 x 10^{-3} mm^2/s and in grade II was 0.64 mm^2/s, while the mean ADC value in endometrioid carcinoma grade I was 1.02 x 10^{-3} mm^2/s and in grade II was 0.88 x 10^{-3} mm^2/s. When compared to this study, lower values were obtained. Low ADC values indicate higher tumor density and decreased fluid diffusion related to tumor aggressiveness. In addition, this can be related to tumor volume, percentage of necrotic area, or tumor growth.[7] Furthermore, this can also occur because the nature of low-risk endometrial cancer consisting of glandular cancer tissue causes an increase in the amount of fluid outside cells, so the ADC value range becomes wider.[13]

Apparent Diffusion Coefficient (ADC) value in high-risk subtype endometrial cancer at Dr. Soetomo Hospital

The number of high-risk endometrial cancer patient samples in this study was 18 patients. ADC values in high-risk subtype endometrial cancer can be seen in table 4, where the minimum value was 0.50 x 10^{-3} mm^2/s and the maximum value was 1.27 x 10^{-3} mm^2/s, with a mean value of 0.73 x 10^{-3} mm^2/s. In Bharwani et al.'s study, the minimum ADC value in endometrioid carcinoma grade III was 0.72 x 10^{-3} mm^2/s, while the mean ADC value in endometrioid carcinoma grade III was 0.94 x 10^{-3} mm^2/s. These results are similar to those depicted in this study. [7]

Although the maximum ADC value in high-risk subtype endometrial cancer was higher than low-risk subtype, only 2 patients out of 18 patients had ADC higher than the maximum ADC limit of low-risk endometrial cancer patients in this study. This higher ADC value can occur partly because the mitotic rate of one of these patients was low, with poorly differentiated carcinoma histopathology type. Poorly differentiated carcinoma histopathologically is a mixture of low-risk endometrioid carcinoma and solid components that are difficult to differentiate, so samples obtained in these areas can still show high ADC values.[14] Meanwhile, the second patient with serous carcinoma histopathology showed a count of 10/10 HPF in mitotic rate. This means the mitotic rate is quite high, and in patients with serous carcinoma, cell size is large, so the possibility of necrosis in this tumor is large, which can cause ADC values to be high.[15,16] Thirteen out of 18 high-risk subtype endometrial cancer patients had ADC values lower than the mean value. This shows a tendency for ADC in high-risk endometrial cancer to have low values.[7]

K^{trans} value in low-risk subtype endometrial cancer at Dr. soetomo hospital

The number of low-risk endometrial cancer patient samples in this study was 47 patients. K^{trans} values in low-risk subtype endometrial cancer can be seen in table 3, where the minimum value was 0.23 min-1 and the maximum value was 1.33 min-1, with a mean value of 0.57 min-1. In Ye et al.'s study, the median K^{trans} value in low-risk subtype endometrial cancer was 0.10 min-1 with a range of 0.09 – 0.12 min-1.[9] Meanwhile, in Satta et al.'s study, the mean K^{trans} value in low-risk subtype endometrial cancer was 0.55 min-1, which is almost the same as the findings in this study.[17] K^{trans} value reflects the rate of contrast from intravascular to extravascular; a low K^{trans} value can mean blood flow in that area is lower or permeability is lower, so higher K^{trans} values in this study can be caused by higher vascular permeability and higher neovascularization[18].

K^{trans} value in high-risk subtype endometrial cancer at Dr. Soetomo Hospital

The number of low-risk endometrial cancer patient samples in this study was 18 patients. K^{trans} values in low-risk subtype endometrial cancer can be seen in table 3, where the minimum value was 0.33 min^{-1} and the maximum value was 1.05 min^{-1}, with a mean value of 0.62 min^{-1}. The maximum K^{trans} value in high-risk histopathological subtype endometrial cancer patients in this study was lower than the maximum

K^{trans} value in low-risk histopathological subtype endometrial cancer patients. In Ye et al.'s study, the median K^{trans} value in high-risk subtype endometrial cancer was 0.05 min^{-1} with a range of 0.04 – 0.05 min^{-1}.[9] Meanwhile, in Satta et al.'s study, the mean K^{trans} value in high-risk subtype endometrial cancer was 0.32 min^{-1}. K^{trans} value reflects the rate of contrast from intravascular to extravascular; a low K^{trans} value can mean blood flow in that area is lower or permeability is lower. This can be influenced by tumor volume, necrotic area, and capillary endothelial wall.[17]

Comparative analysis between ADC values and K^{trans} values in patients with high-risk and low-risk endometrial cancer subtypes at Dr. Soetomo Hospital

Based on the analysis results of the relationship between ADC and high-risk and low-risk histopathological subtypes of endometrial cancer using Mann-Whitney test, showing p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between ADC and histopathological subtypes of endometrial cancer. Descriptively, it was found that the minimum ADC value decreased more in high risk compared to low risk, but the mean ADC value showed no difference in high risk or low risk. In Ye et al.'s and Basant et al.'s studies, it was stated that a decreasing ADC trend was found with increasing tumor grade, but statistically there was also no significant difference between ADC and high-risk and low-risk histopathological subtypes of endometrial cancer.[9] However, in Satta et al.'s study, lower ADC values were found in high-risk endometrial cancer and were statistically significant.[17] Theoretically, high-risk histopathological subtype endometrial cancer should have low ADC values because of high tumor proliferation. However, this difference in results can be caused by extensive necrotic areas in tumors with high proliferation, thus reducing examination sensitivity. In addition, ADC is not only influenced by tumor proliferation but also by tissue perfusion, relative extracellular volume compared to normal tissue, and stromal conditions. Furthermore, the nature of low-risk endometrial cancer consisting of glandular cancer tissue causes an increase in the amount of fluid outside cells, so the ADC value range becomes wider, while high-risk endometrial cancer forms disorganization, without glands and larger tumor size, so the value range becomes narrower; then the ADC values of these two groups will overlap with each other, causing insignificant results.[13] In this study, the highest ADC limit in endometrial cancer patients was 1.27 x 10^{-3} mm^2/s. When compared to Ye et al.'s and Basant et al.'s studies, similar results were obtained, namely 1.28 x 10^{-3} mm^2/s and 1.2 x 10^{-3} mm^2/s. So the highest cut-off of ADC values in endometrial cancer is at approximately +/- 1.2 x 10^{-3} mm^2/s.[9,19] Research on the relationship of ADC with high-risk and low-risk histopathological subtypes of endometrial cancer still requires further research using more samples and multicenter studies, because controversial results are still obtained.

Based on the analysis results of the relationship between K^{trans} and high-risk and low-risk histopathological subtypes of endometrial cancer using t-test, showing p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between K^{trans} and histopathological subtypes of endometrial cancer. These results are the same as those obtained in Fasmer et al.'s and Haldorsen et al.'s studies, where no significant relationship was found between K^{trans} and histopathological subtypes of endometrial cancer[20,21]. However, it differs from the results obtained in Ye et al.'s study, where there was a significant relationship between K^{trans} and histopathological subtypes of endometrial cancer, where K^{trans} values would be lower in high-risk histopathological subtypes of endometrial cancer.[9] K^{trans} describes the rate of contrast transfer from intravascular to extravascular extracellular; this can be influenced by several things that cause differences in results in existing studies, including capillary permeability and heterogeneity of tumor microvascular characteristics.[20] These different results can also be caused by the small number of high-risk histopathological subtype endometrial cancer cases, resulting in selection bias.

Comparative analysis between ADC values and K^{trans} values with mitotic rate of endometrial cancer patients

Based on the analysis results of the relationship between ADC and mitotic rate of endometrial cancer using Spearman's rho test, showing p value results <0.05 (CI 95%), which means that statistically there

is a significant relationship between ADC and mitotic rate of endometrial cancer, with a correlation coefficient of -0.34, which means there is a weak negative correlation between the two variables. This is consistent with Kishimoto et al.'s study results, which stated that there is a significant correlation between ADC and mitotic rate of endometrial cancer with a correlation coefficient of -0.74, which means there is a strong negative correlation between the two variables. This is consistent with existing theory because ADC values will decrease if there is high tumor proliferation, causing restriction of fluid within tumor cells.[13] The difference in correlation strength can be related to differences in tumor volume and extensive necrotic tissue, which are other factors affecting ADC values, which are limitations of this study and can be considerations in subsequent research.[13]

Based on the analysis results of the relationship between K^{trans} and mitotic rate of endometrial cancer using Spearman's rho test, showing p value results >0.05 (CI 95%), which means that statistically there is no significant relationship between K^{trans} and mitotic rate of endometrial cancer, although the correlation coefficient shows a value of -0.05. Until now, no research has been found examining these two variables. However, theoretically, high mitotic rate indicates higher risk of endometrial cancer. This will cause the tumor to proliferate rapidly, triggering hypoxia, thus initiating angiogenesis. K^{trans}, which is expected to reflect the combination of tumor blood flow and blood vessel permeability, with high mitotic rate, is expected to show lower K^{trans}. However, in this study, it was statistically proven that there is no significant relationship between K^{trans} and mitotic rate of endometrial cancer. This can be caused by other factors such as tumor volume, microvessel density, and microvessel heterogeneity, which also have an influence in this regard.[20]

Conclusion

ADC values in low-risk subtype endometrial cancer showed a minimum value of 0.52×10^{-3} mm^2/s and a maximum value of 1.06×10^{-3} mm^2/s, with a mean value of 0.72×10^{-3} mm^2/s. Meanwhile, in high-risk subtype, the minimum ADC value was 0.50×10^{-3} mm^2/s and the maximum value reached 1.27×10^{-3} mm^2/s, with a mean value of 0.73×10^{-3} mm^2/s. For the K^{trans} parameter, low-risk subtype endometrial cancer had a minimum value of 0.23 $minute^{-1}$ and a maximum value of 1.33 $minute^{-1}$, with a mean value of 0.57 $minute^{-1}$. In high-risk subtype, the minimum K^{trans} value was 0.33 $minute^{-1}$ and the maximum value was 1.05 $minute^{-1}$, with a mean value of 0.62 $minute^{-1}$.

Research results showed that there was no significant relationship between ADC or K^{trans} values and histopathological subtypes of endometrial cancer. However, there was a significant relationship between ADC values and mitotic rate of endometrial cancer with a correlation coefficient of −0.34, indicating a weak negative correlation between the two variables. Conversely, no significant relationship was found between K^{trans} values and mitotic rate of endometrial cancer, although the correlation coefficient showed a value of −0.05.

Further research is recommended to examine other variables from DCE quantitative parameters, such as ve, Kep, and vp, considering the possibility of result variations that can be influenced by microvascular heterogeneity. In addition, further research also needs to consider other characteristics of endometrial cancer, such as tumor volume, lymphovascular involvement, and degree of myometrial invasion. It is also recommended to conduct multicenter research examining the relationship between K^{trans} variables and histopathological subtypes of endometrial cancer, considering that the results obtained currently still show controversy.

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