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Original Article

Association of Pre-treatment Serum Fibrinogen-Albumin Ratio Index (FARI) and Concurrent Chemoradiotherapy (CCRT) Therapeutic Response in Patients with Locally Advanced Cervical Cancer (LACC)

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Abstract

Background : Cervical cancer is currently the second most prevalent women malignancy cases in Indonesia. High prevalence of cases diagnosed as locally advanced cervical cancer / LACC (FIGO Stage IIB-IVA), where concurrent chemoradiotherapy (CCRT) is the main treatment modality. Several therapeutic efficacy predictors in other malignancy cases including the pre-treatment serum fibrinogen-albumin ratio index (FARI) have been associated with therapeutic response to CCRT. However, there were no recent studies in cervical cancer cases. The aims of this study was to determine the association of pre-treatment FARI and CCRT therapeutic response in patients with LACC.
Methods : This is a prospective cohort study in patients with LACC from January – May 2024 whose clinical stage was determined. The pre-treatment FARI was calculated in patients who had met both inclusion and exclusion criteria, and undergone the CCRT regimen. Patients who completed the regimen were evaluated for therapeutic response. Data processing was carried out using SPSS 25 for Windows software.
Results : In this study, it was found that the complete response (CR) group with the best outcome had the smallest pre-treatment FARI (9.79 ± 1.71), on the other hand the progressive disease (PD) group had largest pre-treatment FARI (33.72 ± 12.78). In addition, all CCRT therapeutic response groups had significantly different FARI values (*P value* < 0.05) and the FARI cut point value of 12.44 had a sensitivity of 100% and a specificity of 78.1% for predicting complete response (CR) to CCRT.
Conclusion : Low pre-treatment FARI is significantly associated with the likelihood of patients having a complete response (CR), which is the best outcome to CCRT.

Keywords : Fibrinogen-albumin ratio index, concurrent chemoradiotherapy, therapeutic response, cervical cancer

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INTRODUCTION

Cervical cancer until recently is still considered as one of the health problems in women, ranked as the 4th and the 2nd most malignant cases worldwide and in Indonesia, consecutively.[1,2] Based on the data obtained by the Global Burden of Cancer Study (GLOBOCAN) in 2020, it was globally estimated that there were around 604,000 new cases with 342,000 deaths per year, and in Indonesia it was estimated that there were around 36,633 new cases with 21,003 deaths per year.[2–4]

The main contributor to the high incidence and mortality of cervical cancer in Indonesia is predominantly the relative low coverage of HPV vaccination and early screening of cervical pre-cancerous lesions. Based on the data obtained from The World Health Organization-International Agency for Research on Cancer (WHO-IARC) in 2023, it was estimated that only 5–6% of women have been vaccinated against HPV and only 8–9% of women have undergone early screening for cervical pre-cancerous lesions in the last 5 years.[5,6] Another contributor to the high incidence and mortality of cervical cancer in Indonesia is the higher prevalence of cases diagnosed in later stages as locally advanced cervical cancer / LACC (Stage IIB-IVA), A meta-analysis by Monk BJ *et al*. (2022) found that around 37% of cervical cancer cases were LACC with poorer prognosis as the stage increases.[7]

Until recently, concurrent chemoradiotherapy (CCRT) is still the mainstay treatment for LACC.[1,5] A study by Cohen PA *et al*. (2019) found that the 5-year survival/overall survival (OS) of LACC after CCRT was around 70%, however approximately 35% of LACC cases still experienced disease progression or development after CCRT.[8,9] Several prognostic factors that influence the therapeutic response to CCRT in patients with LACC include age, tumor histology type, tumor size, and cancer stage (lymph node involvement and location).[9] Several inflammatory biomarkers from hematological examinations have been studied to be related to CCRT therapeutic response, including hemoglobin (Hb) levels and HPV-DNA viral load.[10–12]

Inflammation is a part of the pathophysiological processes in malignancy, several studies have found that there is more than one inflammatory mediator that is related to the process of tumor formation, development (tumorigenesis), and pre-metastasis process; these mediators include: neutrophils, platelets, lymphocytes, fibrinogen, albumin, and a combination of mediators in the ratio. Recently, several studies have been conducted on the routine mediators above as diagnostic and prognostic modality of prostate, digestive (gastric and colorectal), lung (non-small cell lung cancer), and central nervous (high-grade glioma) malignancies.[13–18] Recent studies by Sabur YA *et al*. (2023), An Q *et al*. (2020) and Huang L *et al*. (2020) have shown a significant increase in the fibrinogen-albumin ratio index (FARI) in cases of precancerous cervical lesions to cervical cancer compared to the control population of healthy patients; so that it can be applied as a promising diagnostic and prognostic modality in cervical cancer cases.[19–21]

In addition to being a diagnostic and prognostic modality for malignancy, several other studies have also found a significant association between pre-treatment FARI and overall survival (OS) prognosis from surgical management to CCRT therapeutic response in breast and digestive (esophageal and colorectal) cancer cases. However, until now there has been no research that assesses the association between pre-treatment FARI and CCRT therapeutic response in cervical cancer patients.[22–25] We conducted a study to determine the association of pre-treatment FARI and CCRT therapeutic response in patients with LACC.

METHODS

Study design and population

This study is a prospective cohort study performed in Prof. Dr. R.D. Kandou Central General Hospital, Manado, North Sulawesi, to determine the association of pre-treatment FARI and CCRT therapeutic response in patients with LACC. Eligible study participant included newly diagnosed and clinically staged patients with LACC (Stage IIB-IVA) who undergone CCRT regimen provided by the hospital from December 2023 – April 2024. The patients were recently diagnosed based on history taking, physical, and histopathological examinations, abdominal-pelvic magnetic resonance imaging (MRI), cystoscopy, rectoscopy, laboratory examination (full blood count, renal function, liver functions, and electrolytes) and chest X-Ray (distant metastasis screening) results. The patients were clinically staged based on The 2018 International Federation of Gynecology and Obstetrics (FIGO) staging of cancer of the cervix uteri.[1] Study participant with anemia (Hb < 11.0 g/dL), leucopenia (< 3,500 /uL); thrombocytopenia (< 100,000 /uL); elevated liver functions (2x increase in SGOT/AST and/or SGPT/ALT); electrolyte imbalance (Natrium < 135 or > 145 mmol/L, Kalium < 3.5 or > 5.2 mmol/L, or Chloride < 97 or > 111 mmol/L); previous history of hypertension or diabetes on treatment; previous malignancy history; previous hysterectomy history; any usage of blood product transfusion, albumin supplementation or fibrate medication before or while undergoing CCRT; and patients who didn't complete the whole regimen or diseased patients while undergoing CCRT were excluded from the study. Pre-treatment serum albumin and fibrinogen were analysed and FARI was calculated before the study participant underwent the CCRT regimen. Study participants who have completed the whole CCRT

regimen were then evaluated for therapeutic response using abdominal-pelvic MRI based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).[26]

Sample Collection

Study participants underwent venipuncture to collect blood for serum fibrinogen analysis (≥ 3 mL in a plasma citrate tube) and serum albumin analysis (≥ 5 mL in a heparin tube), pre-treatment FARI was then calculated. Blood sample collection was performed after the patient had signed the informed consent form but prior to undergoing the CCRT regimen. Patient sociodemographic information such as: patient's name, medical record number, date of birth, age, phone number, body mass index (BMI), tumor histopathologic type, baseline tumor size based on initial abdominal-pelvic MRI result, and LACC stage (FIGO Stage IIB-IVA) were collected prior to undergoing CCRT regimen. All patient data, including sociodemographic data, pre-treatment serum fibrinogen and albumin analysis, calculated pre-treatment FAR, and prospectively collected therapeutic response data were collected and stored in Microsoft Excel (Version 16.59).

Serum Fibrinogen and Albumin Analysis

Serum fibrinogen and albumin analysis was carried out by Prodia Laboratory Manado. For fibrinogen analysis, a minimum of ≥ 3 mL of blood sample collected in a plasma citrate tube; while a minimum of ≥ 5 mL of blood sample collected in a heparin tube for albumin analysis. Both samples were delivered within 30 minutes to an hour time frame to the laboratory, then centrifuged in 1500 g / 3100 rpm for 15 minutes. The plasma/serum separated was analysed, and blood sample collection was repeated when hemolysis, lipemia, or icterus occurred in the post-centrifuged serum. Fibrinogen was analysed from the serum using STart-Max coagulation analyser with Both STA®-Liquid Fib reagent and STA®-Owren-Koller buffer reagent (Stago, Diagnostica Stago, Inc., US), which utilizes the electromechanical clotting method of Clauss; normal serum albumin levels were considered to be 34–48 g/L. Albumin was analysed from the serum using Cobas® C501 analyser with ROCHE Albumin Gen.2 (ALB2) reagent (Roche, F. Hoffmann-La Roche AG, CH), which utilizes the bromocresol green (BCG) colorimetry; normal serum fibrinogen levels were considered to be 2–4 g/L.

Fibrinogen-albumin ratio index (FARI)

Fibrinogen and albumin ratio index (FARI) was calculated by dividing the serum fibrinogen levels (g/L) over the serum albumin levels (g/L) and multiplied by 100%. Both serum fibrinogen and albumin levels were analysed as described above.

Concurrent Chemoradiotherapy (CCRT) Regimen Protocol

Concurrent Chemoradiotherapy (CCRT) regimen for LACC patients were given according to the standard protocol by The Radiotherapy Department of Prof. Dr. R.D. Kandou Central General Hospital, Manado, North Sulawesi. The protocol consisted of External Beam Radiotherapy (EBRT) regimen for 5 days every week with 2-field boxes using Cobalt-60 teletherapy or Linear Accelerator (LINAC) covering the entire pelvic region until a total dose equivalent of 70 Gy was achieved, and chemotherapy regimen with Cisplatin (dose 40 mg/m^2 body surface area/BSA) was carried out once a week for 6 cycles. Study participants who did not complete the whole CCRT regimen were excluded.

Therapeutic Response Evaluation

Therapeutic response of LACC patients after the whole CCRT regimen completed was then evaluated by measuring the tumor (target lesion) size comparing it to the pre-treatment baseline tumor size. Tumor size was assessed by measuring the longest tumor dimension diameter (cm) using post-treatment abdominal-pelvic MRI. Therapeutic response evaluation was classified according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria, into four categories[26]:

- Complete Response (CR): Disappearance of the tumor (target lesion).
- Partial Response (PR): At least a 30% decrease in tumor size compared to the baseline tumor size.
- Stable Disease (SD): Neither sufficient tumor shrinkage to be qualified as PR nor sufficient increase to be qualified as progressive disease (PD).
- Progressive Disease (PD): At least a 20% or a 0.5 cm increase in tumor size compared to the baseline tumor size.

Statistical Analysis

Association was evaluated measuring the significant difference between pre-treatment serum FARI and CCRT therapeutic response with the analysis of variance (ANOVA) using Cohen's F test or Mann-Whitney U, if the first was not fulfilled. Consecutive sampling was used as the sampling method, with a minimum of 12 study participants in each 4 groups of therapeutic responses, calculated with 95% confidence level and 80% power of test with expected drop-out of 20%. Continuous variables were expressed as mean ± standard deviations (SD) for normally distributed variables, and median and ranges

for non-normally distributed variables. Categorical variables were expressed as total and percentages. Receiver operating curve (ROC) analysis were performed. Multivariate regression analysis were performed to control possible confounding factors. All statistical analyses were conducted using Statistical Product and Service Solutions (SPSS) 25.0 software (SPSS, Inc., Chicago, IL, NY., USA) with *P-value* of < 0.05 considered as statistically significant.

Ethics

This study has obtained an ethical clearance and research permit from the Health Research Ethics Commission of Prof. Dr. R.D. Kandou Central General Hospital (Ethical Approval No. 019/EC/KEPK-KANDOU/I/2024, Research Permit No. DP.04.03/DXV/654/2024). All study participants were asked for their consent by signing a written informed consent.

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RESULTS

Baseline Characteristics

There were 78 study participants recruited in a 6 month period of December 2023 April 2024 in our Obstetrics and Gynecology department through our prospective cohort model. A total of 28 patients were excluded while undergoing the CCRT regimen: 8 patients died due to terminal complications, 12 patients received transfusion of blood products, 5 patients received albumin transfusion, and 3 patients refused to finish the whole CCRT regimen (Figure 1). The final cohort of 50 study participants who finished the whole CCRT regimen were evaluated for therapeutic responses. Out of the final cohort, the average age of study participants was 45.56 ± 11.88 years. The average FARI of study participants in the final cohort was 14.88 ± 8.08, However, because these data were not normally distributed (Kolmogorov-Smirnov normality test value <0.05), these data were presented in the form of a median and ranges of 12.44 (44,38) (Table 1).

Of the 50 study participants in the final cohort, it showed that BMI values were generally normal (42%) and baseline tumor size was mostly >4 cm (68%). The histological types obtained were almost equally distributed, only slightly dominant in the squamous cell carcinoma (SCC) type (40%); and the LACC stage was generally higher than stage IIIB (52%). The overall CCRT therapeutic response of patients at Prof. Dr. R. D. Kandou Hospital was still fairly good, with 38 patients (76%) classified as complete response (CR) or partial response (PR) and only 12 patients (24%) were classified as stable disease (SD) or progressive disease (PD) (Table 1).

The association of pre-treatment FARI and CCRT therapeutic response

Based on the results of the serum albumin, fibrinogen and subsequently calculated pre-treatment FARI comparison in each response group, it was found that the complete response (CR) group had the smallest average serum fibrinogen levels of 3.90 ± 0.92 g/L and the largest average serum albumin levels of 39.67 ± 6.22 g/L. This combination produced the smallest average FARI of 9.79 ± 1.71. On the other hand, the progressive disease (PD) group had the largest average serum fibrinogen levels of 7.60 ± 1.78 g/L and the smallest average serum albumin levels of 23.6 ± 3.71 g/L. This combination produced the largest average FARI of 33.72 ± 12.78. Therefore based on these data, it can be indicated that patients with smaller average FARI have a greater possibility of experiencing a complete response (CR) (Table 2).

The results of the multivariate analysis between CCRT therapeutic response groups were performed using the Mann-Whitney U test due to the data not being normally distributed. From this bivariate analysis, it was found that all groups had FARI values that were significantly different and statistically significant (Table 3). This is evidenced by the results of the *P-value* which all showed a value <0.05. The only statistically insignificant difference was found in the albumin value between the complete response (CR) and partial response (PR) groups. However, these two groups still had significant differences in FARI values. Looking at the average difference between groups, it was also found that the worse the CCRT therapeutic response, the greater difference in FARI obtained. The FARI value between CR and PR differed by 3.71; while with SD it differed by 8.67; and with PD it differed by 23.93. This bivariate analysis was continued into the ROC curve analysis (Figure 2).

From the results of this ROC curve analysis, it was found that the FARI value had a significant association with CCRT therapeutic response (Figure 2). The area under the curve (AUC) value of 0.926 produced by this study was also quite large. This value was statistically significant indicated by a *P-value* <0.005. From this curve, it was found that for screening purposes, the best FARI cut-off value to predict the outcome of complete response was 12.44. This cut-off point was found to have the highest sensitivity of 100% with a specificity of 78.1%. that was still considered excellent. In the future, this value can be a reference point used by clinicians in predicting CCRT

TABLE 1
Baseline Characteristics and Distributions of Locally Advanced Cervical Cancer Patients

Characteristics	Final Cohort Study Participants (n = 50)*
Age (years)	46.56 ± 11.88
Hemoglobin/Hb (g/dL)	11.30 (3,60)
FARI	12.44 (44,38)
BMI (kg/m^2)	
Underweight (<18.5 kg/m^2)	7 (14%)
Normal (15.8–22.9 kg/m^2)	21 (42%)
Overweight (23–24.9 kg/m^2)	6 (12%)
Obese (≥25 kg/m^2)	16 (32%)
Histologic type	
SCC	20 (40%)
NSCC	18 (36%)
Adenocarcinoma	12 (24%)
Baseline tumor size (cm)	
≤ 4 cm	16 (32%)
> 4 cm	34 (68%)
Cervical cancer stage	
IIB	10 (20%)
IIIA	6 (12%)
IIIB	8 (16%)
IIIC1R	13 (26%)
IIIC2R	5 (10%)
IVA	8 (16%)
CCRT response	
CR	18 (36%)
PR	20 (40%)
SD	7 (14%)
PD	5 (10%)

***Note:** Continuous variable such as age is displayed in *Mean ± SD*, while Hb and FARI are displayed in *Median (Range)* since data is not evenly distributed (normality test *Kolmogorov-Smirnov* < 0.05). Categoric variables such as BMI, histology types, baseline tumor size, cervical cancer stage, and CCRT response are displayed in *Total (Percentage)*.
Abbreviations: Hb = Hemoglobin, FARI = Fibrinogen-Albumin Ratio Index, SCC = Squamous Cell Carcinoma, NSCC = Non-Keratinizing Squamous Cell Carcinoma, CCRT = Concurrent Chemoradiotherapy, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

therapeutic response in patients with locally advanced cervical cancer (LACC). Besides the FARI value, there are also other indicators that can be used and need to be considered by clinicians so that a more comprehensive scoring system can be formed in predicting patient chemoradiation outcomes.

DISCUSSION

The average age of participants in this study was 45.56 + 11.88 years and most participants (21 people, 42%) had a normal body mass index (BMI). A study in Pontianak also showed similar findings where most participants were

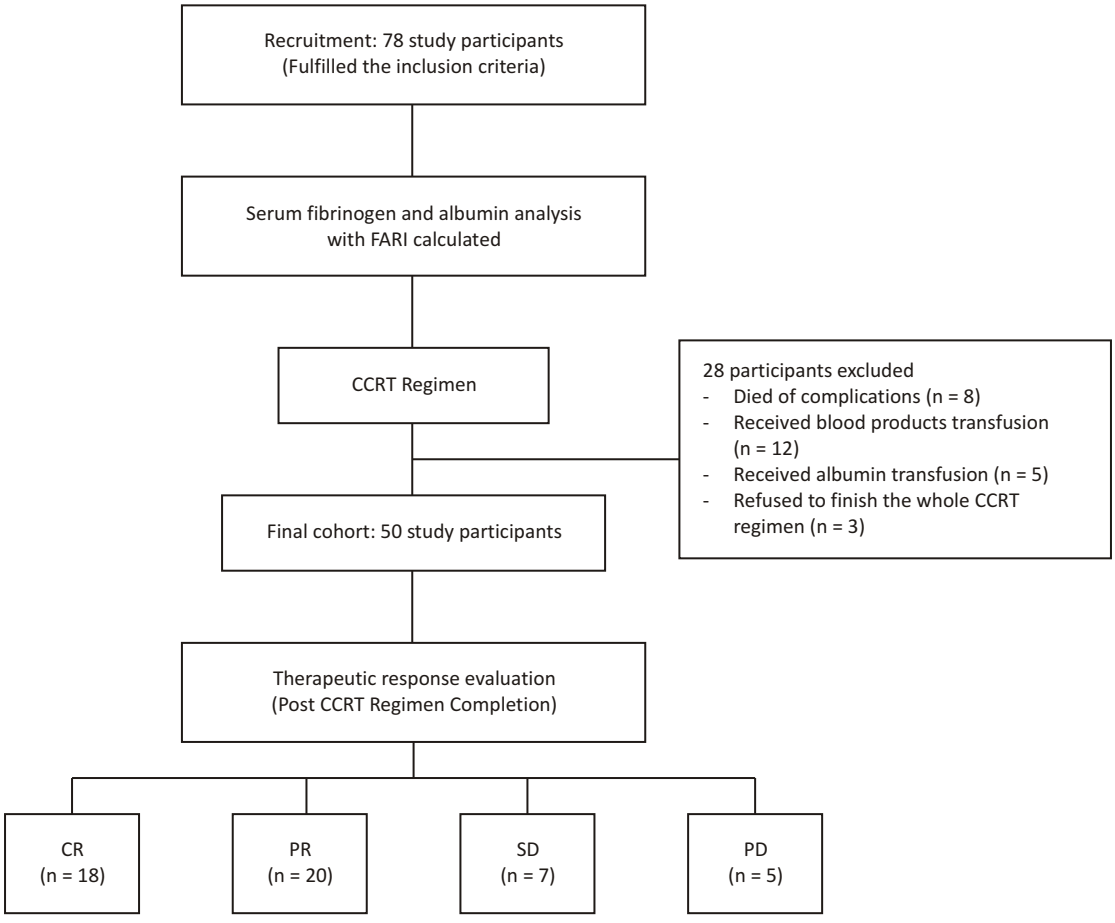

Figure 1. Study participant flowchart. Abbreviations: FARI = Fibrinogen-Albumin Ratio Index, CCRT = Concurrent Chemoradiotherapy, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

TABLE 2
Pre-treatment fibrinogen-albumin ratio index (FARI) comparison in all CCRT therapeutic response groups for locally advanced cervical cancer/LACC (FIGO Stage IIB-IVA)

Variables*	*CR* (n=18)	*PR* (n=20)	*SD* (n=7)	*PD* (n=5)
Fibrinogen (g/L)	3.90 ± 0.92	4.90 ± 0.93	5.67 ± 0.88	7.60 ± 1.78
Albumin (g/L)	39.67 ± 6.22	36.65 ± 4.95	27.63 ± 11.28	23.6 ± 3.71
FARI	9.79 ± 1.71	13.50 ± 2.39	18.46 ± 1.97	33.72 ± 12.78

***Note:** fibrinogen, albumin and FARI in each CCRT therapeutic response group (CR, PR, SD, and PD) are displayed in Mean ± SD
Abbreviations: CCRT = Concurrent Chemoradiotherapy, FARI = Fibrinogen-Albumin Ratio Index, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

aged 41–50 years (40.2%).[28] The most common histological type found in this study was squamous cell carcinoma (20 people, 40%). Studies in Surabaya and Pontianak also revealed that most of the histological types of cervical cancer found were squamous cell carcinoma, but in these studies the proportions were much higher at 82.39% and 70%, respectively. Squamous cell carcinoma is a cancer that originates from squamous epithelial cells and is divided into keratin and non-keratin SCC. The non-keratin type is more associated with human papillomavirus (HPV) infection than the keratin type.[28,29] Most tumors were larger than 4 cm (50 people, 68%) and most participants had stage III cervical cancer (32 people, 64%). Studies in China and

TABLE 3
Multivariate analysis of pre-treatment fibrinogen, albumin, and FARI comparison in other CCRT therapeutic response groups (PR, SD, and PD) vs complete response (CR) group

Variables*	***PR vs CR***	***P value***
Fibrinogen (g/dL)	-1.00 ± 0.30	0.02
Albumin (g/dL)	3.02 ± 1.81	0.20
FARI	-3.71 ± 0.68	0.0005
Variables*	***SD vs CR***	***P value***
Fibrinogen (g/dL)	-1.76 ± 0.41	0.001
Albumin (g/dL)	12.04 ± 3.50	0.001
FARI	-8.67 ± 0.79	0.0005
Variables*	***PD vs CR***	***P value***
Fibrinogen (g/dL)	-3.70 ± 0.58	0.001
Albumin (g/dL)	16.07 ± 2.95	0.002
FARI	-23.93 ± 2.93	0.001

***Note:** Comparison of fibrinogen, albumin and FARI in other chemoradiotherapy response groups (PR, SD, and PD) vs CR are displayed in Mean Difference ± SD
Abbreviations: CCRT = Concurrent Chemoradiotherapy, FARI = Fibrinogen-Albumin Ratio Index, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

Pontianak also showed that most cervical cancers diagnosed were in stage III, 52.5% and 55.7%, respectively.[28,30]

The complete response (CR) group had the lowest fibrinogen levels (3.90 ± 0.92 g/L) and the highest albumin levels (39.67 ± 6.22 g/L) while the progressive disease (PD) group had the highest fibrinogen levels (7.60 ± 1.78 g/L) and the lowest albumin levels (23.6 ± 3.71 g/L). These findings are in accordance with the research by Li *et al.*, namely that low fibrinogen values have a positive prognostic value in cervical cancer patients undergoing chemoradiotherapy. When a tumor-related inflammatory response occurs, various events occur that trigger tumor growth and metastasis, starting from increased release of cytokines and inflammatory mediators, inhibition of apoptosis, and immunosuppressive effects. Inflammatory mediators can trigger pre-metastatic conditions to not be recognized by immunological surveillance and play a role in every stage of tumorigenesis and tumor development.[19,31]

Fibrinogen is an acute phase protein that increases during inflammation or infection and plays an important role in blood clotting, cell adhesion, and thrombosis. Tumor cells and inflammatory cells from tumors can activate the coagulation cascade and there is a relationship between hemostasis factors and advanced tumor stage, large tumor size, and tumor biology. Fibrinogen triggers adhesion, proliferation, and cell migration responses during angiogenesis and tumor cell growth through its role in extracellular matrix formation and increasing binding to growth factors. Other studies have also shown that fibrinogen is an independent parameter for cervical cancer patients and hyperfibrinogenemia can also be used as a parameter to predict early cervical cancer recurrence.[31,32] Fibrinogen is associated with high tumor burden and is often found in patients with advanced cervical cancer.[33]

Albumin is a negative acute phase protein associated with inflammation and tumorigenesis. Hypoproteinemia is associated with poor quality of life in cancer patients and poor prognosis in cancer patients. The findings related to albumin values in this study are also in accordance with a study by Li, *et al.* where high albumin levels are associated with higher survival rates so that it can be concluded that albumin is a prognostic indicator of cervical cancer patients.[31] Albumin values decrease due to systemic inflammatory responses and malnutrition in advanced tumors and can be a predictive factor for therapeutic response and prognostic survival in several gynecologic cancers. Other studies have also shown that hypoalbuminemia is associated with lower progression free survival (PFS) and overall survival (OS).[32–34] Approximately 20% of cancer-related deaths are caused by malnutrition. Malnutrition and inflammation can suppress serum albumin synthesis which reflects the patient's nutritional status, severity, progression, and

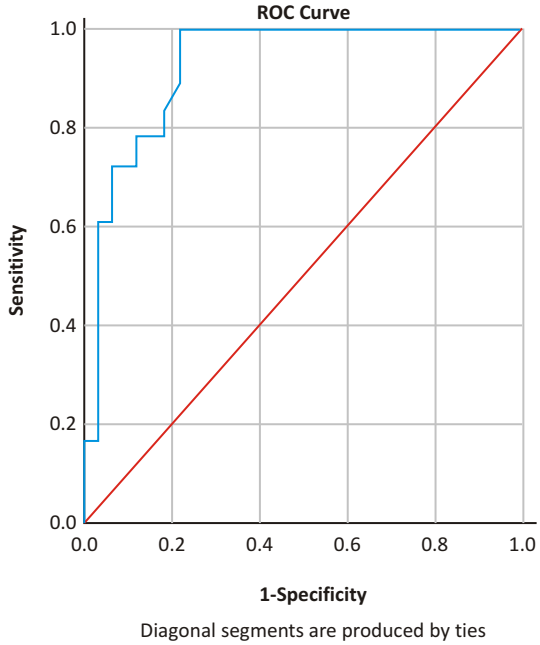

Figure 2. Study participant flowchart. Abbreviations: FARI = Fibrinogen-Albumin Ratio Index, CCRT = Concurrent Chemoradiotherapy, CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

prognosis.[35]

Based on the research results, the lower the FARI values, the greater the possibility of the patient experiencing a complete response (CR) outcome. This finding was established based on the fibrinogen and albumin values of each group. In addition, the greater the difference in FARI between groups, the worse the patient's chemoradiation response. So far, there has been no study that specifically examine the relationship between FARI and CCRT therapeutic response in cervical cancer, but higher FARI is associated with lower recurrence-free survival (RFS) and overall survival (OS).[20] The relationship between FARI and chemoradiotherapy response has been studied in other cancers. A study showed that high FARI values are associated with chemotherapy resistance, low PFS, and low OS in ovarian cancer. The fibrinogen albumin ratio index (FARI) is associated with curative effects and high FARI is associated with poor chemoradiation effects in esophageal squamous cell cancer.[23,36] A low albumin fibrinogen ratio is also associated with better chemotherapy responses in metastatic colorectal cancer and clear-cell ovarian cancer.[37,38] A high FARI is associated with poor adjuvant chemoradiation responses in rectal cancer.[39]

The fibrinogen albumin ratio index (FARI) has a better prognostic value compared to high fibrinogen values and low serum albumin. In addition, FARI also describes systemic inflammation, nutrition, and coagulation status.[32] Systemic inflammation not only plays a role in tumor initiation and metastasis but also in the initiation of chemotherapy resistance.[40] Chronic inflammatory responses are related to tumor proliferation, development, metastasis, and angiogenesis. Patients with malignant tumors experience hypoalbuminemia due to the release of cytokines such as interleukin-6 (IL-6) which inhibits albumin synthesis and secretion from liver cells and TNF-α which is also related to albumin levels. The adverse effects of fibrinogen and hypoalbuminemia may be the reason why the fibrinogen and albumin ratios are able to predict the efficacy of therapy and survival in patients receiving chemoradiation.[23]

Based on the receiver operating characteristic (ROC) curve analysis, the best FARI cut-off value for predicting complete response was 12.44. This figure is not much different from other studies on clear cell ovarian cancer where in that study, the FARI cut-off value of 12 was the optimal number for predicting platinum chemotherapy resistance with a sensitivity of 73.3% and a specificity of 68.2% while this study had a higher sensitivity and specificity of 100% and 78.1%, respectively.[37] This is different from the findings by Zhang *et al*. that the FARI cut-off value for assessing chemotherapy outcomes in metastatic colorectal cancer was 10.63; lower than this study.[38]

CONCLUSION

There was a significant association between pre-treatment FARI and CCRT therapeutic response in LACC stage IIB-IVA patients; the lower the FARI, the higher the

likelihood of the patient having a complete response (CR) outcome to CCRT (*P-value* < 0.05), the pre-treatment FARI cut-off value of 12.44 has a sensitivity of 100% and a specificity of 78.1% to predict a complete response (CR) outcome to CCRT.

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Author Contribution

GNH was involved in the conception of study and manuscript preparation; BJL and JMMS coordinated the study; GNH and BJL analysed the data and interpreted the results; all authors performed data acquisition, table design and laboratory analysis. All authors participated in the critical revision of the manuscript.

Conflict of Interest

All the authors declare that they have no conflicts of interest that might be perceived as influencing the impartiality of the reported research.

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