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Relationship between the AminoIndex™ Cancer Screening (breast) grades and clinical data

Running title: AICS™ (breast) screening for BC

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Abstract

Background: Altered metabolism in the blood of cancer patients is closely related to changes in amino acids. Amino acids play an important physiological role as essential metabolites and regulators thereof. AminoIndex™ Cancer Screening (AICS) was developed to screen for seven cancer types, including breast cancer, through multivariate analysis of plasma-free amino acid profiles.

Methods: To examine the clinical significance of AICS (breast), we retrospectively analyzed the relationships between AICS (breast) scores and inspection items in 390 individuals who underwent the AICS (breast) test. The mean age of the participants was 50.7 years (range: 26–87 years), and all were females.

Results: AICS (breast) grades A–C were found in 250 (64.1%), 90 (23.1%), and 50 (12.8%) participants, respectively. AICS (breast) was significantly correlated with AICS (gastric) ($r = 0.487$, $p < 0.0001$) and AICS (lung) ($r = 0.523$, $p < 0.0001$). Multivariate linear regression analysis did not reveal any significant differences among AICS (breast) grades in terms of age, body mass index, eGFR, dyslipidemia, and blood pressure. However, the neutrophil-to-lymphocyte ratio was significantly different among the AICS (breast) grades at a cut-off value of 1.7 ($p = 0.030$), although the number of cases in the analysis decreased to 72.

Conclusion: To the best of our knowledge, this is the first study to report the relationships between AICS (breast) grades and clinical data.

Key words: AminoIndex™ Cancer Screening (AICS™), AICS (breast), breast cancer (BC), neutrophil to lymphocyte ratio (NLR)

Introduction

Metabolic changes in the blood of cancer patients are closely related to changes in the metabolism of amino acids, fatty acids, proteins, and glucosides. Blood metabolic profiles may be used to distinguish between cancer and non-cancer patients[1–5]. In particular, amino acids are preferred for metabolomic analysis because they play important physiological roles as essential metabolites and regulators thereof[1–6].

AminoIndex™ Cancer Screening (AICS) was developed as a screening test for seven cancer types, including breast cancer, through multivariate analyses of plasma-free amino acid (PFAA) profiles. PFAA concentration ratio changes have been reported in seven cancer types: gastric, lung, colorectal, prostate, gynecological, breast, and pancreatic cancers[1, 7]. In Japan, AICS is used as an optional cancer screening test[1, 7]. AICS has been modified for early detection of various cancer types. The modified test involves evaluation of the health status and probability of disease occurrence, with PFAA concentration serving as a variable in multivariate analyses[1, 2]. In the newly developed index, the ACIS score (range: 0.0–10.0) is based on the PFAA concentration. AICS scores of 5.0 and 8.0 correspond to 80% and 95% specificities, respectively. AICS scores of 0.0–4.9, 5.0–7.9, and 8.0–10.0 correspond to grades A–C, respectively, in order of decreasing

risk of cancer occurrence.

The breast-specific AICS test, i.e., AICS (breast), detects breast cancer based on the PFAA profiles of five representative amino acids [threonine (Thr), alanine (Ala), ornithine (Orn), histidine (His), and tryptophan (Trp)], all of which are altered in breast cancer[1, 8, 9]. The present study aimed to examine the clinical significance of the breast-specific AICS grade; therefore, we retrospectively evaluated the relationships between AICS (breast) values and systemic inflammation-related inspection items pertaining to tumor growth, angiogenesis, and cancer metastasis[10], in 390 individuals who underwent the AICS (breast) test.

Materials and Methods

Ethical considerations

This retrospective study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the review department of Shin-Urayasu Toranomon Clinic (Chiba, Japan). All participants consented to participate in the study by an opt-out option provided on the website. All data were analyzed anonymously.

Recipient recruitment and inspection items

This study included 390 participants who underwent AICS during health checkups between April 2016 and March 2021 at Shin-urayasu Toranomon Clinic (Chiba, Japan). The characteristics of the study participants are summarized in Table 1. A body mass index (BMI) of over 25 was considered positive, and a BMI of below 25 was considered negative. And estimated glemerular filtration rate (eGFR) of less than 60 was considered negative. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level < 40 mg/dL, or triglycerides ≥ 150 mg/dL[11–13]. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg[14].

The median neutrophil-to-lymphocyte ratio (NLR, 1.7), lymphocyte-to-monocyte ratio (LMR, 6.4), and neutrophil-to-monocyte ratio (NMR, 10.7) were calculated and used as cut-off values.

Measurement of PFAA concentrations

Participants underwent blood sampling, including the ACIS test during medical checkups. The blood samples were collected according to the instruction of AICS, and taken to clinical laboratory (SRL, Inc. Tokyo, Japan) based on the contraction.

The AICS test was performed as described previously[15–17]. Briefly, plasma samples were deproteinized using acetonitrile at a concentration of 80%, and PFAA concentrations were measured using high-performance liquid chromatography/electrospray ionization tandem mass spectrometry with pre-column derivatization.

Statistical analysis

Groups were compared using the Mann-Whitney U test and Spearman's rank correlation coefficient. Multiple groups were compared using the Kruskal–Wallis test, followed by a post-hoc Steel–Dwass test. P-values < 0.05 were considered statistically significant.

Multivariate linear regression analysis of breast-specific AICS was performed to identify

clinical factors associated with this index. We calculated the variance inflation factor (VIF) to evaluate multicollinearity among variables. The VIF cut-off for significant collinearity was set at 10.

All statistical analyses were performed using EZR, a modified version of R software (version 1.53; R Foundation for Statistical Computing, Vienna, Austria) with additional biostatistical functions[18].

Clinical information

The following parameters were obtained from the medical records of 390 participants: age, sex, height, weight, blood pressure, complete blood count, biochemical data (liver function test results and lipid levels) and imaging findings (mammography and ultrasonography).

Results

AICS (breast) grade and inspection items

The mean age of the 390 participants in total was 50.7 years (range: 26–87 years), and all were female（Table 1).

Fig.1 shows the AICS grades. Seventeen participants underwent AICS multiple times, but no participants were diagnosed with cancer（Table 2). There were 250 (64.1%), 90 (23.1%), and 50 (12.8%) patients of AICS (breast) grades A–C, respectively (Table 1).

No significant differences were observed in the clinical parameters among the three AICS (breast) grades, except for BMI, which was significantly different between grades A and C ($p = 0.030$).

Univariate analysis of AICS (breast)

No statistically significant associations were observed between AICS (breast) and age, BMI, or epidermal growth factor receptor (eGFR) according to the Mann-Whitney U test. Spearman's rank correlation coefficient revealed no significant correlation between AICS (breast) and dyslipidemia or blood pressure (Table 3).

Multivariate linear analysis of AICS (breast)

Multivariate linear regression analysis was performed to identify clinical factors associated with AICS (breast). Bivariate correlation analyses of the categorical (age, BMI, and eGFR) and continuous (dyslipidemia and blood pressure) variables were performed, and did not reveal significant associations of AICS with any variables (Table 4). The VIFs for age, BMI, eGFR, dyslipidemia, and blood pressure were 1.190, 1.082, 1.131, 1.145, and 1.035, respectively. The VIF value was < 10 for all variables, indicating no significant collinearity.

Spearman's rank correlation between AICS (breast) and other AICSs

We performed Spearman's rank correlations for AICS (breast) and other AICSs. The results showed a significant correlation between AICS (breast) and AICS (gastric) ($r = 0.487$, $p < 0.0001$), and between AICS (breast) and AICS (lung) ($r = 0.523$, $p < 0.0001$) (Table 5).

Comparison of AICS (breast) with other tests

We analyzed the associations of AICS (breast) with mammography, ultrasonography, anti-p53 antibody, NLR, LMR, and NMR using the Mann-Whitney U test. A statistically

significant association was found between AICS (breast) and NLR ($p = 0.030$) (Table 6). Carcinoembryonic antigen (CEA), the most important breast cancer marker, was tested in 40 out of 390 cases, and the result was negative in all of them.

The proportion of AICS (breast) grade A was similar between all participants and the 72 NLR-positive subjects (64.1% and 62.5%, respectively), whereas the proportion of grade C was higher in the NLR-positive group compared to all participants (19.4% and 12.8 %, respectively) (Fig. 1,2).

Discussion

AminoIndex™ was originally developed to screen for various diseases, such as cancer[1,7,19,20], cardiovascular diseases, and metabolic disorders[21-25]. Various mechanisms have been proposed to underlie PFAA profile changes in cancer patients, including local metabolic changes in cancer tissue, “remote organ metabolic changes”, and immune dysfunction[26,27]. AICS is commonly used in Japan to screen for seven cancer types. AICS (breast) is more useful than tumor markers for early cancer detection[28]. Importantly, several promising studies from other countries have reported similar results[29,30].

Several amino acids promote or inhibit the proliferation of cancer cells[4]. Alanine is as an important amino acid involved in apoptosis, as well as the proliferation of cancer cells in vitro[4]. Moreover, recent studies reported that novel tissue-free amino acid profiles were strongly associated with malignant characteristics and carcinogenesis in cancer patients, indicating that they reflect the characteristics of cancer tissues[31]. AICS (breast) detects breast cancer based on aberrant plasma concentrations of Thr, Ala, Orn, His, and Trp [1,8,9]. In breast cancer, Thr, Ala, and Orn are increased, while His and Trp are decreased[32]. Aberrant plasma amino acid profiles are cancer type-specific. For example, in gastric cancer, Ala, His, Trp, valine, leucine, and lysine are decreased. In lung cancer,

Orn and serine are increased, while His and glutamine are decreased. In the present study, AICS (breast) was associated with AICS (gastric) and AICS (lung) (Table 5). The concentration of His is the only parameter included in these three AICSs that is expected to decrease in cancer patients. Therefore, it is possible that the concentration of His influences the three AICS.

A previous large-scale study reported AICS (breast) grades A–C in 53%, 27%, and 20% of breast cancer patients, and 80%, 15%, and 5% in healthy individuals, respectively[32]. The proportions of AICS (breast) grades are apparently intermediate between those of the breast cancer patients and healthy individuals in this study.

Mikami *et al.* suggested that AICS is useful for predicting cancer occurrence, suggesting that annual AICS may be useful to detect malignancy[33]. A previous study of AICS for annual cancer screening[34] reported that some patients who developed breast cancer had a change in AICS grade from A or B to C after multiple tests, which facilitated early cancer detection. Patients with AICS (breast) grades A–C had a cancer risk 0.7-, 1.8-, and 4.0-fold greater than that of the general population, respectively. Therefore, 1 in 250 individuals with AICS (breast) grade C may have breast cancer.

A combination of parameters, including the NLR, platelet-to-lymphocyte ratio (PLR), LMR and NMR, has been used as a cost-effective and simple metric of systemic

inflammation[10]. This combination can also predict breast cancer prognosis[35]. Peng Y *et al.* [36] retrospectively analyzed a cohort of 808 breast cancer patients who underwent neoadjuvant chemotherapy and subsequent surgery, with the aim of identifying the best predictor of the response to neoadjuvant chemotherapy. They used a combination of parameters, including the NLR, PLR, LMR, and NMR, and reported no significant difference in the PLR, LMR, or NMR between the normal and breast cancer groups. However, the mean NLR was significantly higher in breast cancer patients compared to normal individuals (2.28 and 2.04, respectively, $p < 0.05$). The NLR obtained in the present study was significantly associated with the AICS (breast) scores at a cut-off value of 1.7 (Table 6). To the best of our knowledge, this is the first study to investigate the relationship between AICS (breast) and the NLR.

Conclusion

To the best of our knowledge, this is the first study to demonstrate the relationships between AICS (breast) and clinical indices. Importantly, the NLR, which is considered to be associated with cancer, was correlated with AICS (breast) scores.

Conflict of interest

The authors have no conflicts of interest.

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Figure Legends

Fig.1 AminoIndex™ Cancer Screening (breast) scores and grades.

Fig.2 Association of AminoIndex™ Cancer Screening (breast) scores with the neutrophil-to-lymphocyte ratio.

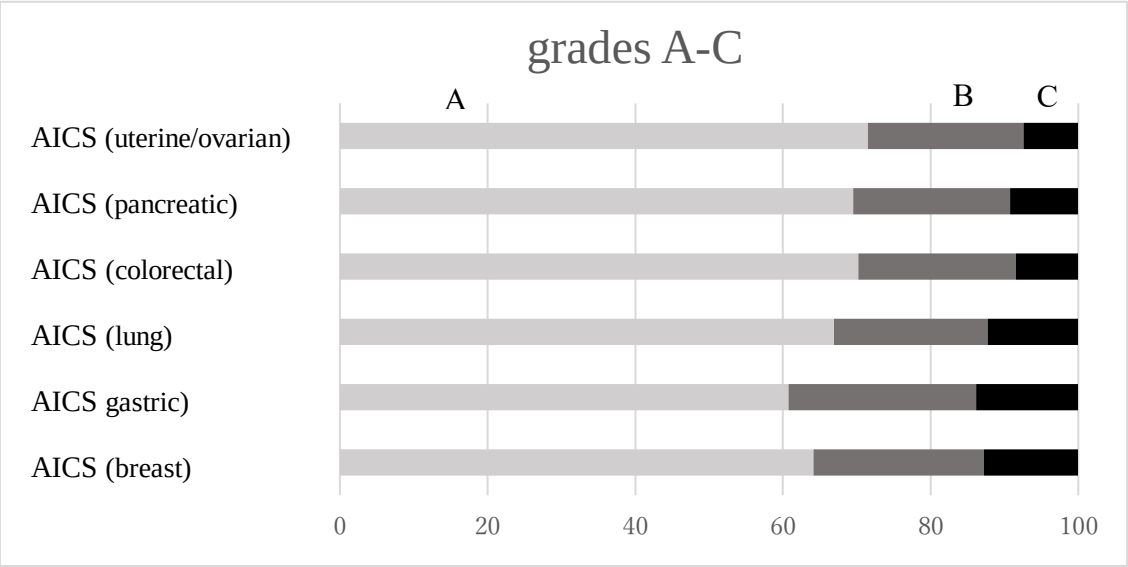

Figure. 1 AminoIndex™ Cancer Screening (breast) scores and grades.
AICS: AminoIndex™ Cancer Screening

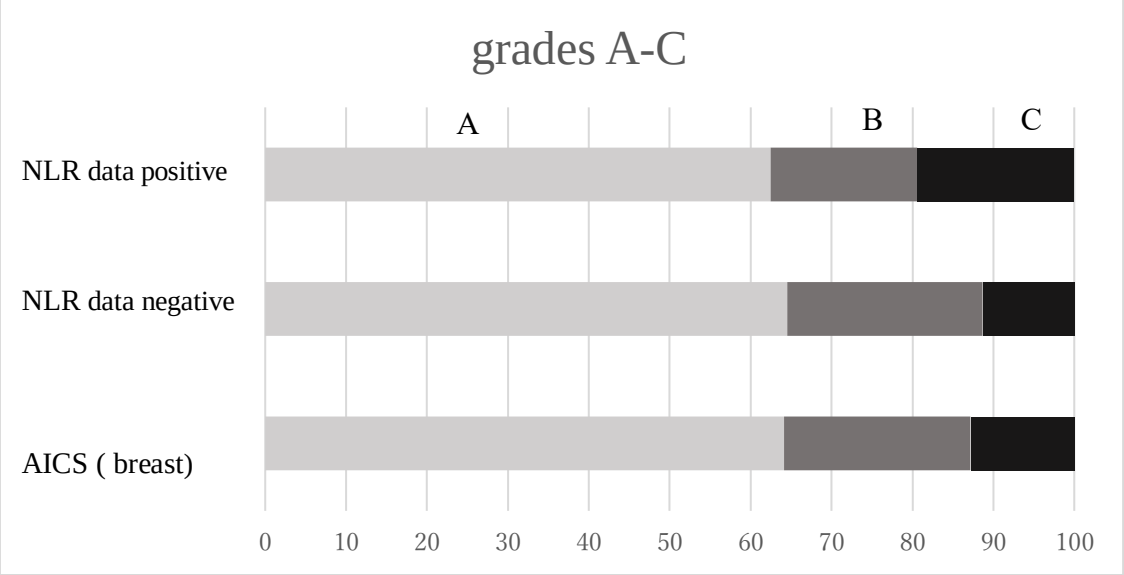

Figure 2. Association of AminoIndex™ Cancer Screening (breast) scores with the neutrophil-to-lymphocyte ratio.

NLR: neutrophil-to-lymphocyte ratio, AICS: AminoIndex™ Cancer Screening

Table 1. Characteristics of study participants.

characteristic	All	Grade A	Grade B	Grade C
age	50.7 (26-87)	50.9 (26-87)	50.6 (31-69)	50.2 (33-74)
	(n=390)	(n=250)	(n=90)	(n=50)
BMI	22.4 (16.1-35.5)	22.2 (16.6-34.2)	22.2 (16.1-31.3)	23.7 (18.2-35.5)
	(n=368)	(n=237)	(n=82)	(n=49)
eGFR	76.2 (35.6-138.4)	75.4 (46.5-132.7)	77.7 (49.8-138.4)	77.2 (35.6-114.4)
	(n=328)	(n=212)	(n=70)	(n=46)
dyslipidemia	127 (34.3%)	86 (40.6%)	27 (38.6%)	14 (30.4%)
	(n=370)	(n=212)	(n=70)	(n=46)
hypertension	45 (12.2%)	31 (14.6%)	11 (15.7%)	3 (6.5%)
	(n=370)	(n=212)	(n=70)	(n=46)

age (year), BMI: body mass index

, eGFR ($mL/min/1.73m^2$): estimated glemerular filtration rate

Table 2. 17 subjects who underwent AminoIndex™ Cancer Screening multiple times

	1st year	2nd year	3rd year	4th year	5th year
Patient 1	A	A	B	A	B
Patient 2	A	A	A	A	
Patient 3	A	C	A	A	
Patient 4	C	A	B	B	
Patient 5	C	B	C	B	
Patient 6	A	C	C	C	
Patient 7	A	A	A		
Patient 8	B	A	B		
Patient 9	C	A	A		
Patient 10	B	C	A		
Patient 11	A	A			
Patient 12	A	A			
Patient 13	B	C			
Patient 14	A	C			
Patient 15	A	C			
Patient 16	C	A			
Patient 17	C	A			

Table 3. Univariate analysis of AminoIndex™ Cancer Screening (breast).

independent variables	number	Spearman's rankcorrelation coefficient (r, P value)	Mann-Whitney U-test (P value)
age	390	0.003, 0.957	
BMI	368	0.092, 0.079	
eGFR	328	0.090, 0.105	
dyslipidemia	370		0.218
presence/ absence	127/ 243		
hypertension	370		0.402
presence/ absence	45/ 325		

age (year), BMI: body mass index, eGFR ($mL/min/1.73m^2$): estimated glemerular filtration rate

Table 4. Multivariate linear analysis of AminoIndex™ Cancer Screening (breast).

independent variables	estimated regression coefficicient	standard error	t value	P value
(intercept)	3.550	17.308	0.205	0.838
age	0.096	0.176	0.547	0.585
BMI	0.777	0.486	1.598	0.111
eGFR	0.218	0.111	1.956	0.051
dyslipidemia	-2.929	3.547	-0.826	0.410
hypertension	1.959	5.049	0.388	0.698

age (year), BMI: body mass index, eGFR ($mL/min/1.73m^2$): estimated glemerular filtration rate

Table 5. Spearman's rank correlation between AminoIndex™ Cancer Screening (breast) and other AminoIndex™ Cancer Screening tests.

	Spearman's rank correlation (r, P value)
AICS (breast) vs AICS (gastric)	0.487, <0.0001
AICS (breast) vs AICS (lung)	0.523, <0.0001
AICS (breast) vs AICS (colorectal)	0.108, 0.0333
AICS (breast) vs AICS (pancreatic)	0.239, <0.0001
AICS (breast) vs AICS (uterine/ovarian)	0.300, <0.0001

Table 6. Comparison of AminoIndex™ Cancer Screening (breast) with mammography, ultrasonography, anti-p53 antibody, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and neutrophil-to-monocyte ratio results.

independent variables	mumber	Mann-Whitney U-test (P value)
MMG	135	0.709
category 3/4/5	19	
category 1/2	116	
US	149	0.238
category 3/4/5	25	
category 1/2	124	
anti-P53 antiboby	41	1
positive	5	
negative	36	
NLR	72	0.03
positive	37	
negative	35	
LMR	72	0.16
positive	37	
negative	35	
NMR	72	0.11
positive	37	
negative	35	

MMG: mammography, US: ultrasonography, NLR: neutrophil-to-lymphocyte ratio, LMR: lymphocyte-to-monocyte ratio, NMR: neutrophil-to-monocyte ratio