Association of body mass and systemic immune-inflammation indices with endocrine therapy resistance in luminal breast cancers

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Abstract

Objective: To explore correlations between body mass index (BMI), preoperative systemic immune-inflammation index (SII) and endocrine therapy resistance, and evaluate BMI and SII as predictors of resistance, in patients with luminal breast cancer.

Methods: This retrospective study included patients with luminal breast cancer who underwent endocrine therapy at Hebei General Hospital. Relationships between BMI and SII subgroups, and clinicopathological parameters were analysed using χ^2-tests. Disease-free survival was assessed using Log-rank statistics. Multivariate analysis of factors related to disease progression were analysed using Cox proportional hazards model.

Results: Out of 161 patients, those with normal BMI and low SII had significantly lower endocrine resistance rates versus those with high BMI and SII, and BMI was significantly positively correlated with SII. High BMI or SII was associated with significantly lower disease-free survival rates. Hazard ratios for disease progression risk were 6.036, 3.508 and 1.733, for SII, BMI and TNM stage, respectively.

Conclusion: In patients with luminal breast cancer, high BMI ($>23 \text{ kg/m}^2$) and SII ($>518 \times 10^9$/L) levels may predict high endocrine resistance rates. BMI, SII and TNM stage were independent prognostic factors for endocrine therapy resistance.

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Introduction

Endocrine therapy is the preferred treatment for patients with hormone receptor-positive breast cancer and slow progression at the very beginning of recurrence or the metastasis period,[1] and has been shown to significantly improve outcomes for patients with early- and advanced-stage hormone receptor-positive breast cancer.[2] Although endocrine therapy is effective, acquired resistance to therapies represents a critical clinical problem,[3] for example, some patients with early-stage disease will experience relapse, and all patients with advanced disease will experience disease progression on endocrine therapy.[2] Thus, research into factors that influence endocrine therapy resistance is crucial.

To date, much effort has been directed towards investigating endocrine therapy resistance, and various associated factors and mechanisms have been proposed.[4–6] Epidemiological evidence has indicated that increased body weight is associated with increased death rates in patients with cancer,[7] and the International Agency for Research on Cancer has determined that individuals who are overweight or obese are at increased risk of developing cancers.[7,8] An exploratory analysis of data from the Arimidex, Tamoxifen Alone or in Combination trial revealed that obesity was associated with poor prognosis in patients with postmenopausal breast cancer, and was associated with an increased risk for resistance to endocrine therapy.[9] Calle et al.[10] showed that higher BMI values were associated with a significant increase in the risk of breast-cancer related mortality in women. Furthermore, the correlation between overweight and postmenopausal breast cancer was demonstrated in a review of epidemiological data.[11] The association between body mass index (BMI) and endocrine therapy resistance remains uncertain, however, and the underlying mechanisms are yet to be explored.

Cancer-related inflammation is an essential component of the cancer microenvironment, and inflammatory cells may play a crucial role in cancer development and progression.[12] The systemic immune-inflammation index (SII), a novel and integrated indicator of prognosis, based on lymphocyte, neutrophil, and platelet counts, was first proposed by Hu et al.[13] The SII may be better able to reflect the balance of host inflammatory and immune response status compared with the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and other conventional parameters, such as Barcelona Clinic Liver Cancer (BCLC) staging, tumour differentiation, and tumour number,[13] and has been confirmed as a powerful prognostic indicator of poor outcome in patients with hepatocellular carcinoma (HCC).[14] In patients with HCC, elevated SII score was associated with lymphatic invasion, early recurrence, and larger tumour size, indicating a more aggressive phenotype.[14] Nevertheless, to the best of the present authors knowledge, the relationship between SII and breast cancer has not yet been established.

Therefore, the aims of the present retrospective study were to investigate the associations between BMI or SII and endocrine therapy resistance in patients with luminal breast cancer, and to conduct a novel investigation into the utility of SII as an indicator of endocrine therapy resistance in such patients.

Patients and methods

Study population and treatment

This single-centre retrospective study included sequentially enrolled Chinese female patients with luminal breast cancer who underwent modified radical mastectomy at the Department of Oncology, Hebei General Hospital, Shijiazhuang, Hebei, China between October 2008 and December 2013, and who met the study inclusion criteria. Pathological examinations were performed at the Department of Pathology, Hebei General Hospital. Inclusion criteria comprised: (1) patients diagnosed with hormone receptor-positive primary breast cancer, where hormone receptor-positive was defined as tumours with ≥1% of tumour nuclei positive for oestrogen receptor and/or progesterone receptor, as previously described;[15] (2) postoperatively, patients had received endocrine therapy only following standard adjuvant chemotherapy and/or radiotherapy; and (3) diagnosis of stage 0, I, II or III cancer. Exclusion criteria were as follows: (1) patients with chronic inflammatory diseases; (2) patients with BMI < 18.5 kg/m^2; (3) patients with stage IV breast cancer; and (4) patients who received treatment other than endocrine therapy after standard adjuvant chemotherapy and/or radiotherapy.

Premenopausal patients were treated with tamoxifen as an endocrine drug, and postmenopausal patients were treated with tamoxifen or aromatase inhibitors. The recurrence or progression of breast cancer during endocrine therapy, or within 12 months following complete adjuvant endocrine therapy, was collectively defined as endocrine resistance.

This study was approved by the Ethics Committee of Hebei General Hospital, and written informed consent was obtained from each patient before the surgical procedures and for the purpose of research. Follow-up was performed by hospital visits, telephone or mail contacts, and the follow-up period ended on 31 May, 2015 or on the date that the patient showed drug resistance. During the follow-up period, data from patients who died for reasons unrelated to the breast cancer, or who discontinued the follow-up, were recorded as censored values.

Data collection and groups

Patients' clinical parameters including age, menopausal status, pathological subtype, TNM stage, lymph node metastasis, lymphatic invasion, luminal subtype, BMI and at baseline were collected and classified. SII was defined as follows: $SII = P \times N/L$, where P, N, and L were the counts of preoperative peripheral platelets (P), neutrophils (N), and lymphocytes (L), respectively.[6] Patients' BMI scores were calculated as weight (kg)/ height (m)^2. For the present analyses, patients with a BMI within the range of 18.5–22.9 kg/m^2 were considered to be normal weight (normal BMI group) and patients with a BMI ≥23 kg/m^2 were considered to be obese (high BMI group), according to BMI grouping criteria for Asian populations.[16,17] A receiver operating characteristic (ROC) curve was constructed to determine the optimal threshold of SII, which was found to be 518×10^9/L with a sensitivity of 80.6 and specificity of 58.5 (Figure 1). Patients were thus divided into two groups: low SII group (SII ≤518×10^9/L) and high SII group (SII > 518×10^9/L). In the present study,
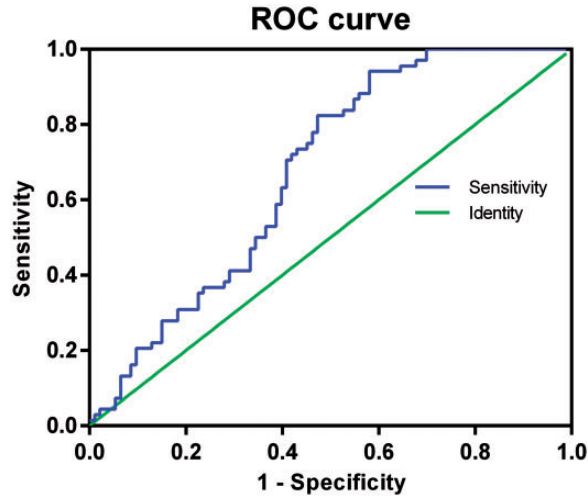
Figure 1. Receiver operating characteristic (ROC) curve for systemic immune-inflammation index in patients with hormone-receptor positive luminal breast cancer who underwent modified radical mastectomy and were treated with endocrine therapy.

patients with stage 0 and stage I cancer were grouped together (stage 0–I group), and patients with noninvasive and early invasive cancer were grouped together (noninvasive–early invasive group), due to the small case numbers. Disease-free survival was defined as the period between modified radical mastectomy and disease progression, including recurrence or metastasis. The endocrine resistance rate was calculated using the following equation: Endocrine resistance rate $= (1$–disease free survival rate$) \times 100$.

Statistical analyses

Data are presented as n (%) prevalence or median (range), and all statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA). The normality of data distribution was determined using Kolmogorov–Smirnov test, and the data distribution was considered normal. The categorical variables were analysed using χ^2-test. Disease-free survival analysis was performed by Kaplan-Meier method, and log-rank statistics were used to compare the subgroups.

χ^2-tests were used to analyse the association between BMI and SII. Multivariate regression analysis was subsequently performed using Cox proportional hazards model for the purpose of determining the independent predictors of endocrine therapy resistance. A P value <0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 161 Chinese female patients with luminal breast cancers were enrolled into this study (median age, 58 years). Complete patient information was available for all 161 of the patients, thus all were included in these analyses. A total of 60 patients (37%) received tamoxifen and 101 patients (63%) received aromatase inhibitors, and the median follow-up duration was 28.4 months (range, 1–79 months).

Patients' demographic and clinical characteristics are shown in Table 1. In summary, 41 patients (25.5%) were classified with

Table 1. Demographic and clinical characteristics in 161 patients with hormone-receptor positive luminal breast cancer treated with endocrine therapy, grouped according to normal/high body mass index (BMI) or low/high systemic immune-inflammation index (SII).

Clinical pathological parameter	BMI			SII		
	Normal (18.5–22.9 kg/m^2) $n = 41$	High (≥23 kg/m^2) $n = 120$	Statistical significance	Low (≤518 × 10^9/L) $n = 32$	High (>518 × 10^9/L) $n = 129$	Statistical significance
Age			NS			NS
<50 years	9	32		4	37	
≥50 years	32	88		28	92	
Menstrual status			NS			NS
Pre-	10	30		5	35	
Post-	31	90		27	94	
Lymphatic invasion			NS			NS
Negative	34	101		30	105	
Positive	7	19		2	24	
Lymph node metastasis			NS			NS
Positive	17	54		13	58	
Negative	24	66		19	71	
Pathological subtype			NS			NS
Noninvasive–early invasive	5	19		4	20	
Specific invasive	30	76		22	84	
Nonspecific invasive	6	25		6	25	
TNM stage			NS			NS
0–I	10	37		11	36	
II	25	63		19	69	
III	6	20		2	24	
Luminal subtype			NS			NS
A subtype	12	41		10	43	
B subtype	29	79		22	86	
Drug resistance status			$P < 0.001$			$P < 0.001$
Non-resistant	33	59		29	63	
Resistant	8	61		3	66	

Data presented as _n_ prevalence.
TNM, tumour node metastasis.
$P < 0.05$, statistically significant between-group differences (χ^2-test).
NS, no statistically significant between-group difference ($P > 0.05$).

normal BMI (18.5–22.9 kg/m^2) and 120 patients (74.5%) with high BMI ($\geq$23 kg/m^2), and 32 patients (19.9%) were classified with low SII ($\leq$518 × 10^9/L) and 129 patients (80.1%) with high SII (>518 × 10^9/L). In terms of TNM stage, 47 patients (29.2%) were classified as stage 0–I, 88 patients (54.7%) as stage II, and 26 patients (16.1%) as stage III cancer. According to the international histologic classification of breast cancer, 24 patients (14.9%) were classified as noninvasive–early invasive subtypes, 31 patients (19.3%) as nonspecific invasive subtypes and 106 patients (65.8%) as specific invasive subtypes.

Relationships between BMI, SII and clinical pathological parameters

In patients grouped by BMI status, there were no statistically significant between-group differences in age ($P = 0.550$), menstrual status ($P = 0.938$), lymphatic invasion ($P = 0.852$), lymph node metastasis ($P = 0.694$), pathological subtype ($P = 0.514$), TNM stage ($P = 0.633$), or luminal subtype ($P = 0.564$). Endocrine resistance rates were 19.5% (8/41 patients) in the normal BMI group and 50.8% (61/120 patients) in the high BMI group (overall between-group difference $P < 0.001$), suggesting that BMI was significantly associated with drug resistance (Table 1).

In patients grouped by SII status, there were no statistically significant between-group differences in terms of age ($P = 0.06$), menstrual status ($P = 0.178$), lymphatic invasion ($P = 0.089$), lymph node metastasis ($P = 0.658$), pathological subtype ($P = 0.899$), TNM stage ($P = 0.228$), or luminal subtype ($P = 0.364$). There was a statistically significant between-group difference in endocrine resistance rates between patients with low SII (9.4% [3/32 patients]) versus patients with high SII (51.2% [66/129 patients]) ($P < 0.001$), suggesting that SII

was also significantly associated with drug resistance (Table 1).

Relationships between BMI, SII and drug resistance

Cumulative disease-free survival was compared in patients with luminal breast cancers and normal BMI or low SSI versus those with high BMI or SSI levels. As shown in Figure 2a, the disease-free survival rate at 1, 3 and 5 years was 95.1%, 83.1% and 62.3% in the normal BMI group, and 78.3%, 48.6% and 18.0% in the high BMI group, respectively. Endocrine therapy resistance rates at 1, 3 and 5 years were calculated to be 4.9%, 16.9% and 37.7% in the normal BMI group, and 21.7%, 51.4% and 82% in the high BMI group, respectively, and were significantly different between the two BMI groups ($P < 0.001$). In the low SII group, disease-free survival rates at 1, 3 and 5 years were 96.9%, 96.9% and 75.0% respectively, and in the high SII group were 92.2%, 72.8% and 65.2%, respectively (Figure 2b). Resistance rates at 1, 3 and 5 years in the low SII group were 3.1%, 3.1% and 25% respectively, and in the high SII group were 7.8%, 27.2% and 34.8%, respectively, and were also significantly different between the two SII groups ($P < 0.001$).

The higher rates of resistance to endocrine therapy in patients with high BMI or SII compared with normal BMI or low SII level suggests that high BMI or SII may be associated with significantly worse prognosis in patients with luminal breast cancers.

Correlation between BMI and SII

A total of 15 patients had normal BMI and low SII, and 103 patients had both high BMI and high SII levels. χ^2-tests showed that BMI was significantly positively correlated with SII (r = 0.245, $P = 0.002$,
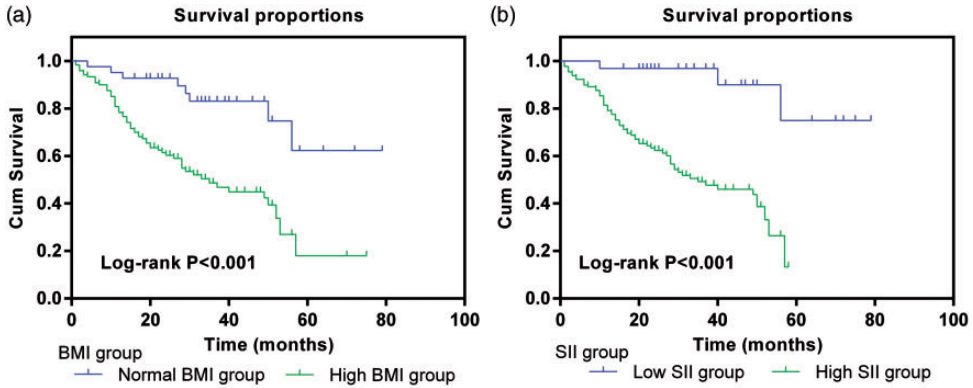
Figure 2. Disease-free survival curves for 161 patients with hormone-receptor positive luminal breast cancer who underwent modified radical mastectomy and were treated with endocrine therapy: (a) patients grouped into normal (18.5–22.9 kg/m^2) or high ($\geq$23 kg/m^2) body mass index (BMI) levels; and (b) patients grouped into low ($\leq$518 $\times$ 10^9/L) or high ($>$518 $\times$ 10^9/L) SII levels. Cum survival, cumulative survival; time, measured in months.

Table 2. Correlation between body mass index (BMI) and systemic immune-inflammation index (SII) in 161 patients with hormone-receptor positive luminal breast cancer treated using endocrine therapy.

Characteristic	SII		Correlation coefficient (r)	Statistical significance
	Low ($\leq$518 $\times$ 10^9/L)	High ($>$518 $\times$ 10^9/L)		
BMI			0.245	$P = 0.002$
Normal (18.5–22.9 kg/m^2)	15	26		
High ($\geq$23 kg/m^2)	17	103		

$P < 0.05$, statistically significant correlation.

Table 2), suggesting that SII levels would increase with the increase in BMI level.

Comparison of hazard ratios

Multivariate regression analysis of nine prognostic factors was performed using Cox proportional hazards model (Table 3). In the Cox regression model, the score test ($P < 0.001$) and the likelihood ratio test ($P < 0.001$) showed that the overall test of the model was statistically significant.

With regard to BMI, compared with normal weight patients, patients with high BMI had significantly increased risks of disease progression (recurrence or metastasis), with hazard ratio (HR) of 3.508 (95% confidence interval [CI] 1.645, 7.480; $P = 0.001$). Patients with high SII levels had significantly higher risks of disease progression compared with patients with low SII levels (HR 6.036, 95% CI 1.824, 19.977; $P = 0.003$). The hazard ratio for TNM stage was 1.733 (95% CI 1.117, 2.688; $P = 0.014$), indicating that TNM stage was associated with a significantly increased risk of breast cancer disease progression.

Table 3. Cox proportional hazards multivariate regression analysis of factors predicting disease progression in 161 female patients with luminal breast cancer treated using endocrine therapy.

Variable	Statistical significance	HR (95% CI)
Age	NS	0.988 (0.959, 1.018)
Menstrual status	NS	0.966 (0.431, 2.164)
Lymphatic invasion	NS	0.991 (0.506, 1.939)
Lymph node metastasis	NS	1.073 (0.614, 1,876)
Pathological subtype	NS	0.917 (0.600, 1.401)
TNM stage	$P = 0.014$	1.733 (1.117, 2.688)
SII group	$P = 0.003$	6.036 (1.824, 19.977)
BMI group	$P = 0.001$	3.508 (1.645, 7.480)
Luminal subtype	NS	0.984 (0.579, 1.672)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SII, systemic immune-inflammation index; TNM, tumour node metastasis.
NS, no statistically significant increased risk of disease progression ($P > 0.05$).

Therefore, BMI, preoperative SII and TNM stage were shown to be independent prognostic factors for endocrine therapy resistance following radical surgery in patients with breast cancer.

Discussion

In the present study, the association between BMI, SII and endocrine therapy resistance in luminal breast cancer was evaluated. On the basis of the present results, BMI and SII were concluded to have a significant correlation with endocrine therapy resistance ($P < 0.05$), and an increase in endocrine resistance rates was associated with increases in both indices. These results are consistent with previously published research.[18,19] Several hypotheses have been proposed to explain the poor prognosis and survival outcomes observed in patients with high BMI, including factors related to diagnosis and treatment of obese patients with breast cancer.[20] However, the effect of BMI on patients with breast cancer in China remain unclear.

A meta-analysis by Maruthur et al.[21] indicated that morbidly obese women may be less likely to undergo mammography, and their increased breast adiposity may delay tumour detection and diagnosis until tumours are larger. Thus, the lower screening rates may partly explain the higher mortality associated with such patients with breast cancer.[21,22] Nonetheless, the present authors hold the opinion that breast cancer progression is mainly related to aggressive tumour biology. Another possible mechanism is that poor outcomes in patients with breast cancer are associated with increased levels of adipose tissue in obese women.[23] Since the production of oestrogen and expression of aromatase in postmenopausal women occurs mainly in adipose tissue, the secretion and activity of aromatase is also increased in obese patients. Large amounts of oestrogen are then produced, stimulating the progression of breast cancer. The present study confirmed the hypotheses that high BMI in obese patients would result in poor prognosis and BMI is a predictive parameter for endocrine treatment. However, the underlying mechanism remains unclear, and cannot be clarified in the present study due to the relatively small study population and lack of direct

evidence. BMI may affect the prognosis of patients with breast cancer through various factors, such as insulin, inflammatory response, oestrogen metabolism, delayed expression and therapeutic dose.

The present results demonstrate novel evidence for a relationship between SII and endocrine therapy resistance rate in patients with breast cancer, in that the endocrine resistance rate was revealed to be significantly associated with SII level. Several good quality reviews have described the independent effect of systemic inflammatory response (SIR) on the prognosis of patients with solid tumours, including gastric cancer[24] and colon cancer.[25] Hu et al.[13] developed a novel SII based on lymphocyte, neutrophil, and platelet counts, and further confirmed that SII was a powerful prognostic indicator of poor outcomes in patients with HCC. However, it has not been reported to date whether SII, as an integrated indicator, might be better able to reflect the balance of host inflammatory and immune status in patients with breast cancer versus neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and other conventional parameters such as BCLC staging, tumour differentiation, and tumour number. Thus, SII and breast cancer was the focus of the present report, and the results supported previous findings in luminal breast cancer.

Tumour cells can release granulocyte growth factors,[26] such as granulocyte colony-stimulating factor (G-CSF), leading to an increase in neutrophils. Neutrophils are able to promote the invasion, proliferation and metastasis of cancer cells, and help the evasion of immune surveillance.[27] Neutrophils have been shown to reshape extracellular matrix by promoting tumour growth and metastasis, and release reactive oxygen species (ROS), nitric oxide and arginine levels to inhibit T cell responses and increase the mutation rate.[28] ROS from neutrophils reduce the adhesion of extracellular matrix, activate nuclear factor κB, and inhibit the apoptosis of tumour cells. In addition, platelets can interact with tumour cells and promote their growth and metastasis through multiple mechanisms.[29] In fact, high platelet count has been associated with the conversion of primary tumour cells into circulating tumour cells (CTCs). Several studies have demonstrated that platelets can protect CTCs from shearing stress during circulation, induce epithelial-mesenchymal transition of CTCs, and promote tumour cell extravasation and metastasis.[29,30] Thus, high SII values with more neutrophils or platelets may result in tumour growth, metastasis, and eventually lead to poor outcomes in patients with cancer. Finally, lymphocytes play an important role in tumour immune surveillance. Elevated levels of cytokines released by lymphocytes, such as interferon-ɣ and TNF-α (tumour necrosis factor-α), can control tumour cell growth and metastasis, which could improve the prognosis of cancer patients. Furthermore, cytotoxic T lymphocytes can be identified and combined with the CD95L (Fas ligand) on the tumour cell through CD95 receptor (Fas) to induce tumour cell apoptosis.[31] Therefore, high SII with less lymphocytes may also promote tumour growth and metastasis, and inhibit the apoptosis of tumour cells, eventually leading to poor outcomes in breast cancer. In summary, increased neutrophils and platelets, and decreased lymphocytes may result in high SII values that reflect changes in the tumour microenvironment that promote cancer initiation, progression, and metastasis, eventually leading to high endocrine resistance rates.

The present results, together with those of published studies, indicate that SII may be a more objective marker of the balance between host inflammatory and immune response status compared with conventional parameters. A systematic evaluation of

the value of neutrophils, lymphocytes, and platelets in breast cancer will contribute to elucidating the association between cancer, immunity, and inflammation. In addition, the detection of SII is simple, inexpensive, and does not require extra equipment to analyse. Thus, SII could be routinely considered for patients with luminal breast cancer. According to studies published to date, the optimal thresholds for SII values vary for different tumour types.[13,32,33] Based on the effect of sample size, research methods, biological characteristics and tumour location on the optimal threshold for SII, further studies are required to verify whether SII is indeed an effective prognostic predictor for breast cancer.

The highlight of the present study was the finding of a significantly positive correlation between BMI and SII, suggesting that increased BMI may promote the increase of SII, and both are involved in the resistance to endocrine therapy in luminal breast cancer. Thus, the present authors suggest that research into SII should take into account the patient's BMI. Moreover, the positive correlation between BMI and SII and the specific mechanisms involved in endocrine therapy resistance need to be further explored. In addition, BMI, preoperative SII and TNM stage were found to be independent prognostic factors in patients with endocrine therapy resistant luminal breast cancer following modified radical mastectomy. Furthermore, this is the first study showing SII as an independent prognostic factor for endocrine therapy resistance in luminal breast cancer.

The results of the present study may be limited by a number of factors. First, the relatively small sample size in this study may have led to biased results. Secondly, only Chinese patients with luminal breast cancer in Hebei General Hospital were enrolled, which means that the results may not be transferable to the wider population. Thus, the prognostic significance of BMI and SII needs to be assessed in patients from other geographical areas. Finally, research that involves longer-term follow-up is needed, as the limited follow-up duration in the present study may have missed some later recurrences that typically occur in hormone receptor-positive breast cancers. In short, further randomized, prospective studies are needed.

Taken together, the present data confirm that BMI is an effective prognostic marker, and indicate that SII may be a novel, independent, and powerful prognostic factor for luminal breast cancer. The predictive significance of BMI and SII in patients with luminal breast cancers may help clinicians identify patients at high risk of recurrence and enable targeted rational adjuvant therapy after surgery.

In conclusion, preoperative BMI and SII levels provide additional prognostic information in patients with luminal breast cancer. High BMI (>23 kg/m^2) and SII (518×10^9/L) levels may be valuable predictors of high endocrine resistance rates. In addition, BMI, preoperative SII and TNM stage were found to be independent prognostic factors for endocrine therapy resistance in patients with luminal breast cancer.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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