—Original—

Associations of AminoIndex Cancer Screening (Breast) Grade with Clinical and Laboratory Variables

Tomoo Jikuzono[1–3], Osamu Ishibashi[1,2], Shoko Kure[4], Yumi Ohmae[3] and Toshimichi Ohmae[3,5]

[1]Department of Endocrine Surgery, Nippon Medical School, Tokyo, Japan
[2]Laboratory of Biological Macromolecules, Department of Applied Life Sciences, Graduate School of Life & Environmental Sciences, Osaka Prefecture University, Osaka, Japan
[3]Shin-urayasu Toranomon Clinic, Chiba, Japan
[4]Department of Integrated Diagnostic Pathology, Nippon Medical School, Tokyo, Japan
[5]Shisui Toranomon Clinic, Chiba, Japan

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 of metabolism. AminoIndex Cancer Screening (AICS) uses multivariate analysis of plasma-free amino acid profiles to screen for seven cancer types, including breast cancer.

Methods: To determine the clinical utility of AICS (breast), we retrospectively analyzed associations of AICS (breast) score with clinical and laboratory variables in 390 patients who underwent AICS (breast) testing. The mean age of participants was 50.7 years (range: 26-87 years) and all were female.

Results: The AICS (breast) grade was A, B, and C for 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 showed no significant difference of AICS (breast) grade with age, body mass index, estimated glomerular filtration rate, dyslipidemia, or blood pressure. However, neutrophil-to-lymphocyte ratio significantly differed in relation to AICS (breast) grade (cut-off value, 1.7; $p = 0.030$), although only data from 72 patients were analyzed.

Conclusion: To our knowledge, this is the first study to report associations of AICS (breast) grade with clinical variables. (J Nippon Med Sch 2022; 89: 377–383)

Key words: AminoIndex Cancer Screening, breast cancer, neutrophil to lymphocyte ratio

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 patients with and without cancer[1–5]. In particular, amino acids are preferred for metabolomic analysis because they play important physiological roles as essential metabolites and regulators of metabolism[1–6].

AminoIndex Cancer Screening (AICS) uses multivariate analyses of plasma-free amino acid (PFAA) profiles to screen for seven cancer types, including breast cancer. 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] and has been modified for early detection of multiple cancer types. The modified test evaluates health status and risk of disease occurrence, and PFAA concentration serves as a variable in multivariate analyses[1,2]. In the newly devel-

Correspondence to Tomoo Jikuzono, MD, PhD, Department of Endocrine Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8602, Japan
E-mail: t-jikuzono@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-403
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Characteristics of screenees

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

BMI: body mass index, eGFR (mL/min/1.73 m^2): estimated glomerular filtration rate

oped index, AICS score (range: 0.0-10.0) is based on 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, B, and C, respectively, in order of decreasing risk of cancer incidence.

The breast-specific AICS test, i.e., AICS (breast), detects breast cancer by analyzing PFAA profiles for 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 examined the clinical utility of breast-specific AICS grade by retrospectively evaluating associations of AICS (breast) scores with variables linked to systemic inflammation that are putatively related to tumor growth, angiogenesis, and cancer metastasis[10] in 390 persons who underwent AICS (breast) testing.

Materials and Methods

Ethical Considerations

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the review department of Shin-Urayasu Toranomon Clinic (Chiba, Japan) (Approval Number: 2021-1). All participants consented to participate in the study, as they were provided an opt-out option on the study website. All data were analyzed anonymously.

Recipient Recruitment and Analyzed Variables

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. An estimated glomerular filtration rate (eGFR) of less than 60 was considered negative. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥140 mg/dL, a high-density lipoprotein cholesterol level <40 mg/dL, or a triglyceride concentration ≥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 AICS test, during medical checkups. Blood samples were collected in accordance with the instructions for AICS and transported to a clinical laboratory (SRL, Inc. Tokyo, Japan).

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 by using high-performance liquid chromatography/electrospray ionization tandem mass spectrometry with pre-column derivatization.

Statistical Analysis

Groups were compared with the Mann-Whitney U test and Spearman rank correlation coefficients. Multiple groups were compared with the Kruskal-Wallis test, followed by the 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 variables associated with this index. To evaluate multicollinearity among variables, we calculated variance inflation factor (VIF). The VIF cut-off for significant collinearity was set at 10.

All statistical analyses were performed using EZR, a

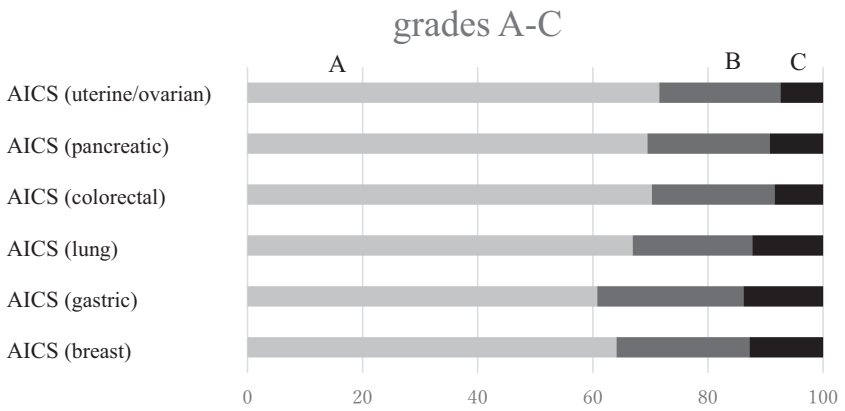

Fig. 1 AminoIndex Cancer Screening (breast) scores and grades.
AICS: AminoIndex Cancer Screening

Table 2 AminoIndex Cancer Screening ranks for 17 patients who underwent multiple screenings

	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			

modified version of R software (version 1.53; R Foundation for Statistical Computing, Vienna, Austria) with additional biostatistical functions[18].

Data Collection

Data on the following variables 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 Variables Analyzed

The mean age of the 390 participants was 50.7 years (range: 26-87 years), and all were female (**Table 1**). **Figure 1** shows their AICS grades. Among the 17 participants who underwent multiple AICS, none was diagnosed with cancer (**Table 2**). There were 250 (64.1%), 90 (23.1%), and 50 (12.8%) patients with AICS (breast) grades of A, B, and C, respectively (**Table 1**). No variable significantly differed in relation to AICS (breast) grade, except for BMI, which significantly differed between grades A and C ($p = 0.030$).

Univariate Analysis of AICS (Breast)

The Mann-Whitney U test showed no significant association of AICS (breast) score with age, BMI, or epidermal growth factor receptor (eGFR) status. Spearman rank correlation coefficients showed no significant correlation of AICS (breast) score with dyslipidemia or blood pressure (**Table 3**).

Table 3 Univariate analysis of AminoIndex Cancer Screening (breast)

independent variables	number	Spearman rank correlation coefficient (r, P value)	Mann-Whitney U-test (P value)
Age, years	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		

BMI: body mass index, eGFR (mL/min/1.73 m^2): estimated glomerular filtration rate

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

independent variables	estimated regression coefficient	standard error	t value	P value
(intercept)	3.550	17.308	0.205	0.838
Age, years	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

BMI: body mass index, eGFR (mL/min/1.73 m^2): estimated glomerular filtration rate

Table 5 Spearman rank correlation between AminoIndex Cancer Screening (breast) and other AminoIndex Cancer Screening tests

	Spearman 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

Multivariate Linear Analysis of AICS (Breast)

Multivariate linear regression analysis was used to identify variables associated with AICS (breast) score. Bivariate correlation analyses of categorical (age, BMI, and eGFR) and continuous (dyslipidemia and blood pressure) variables revealed no significant associations of AICS with any variable (**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 Rank Correlations between AICS (Breast) Rank and Other AICS Tests

Spearman rank correlations for AICS (breast) and other AICS tests 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

The Mann-Whitney U test showed no association of AICS (breast) score with the results of mammography, ultrasonography, anti-p53 antibody, NLR, LMR, or NMR. However, AICS (breast) score was significantly associated with NLR ($p = 0.030$) (**Table 6**). Carcinoembryonic antigen (CEA), the most important breast cancer marker, was tested in 40 of the 390 patients and the result was negative in all of these 40 patients.

The proportion of AICS (breast) grade A patients was similar between the overall sample and the 72 NLR-positive patients (64.1% and 62.5%, respectively), whereas

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

independent variables	Number	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 antibody	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

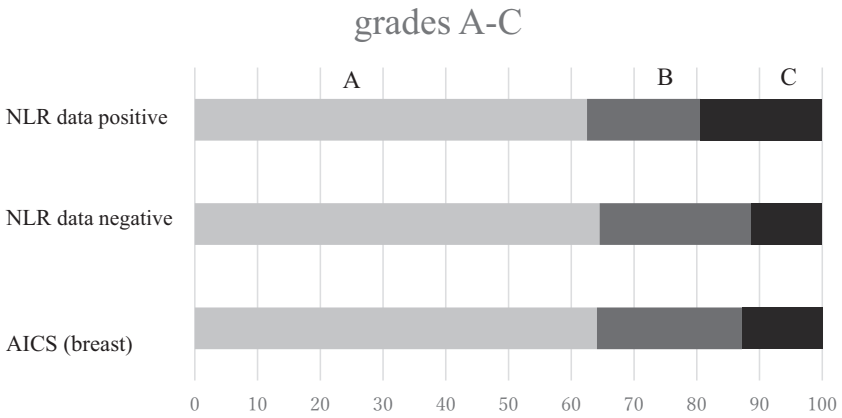

Fig. 2 Association of AminoIndex Cancer Screening (breast) scores with the neutrophil-to-lymphocyte ratio.
NLR: neutrophil-to-lymphocyte ratio, AICS: AminoIndex Cancer Screening

the proportion of grade C patients was higher in the NLR-positive group than in the overall sample (19.4% and 12.8%, respectively) (**Fig. 1, 2**).

Discussion

The AminoIndex was originally developed to screen for illnesses such as cancer[1,7,19,20], cardiovascular disease, and metabolic disorders[21–25]. The mechanisms underlying PFAA profile changes in cancer patients may include 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, and AICS (breast) is more useful than tumor markers for detecting early cancer[28]. Several promising studies from other countries have reported similar results[29,30].

Several amino acids promote or inhibit proliferation of cancer cells[4]. Alanine is as an important amino acid involved in apoptosis, as well as in the proliferation of cancer cells in vitro[4]. Moreover, recent studies reported that novel tissue-free amino acid profile was strongly associated with malignant characteristics and carcinogenesis in cancer patients, indicating that such profiles reflect the characteristics of cancer tissues[31]. AICS (breast) detects breast cancer by identifying abnormal plasma concentrations of Thr, Ala, Orn, His, and Trp[1,8,9]. In breast cancer, Thr, Ala, and Orn are elevated, while His and Trp are diminished[32]. Aberrant plasma amino acid profiles are specific to cancer types. In gastric cancer, Ala, His, Trp, valine, leucine, and lysine are diminished. In lung cancer, Orn and serine are elevated, while His and glutamine are diminished. In the present study, AICS (breast) was associated with AICS (gastric) and AICS (lung) (**Table 5**). His concentration is the only variable included in these three AICSs that is expected to be lower in cancer patients. Therefore, His concentration might affect AICS (breast), AICS (gastric), and AICS (lung).

A previous large-scale study reported AICS (breast) grades of A, B, and C for 53%, 27%, and 20% of patients with breast cancer and in 80%, 15%, and 5% in healthy individuals, respectively[32]. The present proportions of AICS (breast) grades are between those previously reported for breast cancer patients and healthy individuals.

Mikami et al. suggested that AICS is useful for predicting cancer incidence and 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, B, and C had a cancer risk that was 0.7-fold, 1.8-fold, 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 variables, including NLR, platelet-to-lymphocyte ratio (PLR), LMR, and NMR, has been used as a straightforward, cost-effective index of systemic inflammation[10]. This combination can also predict breast cancer outcome[35]. To identify the best predictor of response to neoadjuvant chemotherapy, Peng Y et al.[36] retrospectively analyzed a cohort of 808 breast cancer patients who underwent neoadjuvant chemotherapy and subsequent surgery. They used a combination of variables, including NLR, PLR, LMR, and NMR, and found no significant difference in PLR, LMR, or NMR between healthy persons and patients with breast cancer. However, mean NLR was significantly higher in breast cancer patients than in healthy 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 our knowledge, this is the first study to identify an association between AICS (breast) and NLR.

Conclusion

To our knowledge, this study is the first to identify an association of AICS (breast) with clinical and laboratory variables. NLR, which is believed to be linked to cancer, was associated with AICS (breast) scores.

Conflict of Interest: None declared.

References

1. Miyagi Y, Higashiyama M, Gochi A, et al. Plasma free amino acid profiling of five types of cancer patients and its application for early detection. PLoS One. 2011;6(9): e24143.
2. Okamoto N. Use of "AminoIndex Technology" for cancer screening. Ningen Dock. 2012;26(6):911−22.
3. Gu Y, Chen T, Fu S, et al. Perioperative dynamics and significance of amino acid profiles in patients with cancer. J Transl Med. 2015;13:35.
4. Mazzone PJ, Wang XF, Beukemann M, et al. Metabolite profiles of the serum of patients with non-small cell carcinoma. J Thorac Oncol. 2016;11(1):72−8.
5. Yamakado M, Tanaka T, Nagao K, et al. Plasma amino acid profile associated with fatty liver disease and co-occurrence of metabolic risk factors. Sci Rep. 2017;7(1): 14485.
6. Hiller K, Metallo CM. Profiling metabolic networks to study cancer metabolism. Curr Opin Biotechnol. 2013;24 (1):60−8.
7. Mikami H, Kimura O, Yamamoto H, et al. A multicentre clinical validation of AminoIndex Cancer Screening (AICS). Sci Rep. 2019;9(1):13831.
8. Maeda J, Higashiyama M, Imaizumi A, et al. Possibility of multivariate function composed of plasma amino acid profiles as a novel screening index for non-small cell lung cancer: a case control study. BMC Cancer. 2010;10:690.
9. Shingyoji M, Iizasa T, Higashiyama M, et al. The significance and robustness of a plasma free amino acid (PFAA) profile-based multiplex function for detecting lung cancer. BMC Cancer. 2013;13:77.
10. Noh H, Eomm M, Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer. 2013;16(1):55−9.
11. Yamashita S, Masuda D, Akishita M, et al. Guidelines on the clinical evaluation of medicinal products for treatment of dyslipidemia. J Atheroscler Thromb. 2020;27(11):1246−54.
12. Teramoto T, Sasaki J, Ueshima H, et al. Diagnostic criteria for dyslipidemia. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and pre-

vention of atherosclerotic cardiovascular diseases for Japanese. Japan Atherosclerosis Society (JAS) Committee for Epidemiology and Clinical Management of Atherosclerosis. J Atheroscler Thromb. 2007;14(4):155–8.
13. Hata Y, Mabuchi H, Saito Y, et al. Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. Working Committee on JAS Guideline for Diagnosis and Treatment of Hyperlipidemias. J Atheroscler Thromb. 2002;9(1):1–27.
14. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res. 2019;42(9):1235–481.
15. Shimbo K, Kubo S, Harada Y, et al. Automated precolumn derivatization system for analyzing physiological amino acids by liquid chromatography/mass spectrometry. Biomed Chromatogr. 2010;24:683–91.
16. Shimbo K, Oonuki T, Yahashi A, Hirayama K, Miyano H. Precolumn derivatization reagents for high-speed analysis of amines and amino acids in biological fluid using liquid chromatography/electrospray ionization tandem mass spectrometry. Rapid Commun Mass Spectrom. 2009;23: 1483–92.
17. Shimbo K, Yahashi A, Hirayama K, Nakazawa M, Miyano H. Multifunctional and highly sensitive precolumn reagents for amino acids in liquid chromatography/tandem mass spectrometry. Anal Chem. 2009;81:5172–9.
18. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452–8.
19. Fukutake N, Ueno M, Hiraoka N, et al. A novel multivariate index for pancreatic cancer detection based on the plasma free amino acid profile. PLoS One. 2015;10(7):e 0132223.
20. Miyagi E, Maruyama Y, Mogami T, et al. Comparison of plasma amino acid profile-based index and CA125 in the diagnosis of epithelial ovarian cancers and borderline malignant tumors. Int J Clin Oncol. 2017;22(1):118–25.
21. Yamakado M, Tanaka T, Nagao K, et al. Plasma amino acid profile is associated with visceral fat accumulation in obese Japanese subjects. Clin Obes. 2012;2(1-2):29–40.
22. Kume S, Araki S, Ono N, et al. Predictive properties of plasma amino acid profile for cardiovascular disease in patients with type 2 diabetes. PLoS One. 2014;9(6): e101219.
23. Mahbub MH, Yamaguchi N, Takahashi H, et al. Alteration in plasma free amino acid levels and its association with gout. Environ Health Prev Med. 2017;22(1):7.
24. Yamaguchi N, Mahbub MH, Takahashi H, et al. Plasma free amino acid profiles evaluate risk of metabolic syndrome, diabetes, dyslipidemia, and hypertension in a large Asian population. Environ Health Prev Med. 2017; 22(1):35.
25. Kaelin WG, Thompson CB. Q&A: Cancer: clues from cell metabolism. Nature. 2010;465(7298):562–4.
26. Luo Y, Yoneda J, Ohmori H, et al. Cancer usurps skeletal muscle as an energy repository. Cancer Res. 2014;74:330–40.
27. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest. 2007;117(5):1147–54.
28. Miyagi Y, Higashiyama M, Gochi A, et al. Clinical utility of AminoIndex Cancer Screening (AICS) for early detection of various cancers in comparison with detection using tumor markers. Ningen Dock. 2014;29:585–91.
29. Kim HJ, Jang SH, Ryu JS, et al. The performance of a novel amino acid multivariate index for detecting lung cancer: A case control study in Korea. Lung Cancer. 2015; 90(3):522–7.
30. Klupczynska A, Dereziński P, Dyszkiewicz W, Pawlak K, Kasprzyk M, Kokot ZJ. Evaluation of serum amino acid profiles' utility in non-small cell lung cancer detection in Polish population. Lung Cancer. 2016;100:71–6.
31. Zhao Q, Cao Y, Wang Y, et al. Plasma and tissue free amino acid profiles and their concentration correlation in patients with lung cancer. Asia Pac J Clin Nutr. 2014;23 (3):429–36.
32. Ajinomoto Co., Inc. AminoIndex [Internet]. Available from: https://www.ajinomoto.co.jp/company/jp/rd/our_innovation/aminoindex/
33. Mikami H, Kimura O, Yamamoto H, et al. A multicentre clinical validation of AminoIndex Cancer Screening (AICS). Sci Rep. 2019;25:9(1):13831.
34. Yamakado M, Yamamoto H, Yamamoto M, et al. AminoIndexTM gan sukurining no keinen jushin no yuyousei no kento [A study on the usefulness of AminoIndexTM cancer screening for annual cancer screening]. Official Journal of Japan Society of Ningen Dock. 2017;32(5):748–57. Japanese.
35. Pistelli M, De Lisa M, Ballatore Z, et al. Pre-treatment neutrophil to lymphocyte ratio may be a useful tool in predicting survival in early triple negative breast cancer patients. BMC Cancer. 2015;15:195.
36. Peng Y, Chen R, Qu F, et al. Low pretreatment lymphocyte/monocyte ratio is associated with the better efficacy of neoadjuvant chemotherapy in breast cancer patients. Cancer Biol Ther. 2020;21(2):189–96.

(Received, September 16, 2021)
(Accepted, December 15, 2021)
(J-STAGE Advance Publication, January 25, 2022)