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Adjuvant! Online is overoptimistic in predicting survival of Asian breast cancer patients

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Abstract ***Background:*** Adjuvant! Online is a free web-based tool which predicts 10-year breast cancer outcomes and the efficacy of adjuvant therapy in patients with breast cancer. As its prognostic performance has only been validated in high income Caucasian populations, we validated the model in a middle income Asian setting.

Methods: Within the University Malaya Hospital-Based Breast Cancer Registry, all 631 women who were surgically treated for invasive non-metastatic breast cancer between 1993 and 2000 were identified. The discriminative performance of Adjuvant! Online was tested using receiver operating characteristic (ROC) analysis. Calibration of the model was evaluated by comparing predicted 10-year overall survival with observed 10-year survival.

Findings: Adjuvant! Online was fairly capable in discriminating between good and poor survivors, as attested by the area under ROC curve of 0.73 (95% Confidence Interval: 0.69–0.77). Overall, Adjuvant! Online predicted 10 year survival (70.3%) was significantly higher than the observed 10 year survival (63.6%, difference of 6.7%; 95% CI: 3.0–10.4%). The model was especially overoptimistic in women under 40 years and in women of Malay ethnicity, where survival was overestimated by approximately 20% (95% CI: 9.8–29.8%) and 15% (95% CI: 5.3–24.5%) respectively.

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Interpretation: Even though Adjuvant! Online is capable of discriminating between good and poor survivors, it systematically overestimates survival. These findings suggest that the model requires adaptation prior to use in Asian settings.

1. Introduction

In contrast to the West, where breast cancer incidence rates have stabilised or even decreased,[1–3] breast cancer incidence[4] and mortality[5] have increased sharply in Asian countries. Despite this disturbing trend, surprisingly little research has addressed determinants of survival following breast cancer in Asia. Most prognostic factors for breast cancer have been established in affluent Western settings. The validity of these prognostic factors has hardly been evaluated in most other settings.

Adjuvant! Online for Breast Cancer is a free web-based prognostication tool which was developed based on the Surveillance, Epidemiology and End Results (SEER) database and treatment efficacy data from meta-analyses.[6] It estimates individual ten year survival probabilities, and risks of relapse in patients with breast cancer, based on their clinical characteristics and systemic treatment. In addition, Adjuvant! Online helps to predict the absolute benefit of adjuvant therapy in individual patients. Since its introduction in the early 2000s, Adjuvant! Online has gained worldwide recognition among clinicians as a tool to aid patient counselling and clinical decision making for women with early breast cancer.[7] The programme has been validated by several groups in Canada and Europe.[7–9] Two studies have shown that the model accurately predicts survival probabilities across most patient groups,[7,8] whereas a study conducted in the United Kingdom found that Adjuvant! Online systematically overestimated survival by about 5.5 percent.[9]

Little is known on the prognostic performance of Adjuvant! Online in non-Western, low or middle income settings. In multi-ethnic Asia, genetic backgrounds, socio-economic profiles, lifestyles and cultures are substantially different from those in the US and Europe, and each of these factors may play a distinct role in breast cancer prognosis and treatment. In fact, an urgent need to validate Adjuvant! Online in different regions had been highlighted.[10] Malaysia is a middle income country in South East Asia comprising 3 major ethnic groups i.e. Malays, Chinese and Indians.[11]

In the present study, we evaluated whether Adjuvant! Online is a valid prognostic tool in a cohort of Malaysian women with early breast cancer.

2. Methods

Data from the University Malaya Medical Center (UMMC) Breast Cancer Registry was used.[12] UMMC is an academic tertiary hospital situated in the relatively affluent part of Kuala Lumpur, Malaysia and caters to a predominantly middle class urban population. The UMMC Breast Cancer Registry is a prospective hospital-based database of 3795 consecutive women who were newly diagnosed with breast cancer between 1993 and 2008. This registry has been approved by the institution's ethical review committee and encompasses data on patient's demography (including age and ethnicity), tumour characteristics (including pathological data on tumour size, number of involved lymph nodes, tumour grade based on the Modified Bloom and Richardson classification and oestrogen receptor status [determined via immunohistochemical staining and positive when >10% tumour cells stained positive]). Treatment data include type of treatment (surgery, chemotherapy, radiotherapy and hormone therapy), type of surgery (mastectomy, breast conserving surgery), chemotherapy regimen and type of hormone therapy.

Between 1993 and 2000, metastatic work up was performed by means of chest X-ray and liver function test in patients with clinical stage I and II disease, whereas patients with clinical stage III breast cancer underwent computed tomography of the abdomen and pelvis, and a bone scan. During the above period, the treatment protocol in UMMC for invasive non-metastatic breast cancer was mastectomy and axillary clearance for larger tumours, and breast conservation surgery followed by radiotherapy for localised small tumours. Between 1993 and 1996, six cycles of intravenous cyclophosphamide: 500 mg/m^2, methotrexate: 50 mg/m^2 and 5-fluorouracil: 500 mg/m^2 (CMF) three-weekly was the routine chemotherapy regimen for all patients. Since 1997, six cycles of 5-fluorouracil: 500 mg/m^2, epirubicin: 75 mg/m^2 and cyclophosphamide: 500 mg/m^2 (FEC-75) three-weekly was widely used. Other less commonly used regimes include four cycles of intravenous adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2 with paclitaxel 175 mg/m^2 three-weekly (AC-Paclitaxel), and 6 cycles of intravenous mitomycin, methotrexate and mitoxantrone (given in a clinical trial). Tamoxifen was prescribed routinely for women with hormone-receptor positive breast cancer and postmenopausal women with unknown hormone receptor status.

For the present study, all 824 women who were newly diagnosed with invasive non-metastatic breast cancer between 1993 and 2000 (allowing at least 10 years of follow-up) were identified. Patients were included if they had undergone standard surgical treatment (i.e. mastectomy or breast conserving surgery followed by radiotherapy, $n = 725$). Women treated with neoadjuvant

chemotherapy were excluded ($n = 56$), as were patients with missing information on tumour size and/or axillary lymph node status ($n = 38$). The final study population consisted of 631 women.

Data on vital status and death were obtained from the hospitals' medical records, and by means of active follow-up through the patients' next-of-kin. In addition, patients' vital statuses were verified through direct linkage with the National Registration Department in Malaysia which has the mortality records of all Malaysians. In the current study, follow-up time was calculated for all patients, starting at the date of diagnosis with breast cancer until death (all causes), date of last contact (for those who emigrated or loss to follow-up) or Nov 2010 (linkage with national mortality registry). In this hospital based cancer registry, data on local or systemic recurrences were not routinely available. Information on co-morbidity was also incomplete.

For each patient, data on age (continuous), tumour size (0.1–1.0 cm, 1.1–2.0 cm, 2.1–3.0 cm, 3.1–5.0 cm, >5.0 cm), number of involved lymph-nodes (0, 1–3, 4–9, >9 nodes), oestrogen-receptor status (positive, negative, undefined) and tumour grade (grade 1, grade 2, grade 3, undefined) were manually entered into the Adjuvant! Online (Version 8·0) programme. Type of adjuvant chemotherapy was categorised as first generation (CMF regime), or second generation (FEC-75, AC-Paclitaxel, as well as mitomycin, methotrexate and mitoxantrone). Third generation regimen was not administered in our setting during the study period. Hormone treatment was categorised as tamoxifen, aromatase inhibitors, tamoxifen for 2–3 years followed by aromatase inhibitor for 2–3 years, ovarian ablation or ovarian ablation plus tamoxifen (or other hormones). Comorbidity was set at 'average for age' for all patients. For every entry, Adjuvant! Online predicted ten-year overall survival for four different scenarios i.e. survival without any adjuvant treatment, survival with adjuvant chemotherapy only, survival with adjuvant hormone therapy only and survival with both chemotherapy and hormone therapy. The survival probability corresponding to the actual treatment received by the patient was recorded. An accuracy check, performed by recalculating Adjuvant! Online predicted survival probabilities in a random sample of 100 patients showed minor deviations in four patients resulting from wrong data entry.

3. Statistical analysis

Kaplan-Meier analysis was used to estimate the observed ten year overall survival in the entire study population and within subgroups. The mean predicted ten year overall survival was calculated by averaging the individual predicted survival probabilities derived from Adjuvant! Online. To assess the calibration of the Adjuvant! Online model, the observed and predicted ten year overall survivals were compared using a one-sample t-test for proportions.[7,8] This test was based on the assumption that the Adjuvant! Online predicted survival was the true population value and thus fixed.[7] Observed 10 years survival probabilities were subsequently plotted against the means of deciles of Adjuvant! Online predicted survival.

As Adjuvant! Online provides an estimate of survival at a single time point i.e. 10-years, we used the receiver operating characteristic (ROC) analysis. The Area under the ROC Curve (AUC) gives an indication of the discriminatory performance of the model, and can be interpreted as the proportion of patients who are correctly predicted to be alive or dead at 10 years. An AUC of 0.5 indicates no discriminative performance while an AUC of 1.0 indicates perfect discrimination. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA).

4. Role of funding source

The study sponsor did not play any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report and in the decision to submit the paper for publication.

5. Results

In this cohort of 631 Asian women with early breast cancer, the median age at diagnosis was 49 years. The majority of patients were Chinese (66.9%), followed by Malays (16.8%), Indians (15.2%) and other races (1.1%). The median tumour size at presentation was 3·0 cm and approximately half of the patients had lymph node involvement. Oestrogen receptor status and tumour grade were unknown in approximately 25% of the patients. Four-hundred-fifty-eight (72.6%) patients were given hormonal treatment, two (0.4%) of which received aromatase inhibitors while the rest received tamoxifen. Among 396 (62.8%) patients who were given chemotherapy, 146 (36.9%) had received CMF, 218 (55.1%) received FEC-75, 24(6.0%) received AC-paclitaxel and 4 (1.0%) received mitomycin, methotrexate and mitoxantrone. Chemotherapy was unspecified in four (1.0%) patients (Table 1).

Of the 631 patients, 225 women died within 10 years of follow up (Fig. 1). Overall, Adjuvant! Online predicted 10-years overall survival was 70.3%, whereas the actual observed 10-years overall survival was 63.6%, indicating an overestimation of survival of 6.7% (95% CI: 3.0% to 10.4%). The model was especially overoptimistic in patients aged less than 40 years at diagnosis ($n = 96$), and in women of Malay ethnicity ($n = 106$), where survival was over-estimated by approximately 20% (95% CI: 9.8–29.8%) and 15% (95% CI: 5.3–24.5%) respectively. In patients with tumours smaller than 2 cm, lymph node negative disease, oestrogen receptor positive tumours and low grade tumours, observed and predicted

Table 1
Calibration of Adjuvant! Online in 631 South East Asian Women with Breast Cancer.

	Number (%)	Overall Survival (%)			
		Adjuvant! Predicted	Observed (SE)	Predicted–Observed (95% CI)	*P* value
All patients	631 (100)	70.3	63.6 (1.9)	6.7 (3.0 to 10.4)	<0.001
Year of diagnosis					
1990–1995	225 (35.6)	67.9	59.1 (3.3)	8.8 (2.3 to 15.3)	0.008
1996–2000	406 (64.3)	71.7	66.2 (2.4)	5.5 (0.8 to 10.2)	0.022
Age (years)					
<40	96 (15.1)	75.6	55.8 (5.1)	19.8 (9.8 to 29.8)	<0.001
40–64.9	469 (74.3)	71.9	67.3 (2.2)	4.6 (3.7 to 8.9)	0.037
>=65	67 (10.6)	51.8	49.0 (6.2)	2.8 (–9.4 to 15.0)	0.653
Ethnicity[a]					
Chinese	422 (67.6)	71.6	67.7 (2.3)	3.9 (–0.6 to 8.4)	0.091
Malay	106 (17.0)	71.2	56.3 (4.9)	14.9 (5.3 to 24.5)	0.003
Indians	96 (15.4)	64.9	55.5 (5.1)	9.4 (–0.6 to 19.4)	0.068
Tumour size					
<2	123 (19.5)	81.5	80.0 (3.7)	1.5 (–5.8 to 8.8)	0.686
2–5	385 (61.0)	71.4	64.2 (2.5)	7.2 (2.3 to 12.1)	0.004
>5	123 (19.5)	55.8	45.9 (4.5)	9.9 (1.1 to 18.7)	0.030
Lymph node involvement					
No	329 (52.1)	79.8	77.8 (2.3)	2.0 (–2.5 to 6.5)	0.385
Yes	302 (47.9)	60.0	48.5 (2.9)	11.5 (5.8 to 17.2)	<0.001
Oestrogen receptor status					
Negative	212 (33.6)	61.0	51.2 (3.5)	9.8 (2.9 to 16.7)	0.006
Positive	262 (41.5)	78.0	72.6 (2.8)	5.4 (–0.1 to 10.9)	0.055
Unknown	157 (24.9)	70.2	65.3 (3.8)	4.9 (–2.5 to 12.3)	0.199
Grade					
Low	73 (11.6)	82.6	85.9 (4.1)	–3.3 (–11.3 to 4.7)	0.424
Moderate	243 (38.5)	72.5	63.3 (3.1)	9.2 (3.1 to 15.3)	0.003
High	158 (25.0)	64.2	53.8 (4.0)	10.4 (2.6 to 18.2)	0.010
Unknown	157 (24.9)	67.5	63.7 (3.9)	3.8 (–3.8 to 11.4)	0.331
Chemotherapy					
Yes	396 (62.8)	69.7	59.6 (2.5)	10.1 (5.2 to 15.0)	<0.001
No	235 (37.2)	71.4	70.6 (3.0)	0.8 (-5.1 to 6.7)	0.790
Hormone therapy					
Yes	458 (72.6)	72.1	66.3 (2.2)	5.8 (1.5 to 10.1)	0.009
No	173 (27.4)	65.7	56.5 (3.8)	9.2 (1.8 to 16.6)	0.017

[a] Excluding patients from other races ($n = 7$).

survival probabilities were not significantly different. Fig. 2 shows the observed 10-years survival probabilities against the predicted 10-years survival from Adjuvant! Online, and shows that the model systematically overestimated survival for the entire range of predicted probabilities. ROC analysis of the whole cohort showed that the model discriminated fairly between good and poor survivors with an AUC of 0.73 (95% CI: 0.69–0.77), and also within the subgroups (Table 2).

In this study, 23 patients did not complete chemotherapy (received less than 4 cycles of CMF/FEC). When these patients were excluded, Adjuvant! Online still overestimated survival, both in the overall cohort (by 5.8%; 95% CI: 2.1–9.5%) and in the subgroup of patients subjected to chemotherapy (by 9.5%; 95% CI: 4.6–14.5%). Since previous studies have excluded patients with tumour size of more than 5 cm[6–8], we repeated the analysis excluding 123 patients with tumours larger than 5 cm. The over-optimism of Adjuvant! Online still persisted with a difference between the predicted and observed 10-years overall survival of 5.9% (95% CI: 1.7–10.0%).

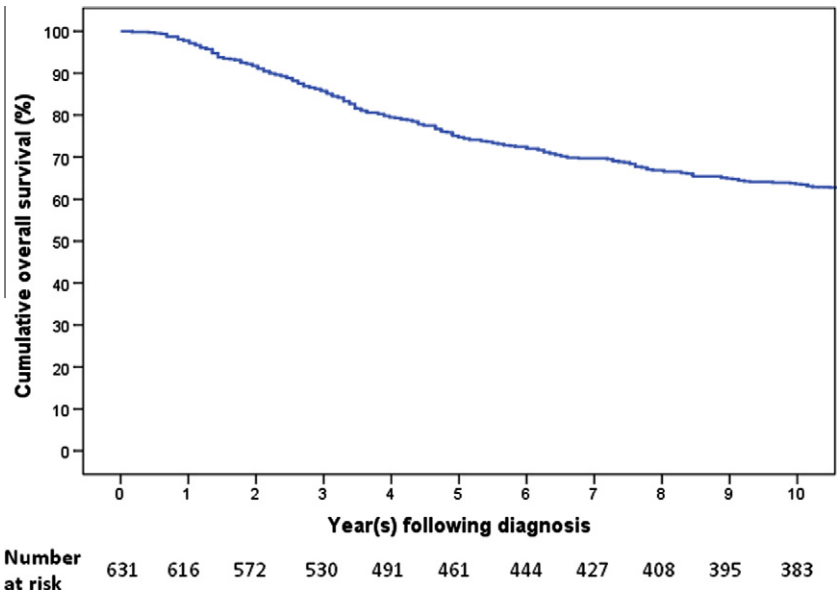

Fig. 1. Overall survival following breast cancer in 631 South-East Asian Women.

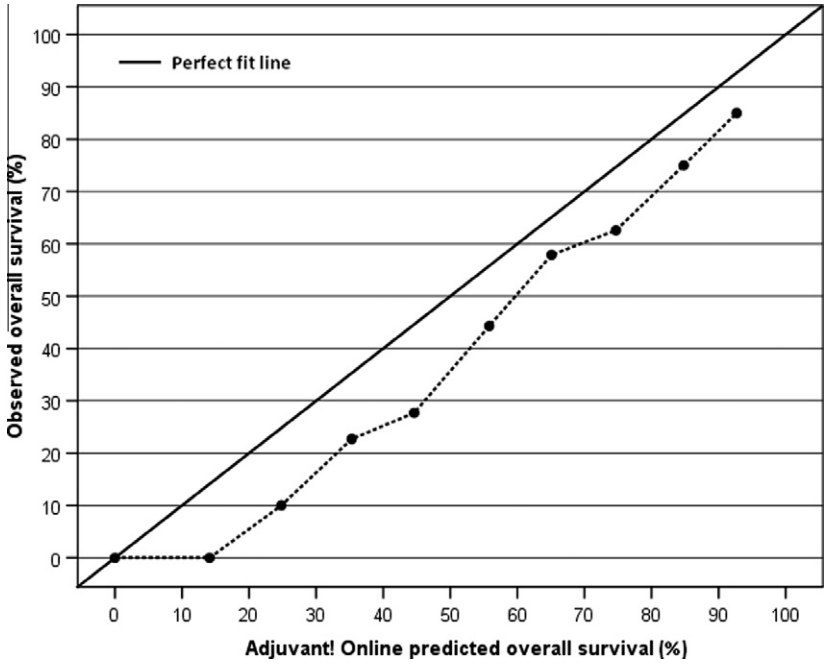

Fig. 2. Observed overall survival against Adjuvant! Online predicted overall survival in 631 South East Asian Women.

As tumour grade and ER status was not known in approximately 25% of the study population, a sensitivity analysis was conducted within 394 women whose ER status and tumour grade were known. It was found that Adjuvant! overestimated survival by 8.1% (95% CI: 3.2–13.0%) in this subgroup.

6. Discussion

In this cohort of Asian patients, Adjuvant! Online was capable of discriminating between good and poor survivors, but it systematically overestimated survival. This overestimation was present in most subgroups and especially obvious in the young (aged less than 40 years), as well as in patients of Malay ethnicity.

Adjuvant! Online is used in oncology practices not only in the United States[13,14] and Europe[7,15] but also in Asia.[16] A study conducted in Hong Kong which assessed the utility of Adjuvant! Online among a group of experienced cancer specialists revealed that regular use of such software for predicting breast cancer outcomes and treatment benefits resulted in a significant impact on their clinical decisions.[16] To our knowledge, Adjuvant! Online for breast cancer has never been validated in non-Western

settings, and this study provides some useful insight into its clinical utility in such settings. We do acknowledge that this study suffers from several limitations. Firstly, the study sample is rather small, resulting in rather unstable estimates in some subgroups. Furthermore, information on breast cancer recurrences was incomplete, making it impossible to study recurrence free survival. While tumour grade and ER status were unknown in approximately 25% of our patients, this is unlikely to have influenced our results as a sensitivity analysis in women whose ER status and tumour grade were known, revealed that the main results remained essentially unchanged.

Discrepancies in the observed and Adjuvant! Online predicted survival in the Asian setting may be partly explained by differences in life expectancy between our study population and population in the United States where the model was developed.[17] However, this is unlikely to completely explain the observed discrepancies. Other possible explanations include differences in tumour biology, effects of anti-cancer therapy, treatment compliance and differences in lifestyle after cancer.

There is increasing evidence that tumour biology of Asian patients is different from that of Caucasian women, as certain prognostic factors, such as HER2 expression, are more prevalent in Asian populations.[18] In addition, the case-mix of the Asian population is different compared to the Western population.[12,19] In Asia, a higher proportion of young women are diagnosed with

Table 2
Discriminatory Performance of Adjuvant! Online in 631 South East Asian Women.

	Number	Area under curve	95% Confidence interval for Area under curve[a]	
			Lower limit	Upper limit
All patients	631	0.73	0.69	0.77
Age				
<40 years	96	0.78	0.69	0.88
40–64 years	469	0.70	0.66	0.75
>=65 years	67	0.82	0.72	0.92
Ethnicity				
Chinese	422	0.74	0.69	0.79
Malay	106	0.73	0.63	0.82
Indians	96	0.65	0.54	0.76
Tumour size				
<2 cm	123	0.65	0.54	0.76
2–5 cm	385	0.71	0.65	0.76
>=5 cm	123	0.75	0.66	0.83
Lymph node involvement				
Negative	329	0.65	0.59	0.72
Positive	302	0.71	0.65	0.76
Oestrogen receptor status				
Negative	212	0.67	0.60	0.74
Positive	262	0.72	0.65	0.79
Unknown	157	0.77	0.69	0.84
Grade				
Low	73	0.74	0.60	0.89
Moderate	243	0.74	0.68	0.81
High	158	0.63	0.54	0.71
Unknown	157	0.76	0.68	0.84
Chemotherapy				
Yes	396	0.69	0.64	0.74
No	235	0.79	0.72	0.85
Hormone therapy				
Yes	458	0.75	0.70	0.79
No	173	0.66	0.58	0.74

[a] 95% CI for area under curve that does not include 0.5 is considered as statistically significant.

breast cancer compared to their Caucasian counterparts[19–21], and they are also more likely to present with unfavourable tumour characteristics such as lymph node involvement, large tumour size, and ER negative disease.[12,22] In the current study, Adjuvant! Online performed well in elderly women and in women with favourable tumour characteristics (small size, lymph node negative, oestrogen receptor positive and low grade). These profiles represent the majority of breast cancer patients in Caucasian settings[22] and our results suggest that Adjuvant! Online may be over fitted to Western populations.

Differences in response to systemic anticancer therapy may also explain some of the discrepancy between observed and predicted survival. The metabolism of anticancer drugs for instance may differ between individuals due to presence of underlying genetic variations.[23] In our cohort, Adjuvant! Online was able to predict survival accurately in the group not receiving chemotherapy, whereas it overestimated survival in patients subjected to chemotherapy by approximately ten percent. A recent review looking at differences in toxicity and clinical outcome following treatment with anticancer drugs highlighted that there may be ethnic differences in tolerability and response to cytotoxic chemotherapy in breast cancer suggesting that anti-cancer drugs may be more effective in certain ethnic groups.[24] Given the presence of underlying pharmacogenomic differences in drug metabolism and response, it is also plausible that a higher proportion of breast cancer patients in our settings had been subjected to reductions in chemotherapy relative dose intensity due to toxicity,[25] hence resulting in poorer survival.

Furthermore, non-adherence with adjuvant therapy may be responsible for some of the differences in predicted and observed survival. Non-adherence in Asian breast cancer patients can be attributed to financial barriers (in the absence of a health insurance schemes), and socio-cultural factors such as lack of decision making power, belief in alternative therapy and fatalistic views.[26,27] Cancer fatalism, i.e. the belief that death is inevitable when one has cancer, has been hypothesised to affect cancer prevention behaviour and treatment adherence.[28] Exclusion of patients who did not complete their chemotherapy treatment did not attenuate our findings. However, data on hormone therapy adherence was not available.

Lifestyle factors, such as diet and body weight, are increasingly being recognised as important prognostic factors of breast cancer.[29] Owing to cultural and religious differences, lifestyle profiles of Asian women differ substantially within South East Asia. For instance, obesity which is an unfavourable prognostic factor in breast cancer,[30] is more common in Malay and Indian women, whereas the Chinese have the lowest body mass index.[31] This factor could explain some of the overestimation in Adjuvant! Online predicted survival in Malay women,[32] in whom survival was overestimated by almost 15%.

In conclusion, this is the first study in a middle income, non-Caucasian setting, showing that Adjuvant! Online is capable of discriminating between good and poor survivors after breast cancer in Asian women. However, as the model is overoptimistic, we propose to adapt Adjuvant! Online using a large multicentre cohort of Asian breast cancer patients to improve its utility in Asian settings.

Contributors

NB, MH, YVG and HMV designed the study. NB, CHY, NAT, GFH and LML collected data. NB, NS and HMV analysed data. NB, CHY, MH, NAT, AMB YVG and HMV interpreted data. NB, CHY, MH, NS, NAT, GFH, LML, AMB, YVG and HMV wrote the paper.

Conflict of interest statement

All authors declare no potential conflict of interest.

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