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The Relationship Between Leucine-Rich- α-2-Glycoprotein-1 Plasma Protein with Cervical Cancer

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ABSTRACT

Introduction: Leucine-rich-α-2-glycoprotein-1 (LRG-1) has been identified as a significant role in the pathogenesis of disease development, including cancer, and serves as a prognostic marker for cancer. However, there has been no research on the use of LRG-1 as a marker for cervical cancer (CaCx). This study analyzes the relationship between plasma LRG-1 and the stage, histological type, and degree of differentiation of CaCx.

Methods: This cross-sectional study was conducted on patients diagnosed with CaCx who underwent examination at our institution. The results of the anatomical pathology examination, including stage, histological type, and degree of differentiation of CaCx, were recorded. Serum LRG-1 was measured using an ELISA kit. Statistical analysis used the Kruskal Wallis, Mann Whitney, and Fisher Exact tests.

Results: A total of 88 women diagnosed with CaCx were collected, consisting of 23 patients in the early stage and 65 patients in the advanced stage. There was a significant relationship between plasma LRG-1 levels and the stage of CaCx ($p < 0.05$). Advanced CaCx had a higher average plasma LRG-1 level than early stage. Histopathological type and differentiation grade were not significantly related to plasma LRG-1 levels ($p > 0.05$).

Conclusion: Plasma LRG-1 can be a biomarker in predicting the stage of CaCx.

Keyword: *Cell differentiation, pathology, LRG1 protein, neoplasm staging, Uterine Cervical Neoplasms*

1. INTRODUCTION

Cervical cancer (CaCx) is a malignant tumor in the cervix [1]. CaCx is a global problem, with new cases globally in 2020 as many as 604,127 (6.5%), ranking 4th highest of all cancers [2]. In Indonesia, the incidence of CaCx was 36,633 (17.2%) new cases, ranking third highest for cancer cases in women in 2020 [3,4]. The incidence of CaCx in South Sulawesi is around 120 cases per 100,000 population, and around 18 new cases per 100,000 population in 2017 [5].

The primary etiological factor of CaCx is chronic infection by the human papillomavirus (HPV). HPV is implicated in 90-100% of CaCx instances among females, particularly in those under 35 years of age. HPV types can be classified as low-risk and high-risk about precancerous lesions. High-risk HPV subtypes 16 and 18 are the most common HPV subtypes, causing 70% of CaCx cases [1].

Clinicopathological risk factors, including lymph node metastasis and tumor characteristics, are prognostically significant in cervical cancer (CaCx). Lymphovascular space invasion (LVSI), large tumor size, and deep stromal invasion are considered intermediate risk factors. The combination of these factors may elevate the risk of postoperative recurrence by 15-20%. While pathological factors influence prognosis, the clinical stage as per FIGO also plays a critical role in CaCx outcomes. Integrating clinical and pathological stage factors can enhance the precision of prognosis predictions [6]

Ineffective treatment and lack of screening for CaCx can lead to high mortality. Informative biomarkers are essential for CaCx diagnosis and prognosis [7]. In developing countries, approximately 66% of patients present at an advanced stage upon diagnosis; the prognosis remains unfavorable, with elevated chances of recurrence or metastasis. Therefore, CaCx biomarkers are also needed to monitor the treatment outcomes of CaCx [8]. Leucine-rich alpha-2-glycoprotein-1 (LRG-1) is implicated in disease progression, particularly in cancer. Following various inflammatory stimuli in tumors, LRG-1 can be produced systemically and/or at the local tissue level. The dominant cellular sources of LRG-1 include hepatocytes, neutrophils, endothelial cells, as well as other components of the tissue microenvironment, such fibroblasts, epithelial cells, and other myeloid cell types. The pathogenic role of LRG-1 can be activated via paracrine and autocrine mechanisms. LRG-1 facilitates immune cell involvement in inflammation by inhibiting TGFβ-induced anti-proliferative effects in hematopoietic progenitors, encouraging neutrophil migration and activation, and promoting the differentiation of naive CD4pos T cells into pro-inflammatory Th17 lymphocytes. LRG-1 contributes to the malignancy of cancer cells by promoting epithelial-to-mesenchymal transition (EMT) and supporting anti-apoptotic and proliferative functions [9]. LRG-1 is a glycoprotein with a 38–50 kDa molecular weight encoded by the LRG-1 gene. LRG-1 was discovered in human serum in 1977 by Haupt and Baudner. LRG-1 consists of 312 amino acid residues and 66 leucine residues [10]. Under physiological conditions, LRG-1 is mainly synthesized by neutrophils and hepatocytes; marginal expression levels of LRG-1 have also been reported in the testis, brain, skin, heart, kidney, and lung [9]. LRG-1 is widely distributed in the body and has been reported to be expressed in macrophages, neutrophils, endothelial cells, and hepatocytes [10]. LRG-1 is expressed in tissues and found in the serum of healthy individuals [9]. LRG-1 serum of healthy individuals ranges from 10–50 μg/mL [11].

Several studies have reported the role of LRG-1 levels as a prognostic marker in cancer. Agameia et al. (2020) examined serum LRG-1 levels in epithelial ovarian cancer (EOC) versus benign ovarian masses in relation to CA125. The findings indicate that LRG-1 is a potential tumor marker for diagnosing malignant EOC, independent of CA125, due to its elevated levels in affected patients. LRG-1 is identified as one of five plasma proteins for diagnosing colorectal cancer (CRC) [12]. Additionally, LRG-1 protein expression serves as a prognostic marker for stage III CRC and aids in its general diagnosis [13]. LRG-1 expression was also significantly associated with LVSI, histological type, node, tumor size factors, and stage of gastric cancer. Serum LRG-1 was significantly higher in gastric cancer patients than in healthy controls, and LRG-1 levels increased with the advancement of pathological stages [14]. In CaCx it has been reported that urinary LRG-1 protein is overexpressed in CaCx, so urinary LRG-1 levels are used to detect CaCx [15]. Astari, et al. (2022) found a significant correlation between urine LRG-1 levels and CaCx stage, but LRG-1 levels in urine were not significantly related to the histological type and degree of differentiation of CaCx [16]. However, plasma LRG-1 levels in CaCx and their relationship to the prognosis of CaCx have never been studied before. Therefore, this study needs to analyze the relationship between plasma LRG-1 and the Stage, Degree of Differentiation, and histological type of CaCx

2. METHODS

This analytical study with a cross-sectional design was conducted at the DR. Wahidin Sudirohusodo General Hospital from April to September 2024. The study population comprised women diagnosed with cervical cancer (CaCx) evaluated at our institution. The participants consisted of women diagnosed with CaCx, fulfilling the study's inclusion and exclusion criteria, and consenting to participate. The inclusion criteria included patients diagnosed with CaCx based on biopsy results and who were willing to participate in the study by signing an informed consent form. Exclusion criteria included CaCx patients with other malignancies, patients diagnosed with autoimmune diseases or HIV/AIDS, patients with a history of previous therapy (chemotherapy or radiotherapy), or metastatic patients with cancer in other locations (secondary tumors).

Sampling was carried out by consecutive sampling. Namely, all members of the population at the research site who met the inclusion requirements were taken as samples until the number of samples was met. Based on calculations based on the stage of CaCx, the minimum sample size for each group was 27 people. Thus, the minimum sample size for all research samples was 54 people.

This study collected 88 women diagnosed with CaCx. All patients collected were successfully examined for LRG-1 levels in venous blood samples. The flow of research subjects is explained as follows: Patients diagnosed with CaCx from a biopsy examination were screened, and 88 patients met the inclusion criteria; this sample exceeded the estimated target sample where the estimated target was 54 samples. Patients who met the inclusion criteria were given an explanation and informed consent for approval to participate in the study. Data from the anatomical pathology examination results, such as histopathology type and degree of differentiation, were recorded. Researchers also recorded personal data such as age, parity, BMI, number of marriages, and age of first sexual intercourse. A total of 88 patients underwent physical examinations, vital signs, and clinical examinations, and blood samples were taken from the patient's peripheral veins as much as three cc, then stored in a tube containing EDTA as an anticoagulant. All collected blood samples will be taken to the laboratory to measure LRG-1 protein levels with an ELISA kit.

The tools used were a centrifuge, vortex, micropipette (1000 μl, 100 μl, 200 μl, and 20 μl), Eppendorf tubes, freezers, and Eppendorf tube racks. The materials used were a Research Consent letter, research form, three ccs of the research subject's blood ccs, and Human LRG-1 ELISA KIT from AssayGenie (Dublin, Ireland) with Catalogue code HUDL01751. For the

flow of the research implementation, the researcher explained the intent and purpose of the research to CaCx patients who participated in this study; previously, participants who agreed to participate in this study signed the consent form that had been provided. Then, data collection was carried out by filling out a questionnaire on the sheet provided, in the form of filling in the results of anamnesis, physical examination, and supporting examinations, and taking blood samples for measuring the levels of LRG-1 Protein. The collected data was input into Excel, which was then processed and analyzed.

The data obtained was processed using bivariate and univariate analysis. Univariate analysis was carried out by calculating the percentage of patient characteristics. Univariate analysis was also carried out by calculating the average and standard deviation of the levels of LRG-1 Protein. Furthermore, the Shapiro-Wilk normality test was carried out. Bivariate analysis was carried out using the Mann-Whitney test for abnormal data in the comparison test of two sample groups, and the Kruskal Wallis test if the data was not standard for the comparison test of more than two sample groups. The chi-square test was carried out to test categorical data. The test was carried out at a confidence level of 5%.

Before the study was conducted, the researcher requested an ethical clearance from the Human Research Ethics Commission, Faculty of Medicine, Hasanuddin University, Makassar. Research approval was given in the form of written informed consent. The research subjects were given an explanation of the purpose, benefits, and procedures of the study, which did not cause harm to the research subjects. The identity of the research subjects was kept confidential and was not published without the permission of the research subjects. Patients have the right to refuse to be included in the study.

3. RESULTS

Table 1. Distribution of cervical cancer stages.

Staging	**n**	**%**
Early stage		
IAI	2	2.3
IA2	4	4.5
IB	1	1.1
IB2	5	5.7
IB3	3	3.4
IIA	8	9.1
Advanced stage		
IIB	20	22.7
IIIA	7	8.0
IIIB	22	25.0
IIIC	5	5.7
IIIC1	1	1.1
IIIC2	2	2.3
IVA	6	6.8
IVB	2	2.3

In this study, 23 patients were in the early stage, and 65 patients were in the advanced stage. Table 1 presents the distribution of patient data based on stage.

Table 2. Demogprahic characteristics.

Characteristics	**Early stage**	**Advanced stage**	***p-value****

	n (%)	**n (%)**	
Age (years)			
25-50	17 (73.9)	41 (63.1)	0.346
<25 or >50	6 (26.1)	24 (36.9)	
Education (years)			
≤ 9	9 (39.1)	22 (33.8)	0.648
> 9	14 (60.9)	43 (66.2)	
Occupation			
Employed	11 (47.8)	37 (56.9)	0.451
Unemployed	12 (52.2)	28 (43.1)	
Parity			
Nullipara	3 (13.0)	6 (9.2)	
Primipara	3 (13.0)	4 (6.2)	0.473
Multipara	12 (52.2)	31 (47.7)	
Grand multipara	5 (21.7)	24 (36.9)	
BMI			
Underweight	3 (13.0)	7 (10.8)	
Normal	19 (82.6)	51 (78.6)	0.643
Overweight/Obese	1 (4.3)	7 (10.8)	

Note: *Fischer exact test

A comparison of the characteristics of research subjects between early and advanced stages is presented in Table 2. It shows that most of the subjects of this study were under 50 years old, educated ≤ 9 years, multiparous, normal BMI, with histopathological type of Squamous cell carcinoma keratinizing and the degree of differentiation could not be determined (Gx) both in CaCx patients with early and advanced stages. Most of the early-stage patients did not work, and most advanced-stage patients worked. The statistical test results showed that age, education, occupation, parity, BMI, histopathological type, and degree of differentiation were not significantly related to the stage of CaCx ($p > 0.05$). Thus, the subjects of this study were homogeneous.

Table 3. Cervical cancer risk factors based on stage

Characteristics	**Early stage n (%)**	**Advanced stage n (%)**	***p-value****
Marital Status			
Married once	15 (65.2)	45 (69.3)	0.722
Married more than once	8 (34.8)	20 (30.7)	
Age of first sexual intercourse (years)			
< 18	8 (34.8)	26 (40.0)	0.659
≥ 18	15 (65.2)	39 (60.0)	

Note: *Fischer exact test

The relationship between CaCx risk factors and the stage is presented in Table 3. It shows that most of the subjects in this study were married once, and the age of first sexual intercourse was more than or equal to 18 years in both early and advanced-stage patients. In this study, there were two unmarried patients and one patient who had not had sexual intercourse. The results of statistical tests showed that there was no significant relationship between the number of marriages and the age of first sexual intercourse with the stage of CaCx ($p > 0.05$).

Table 4. The relationship between plasma LRG-1 and cervical cancer stage

Characteristics	**Early stage (Mean ± SD)**	**Advanced stage (Mean ± SD)**	***p-value***
Plasma LRG-1 (ng/mL)	67.53 ± 46.54	308.66 ± 896.92	< 0.001**
Histopathology			
Squamous cell carcinoma	15 (65.2)	40 (61.5)	
Adenocarcinoma cervix	6 (26.1)	18 (27.7)	0.940
Adenoaquamous carcinoma cervix	2 (8.7)	7 (10.8)	
Degree of Differentiation			
Gx	11 (47.8)	27 (41.5)	
G1	7 (30.4)	11 (16.9)	0.233
G2	3 (13.0)	22 (33.9)	
G3	2 (8.7)	5 (7.7)	

Note: Mann Whitney Test; **Significance at $p < 0.001$.

Table 4 presents the results of the relationship between plasma LRG-1 levels and CaCx stages. It shows that patients with advanced CaCx have an average plasma LRG-1 level greater than that of early-stage patients. The statistical test results indicate a significant relationship between plasma LRG-1 levels and CaCx stages.

Table 5. The relationship between plasma LRG-1 levels and histopathological type and degree of differentiation.

Factors		**LRG-1 Levels (ng/mL)**			***p-value****
	n	**Min**	**Max**	**Mean ± SD**	
Histopathology					
Squamous cell carcinoma	55	5.58	2094.04	185.59 ± 329.96	
Adenocarcinoma cervix	24	7.51	7026.59	447.17 ± 1046.22	0.060
Adenoaquamous carcinoma cervix	9	17.22	262.36	75.14 ± 73.00	
Degree of differentiation					
Gx	38	5.58	954.66	144.216 ± 184.27	
G1	18	10.40	326.79	105.54 ± 78.60	0.418
G2	25	7.51	2100.04	264.02 ± 421.85	
G3	7	14.92	7026.59	1090.78 ± 2618.42	

Note: *Kruskal Wallis Test

Table 5 shows that the histopathological type and degree of differentiation are not significantly related to plasma LRG-1 levels ($P > 0.05$).

4. DISCUSSION

CaCx in this study mainly occurred in advanced stages. CaCx patients in this study mostly had the histopathological type of Squamous cell carcinoma (SCC) keratinizing, and the degree of differentiation could not be determined (Gx) both in the early and advanced stages of CaCx patients. The majority of CaCx patients from the United States and China were diagnosed with stages II and I, while CaCx from Uganda was diagnosed with stages III and II. The difference in CaCx prevalence by stage is influenced by HPV vaccine accessibility, awareness levels, and screening services. HPV infections are typically identified in early cervical lesions, including high-grade and low-grade squamous intraepithelial lesions. The occurrence of HPV integration increases as CaCx advances, particularly in its later stages [17]. HPV infection is a precursor to the development of CaCx and can be detected in 99.7% of adenocarcinoma and SCC cases [18]. Similar to this study, a study by Pratiwi et al. (2022) also reported that SCC was the highest (70.1%) type of CaCx cases [19].

CaCx patients were primarily under 50 years old, across various disease stages. Previous research indicates that a majority of sexually active individuals will encounter HPV, with over 50% of adults aged 20-24 being infected. The immune response eliminates the virus within six months for 50% of infected women and within two years for 90%. Persistent HPV infection in the cervical transformation zone's metaplastic epithelium may lead to dysplastic alterations. While low-grade dysplasia (CIN1) typically regresses, it may advance to high-grade dysplasia (CIN3 or CIN2). CaCx manifests when high-grade lesions breach the cervical epithelium's basement membrane. Approximately 20% of women with high-grade dysplasia may develop invasive CaCx within five years if untreated [18]. One study in Indonesia reported that CaCx is most often diagnosed in women aged between 35 and 44 years, with an average age of 50 years. More than 20% of CaCxs are found in women over 65 years of age. However, this cancer is rare in women who have undergone routine tests for CaCx screening before they were 65 years old [19]. Similar results in this study were reported by Noguchi et al. (2020) that most cases of CaCx in Japan occur in women aged 30-39 years (<50 years) with SCC and in the early stages [20]. The results are in line with the study of Raveinthiranathan et al. (2023) that indicated 70% of CaCx cases in women aged 18-39 were identified at Stage I due to effective screening programs. The incidence of Stage IV diagnoses escalates with age, with 20% of cancers identified at Stage IV in women exceeding 55 years. Thus, the early stages that occur more often in CaCx patients in the study may be related to younger age and the possibility of early detection due to CaCx screening programs. Patients with CaCx in this study predominantly exhibited multiparity at various stages. Previous research indicates that high parity influences CaCx incidence in West Kalimantan (19). A meta-analysis found that high parity increases CaCx risk by 2.65 times. HPV-infected women with high vaginal parity are at greater risk for CaCx due to potential viral integration from birth trauma. Furthermore, hormonal fluctuations during pregnancy induce alterations in cervical cells. Additionally, high parity may correlate with prolonged oral contraceptive use, contributing to CaCx development [21].

In this study, most CaCxs were married once and had their first sexual intercourse at an age of more than or equal to 18 years. Previous studies reported that CaCx can occur due to the number of sexual partners of the husband [22]. Women who initiate coitarche at a young age (below 18 years) can elevate the likelihood of developing cervical cancer (CaCx) by a factor of 6.761 compared to those aged 18 years and above [23]. Regarding age, the optimal period for women to engage in sexual activity for the first time is at or beyond the age of 18, as the mucosal cells within their genitalia are not yet predisposed to undergoing pathological transformations, commonly referred to as cancer. The age of less than 18 years represents a developmental stage characterized by adolescent girls rather than adult women. Bad sexual activity can adversely influence the detrimental sexual experiences or incidence of early marriage. Adolescents with early coitarche can engage in extreme sexual activities such as oral sex and anal sex, which can affect sexually transmitted diseases (STDs). Anal intercourse without the use of protective barriers can elevate the likelihood of HIV transmission by a factor ranging from five to twenty in comparison to vaginal intercourse. Therefore, the mucosal cells in females who undergo late coitarche (>18 years) exhibit incomplete maturation, and their immune system is not optimally functional. Females engaging in their initial sexual intercourse prior to the age of 18 may sustain abrasions or lacerations in the cervical region as a result of the act. The stimulation of male genitalia and their associated secretions may lead to these lacerations, thereby facilitating the entry of oncogenic viruses. Prolonged exposure of the cervix to these spermatozoa renders the cervical tissue increasingly vulnerable to carcinogenic stimuli, particularly due to the active process of squamous metaplasia which may result in CaCx [24]. However, cleanliness in sexual intercourse also contributes to preventing the risk of CaCx. Women who diligently bathe during menstruation prevent the risk of CaCx [22]. The risk of CaCx in women who have coitarchy at the age of less than 18 years is related to sexual behavior where the tendency to have sex with multiple partners and with HPV-infected partners is at risk of increasing CaCx [25]. In this study, women who experienced CaCx were more likely to be over 18 years of age and were also only married once, which is possible due to aspects of sexual hygiene and low immunity in patients. These results indicate that patients with advanced CaCx have an average plasma LRG-1 level that is higher than in the early stages. Similar results have been reported, but not in plasma LRG-1 levels but in urinary LRG-1 levels. These results, as explained by Astari et al. (2023), show that there is a significant relationship between urinary LRG-1 levels and CaCx stage. The higher the stage of CaCx, the higher the level of LRG-1 protein in the urine. LRG-1 plays a role in angiogenesis and antiapoptosis

in cancer [16]. Another study reported a positive correlation between serum and urinary LRG-1 in patients receiving kidney transplantation [26]. LRG-1 is synthesized and released by neutrophils, macrophages, intestinal epithelial cells, and hepatocytes, with its levels elevated during the acute phase response to microbial infections at sites of inflammation [27].

In this study, patients with advanced CaCx had an average plasma LRG-1 level of 308.66 ng/mL, while in patients with early-stage CaCx it was 67.53 ng/mL. A previous study reported that serum LRG-1 levels in healthy individuals were estimated to be less than 45 ng/mL [26]. Thus, plasma LRG-1 levels in patients with early-stage and advanced CaCx were in the range of values that exceeded normal values. Previous studies have reported that abnormal expression of LRG-1 is involved in the occurrence and development of cervical squamous carcinoma [28]. LRG-1 is a secreted glycoprotein that is constitutively synthesized by hepatocytes and neutrophils under physiological conditions. Following various inflammatory stimuli, including interleukin (IL)-33, IL-22, IL-17, IL-10, IL-6, IL-1β, transforming growth factor (TGF)-β, and tumor necrosis factor-alpha. LRG1 secretion is increased mainly by endothelial, neutrophil, and hepatocyte cells and can be detected at the local tissue level and/or systemically. Additionally, neoplastic and stromal cells within the tumor microenvironment (TME) may also contribute to LRG-1 production, with circulating levels of LRG-1 demonstrating a correlation with the progression of cancerous diseases [29]. LRG1 expression primarily occurs in the liver under normal conditions, but is significantly elevated in cancer. This induction is part of the acute innate immune response, modifying TGF-β signaling to activate endothelial cells and pericytes, leading to destabilized blood vessels and enhanced angiogenesis. It is posited that LRG1 also promotes EMT via TGF-β signaling alterations, facilitating loss of epithelial integrity and necessary cellular processes for wound healing. LRG1 expression decreases when the inflammatory response subsides in normal conditions. Conversely, ongoing chronic inflammation sustains and even escalates LRG1 expression. Notably, LRG1 directly influences tumor cell behavior, enhancing proliferation, migration, and invasion, thus supporting tumor growth and survival. LRG1 is pivotal in cancer-related angiocrine and angiopathic activities, fostering the formation of unstable neo-vessels and harming existing vasculature. Tumors necessitate a continuous supply of oxygen and nutrients, reliant on the concurrent development of a vascular network. However, tumor blood vessels are typically abnormal, exhibiting structural and functional disorders. Specifically, tumor blood vessels are tortuous, immature, and chaotically organized, with abnormal vessel walls characterized by incomplete mural cell coverage, discontinuous endothelium, and unusual basement membrane structures that lead to leakage and poor perfusion. These characteristics also create an acidic and hypoxic environment within the tumor tissue that favors tumor malignancy. Thus, LRG-1 promotes abnormal blood vessel formation in solid tumors. LRG1 induction in tumor masses and systemically in cancer is likely via STAT3 and IL-6, with contributions from other signaling pathways [30].

These results indicate a relationship between plasma LRG-1 levels and the CaCx stage. Similar results were reported in a study by Tian, Duan, and Jing (2018) conducted on 20 normal cervical tissues, 20 CIN II-III tissues, and 40 CaCx tissues, showing that LRG-1 expression correlates with the clinical stage. This is because LRG-1 is said to increase cancer pathogenesis directly and indirectly. LRG-1 contributes to tumor cell proliferation and viability, dysfunctional angiogenesis, and increasing EMT [28]. LRG-1 also works indirectly by modifying the TGFβ signaling pathway and increasing the expression of proangiogenic factors (angiopoietin-1 and vascular endothelial growth factor-A) [28]. TGFβ signaling directly inhibits the antitumor immune response [29]. High LRG-1 expression predicts advanced tumor stage and poor survival. LRG-1 significantly increases cancer cells' viability, proliferation, migration, and invasion [31].

LRG-1 functions as an acute phase protein (APP), with serum levels rising rapidly post-infection and inflammation. Synthesized by the liver in response to pro-inflammatory cytokines, APP is a non-specific innate immune component that acts prior to acquired immunity activation. APP concentrations can increase over 1000-fold during inflammatory responses, correlating with insult severity. In addition to hepatic synthesis, LRG-1 is also produced by neutrophils. Neutrophils, key innate immunity mediators, differentiate from myeloid progenitors in the bone marrow under granulocyte colony-stimulating factor (G-CSF) influence. LRG-1 is synthesized early during G-CSF-induced neutrophilic granulopoiesis and persists until the final differentiation stage, explaining its detection in progenitor-rich bone marrow but absence in peripheral monocytes and lymphocytes. In human neutrophils, LRG-1 is primarily found in cytoplasmic secondary granules with lactoferrin and less so in tertiary granules with gelatinase. LRG-1 can be released into the extracellular space following neutrophil activation at infection or inflammation sites. In this study, LRG-1 levels did not correlate with histopathological type, degree of differentiation, number of marriages, or age at first sexual intercourse. Therefore, these factors do not confound the relationship between plasma LRG-1 and CaCx stage.

The limitations of this study are that measurements on different samples can provide a more comprehensive understanding of the role of LRG-1 in the stage of CaCx. This study also only measured LRG-1 levels at one point in time before treatment, and the number of samples in the early stages of CaCx was less than in the advanced stages. In addition, in this study, there was no anamnesis data regarding the history of STDs and changing partners.

5. CONCLUSION

Based on the results of the study, it shows that CaCx in this study was mostly advanced stage. Most patients were under 50 years old, multiparous, normal BMI, histopathological type of SCC keratinizing, degree of differentiation could not be determined (Gx), number of marriages 1 time and age of first sexual intercourse more than 18 years both in CaCx patients

with early stage and advanced stage. Plasma LRG-1 levels in advanced-stage CaCx patients were more significant than in the early stage. Histopathological type and degree of differentiation were not significantly related to plasma LRG-1 levels. Plasma LRG-1 can be a biomarker in predicting the stage of CaCx.

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