PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of Nottingham Prognostic Index and Adjuvant Online prognostic tools in young women with breast cancer: Review of a single-institution experience
AUTHORS	Hearne, Benjamin; Teare, M; Butt, Mohammad; Donaldson, Leslie

VERSION 1 - REVIEW

REVIEWER	Dr. Zubair Ahmad Aga Khan University Hospital, Karachi, Pakistan
REVIEW RETURNED	11-Jul-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Rajnish Gupta Department of Medical Oncology Mid-Western Cancer Centre University Hospital Limerick Dooradoyle Limerick Ireland
REVIEW RETURNED	13-Jul-2014

GENERAL COMMENTS	1. 'Will I live?' in my experience is rarely asked. More often, patients are concerned as to whether they may die as a consequence of the recent diagnosis. 2. Pag4 line 18: Why Belfast rather than incidence rate of the UK or England? 3. Page 5 line 11: Interesting that the authors used death from any cause and not disease-specific (breast-cancer related) death - especially given that this is a prospective and not a retrospective study. 4. Page 6 line 43: In Strengths and Limitations, page 2 bullet point 4 under Strengths the authors quote a median FU of 91 months! 5. Page 6 line 44: Why mean and median here and only median is quoted elsewhere in text? 6. Page 7 line 50: Table 2. Is this seemingly low rate a reflection of the time period of the study, i.e. patients diagnosed between 1998 and 2007? 7. Page 8 line 32: road CI range, presumably due to low numbers

	(92 patients) in study. 8. Page 9 line 13: Again find it interesting that the authors quote Northern Ireland as opposed to UK as a whole. 9. Page 9 line 15: Data only collected at MDM - was it not validated against pathology reports, patient charts etc? Would not like to rely on MDM data only. 10. Page 9 line 52: typo - should read "caused" 11. Page 10 line 13: "single-institue" - "single institution" not a better term? 12. Page 10 line 15: This seems incorrect as published experience is that Adjuvant Online overestimates not underestimates survival - as indicated in Table 3. 13. Page 16 figure 3: Whilst the authors state that the overall 10y survival of the patients in this study demonstrate a survival rate similar to that predicted by NPI and slightly less than that predicted by AO, they omit to mention that their patients exhibit significantly worse survival from 2 to 7y than predicted by the clinical tools. Thus the observed correlation of the 10y survival rate with NPI could have more to do with the poorer expected survival (death from all causes and not disease specific) due to the median age of the patients that the NPI and AO are based on (i.e. death due to old age, other co-morbidities etc). The authors should perhaps add a comment in the text. The manuscript appears acceptable once the comments have been addressed.

REVIEWER	Peter Baade Cancer Council Queensland Australia
REVIEW RETURNED	07-Aug-2014

GENERAL COMMENTS	Given the purpose of this study is to determine how accurately the Nottingham Prognostic Index and Adjuvant Online predict actual survival, the small cohort size is a concern. Were power calculations conducted to ascertain what differences could be detected? This is particularly relevant when a null result (ie. no differences between the Indices and observed survival) is considered an ideal outcome. I'm not sure how this study is able to discuss the accuracy of the two Indices in relation to 10-year survival when the median follow up among the study cohort was 91 months (~7.5 years). Based on the details in Figure 2, a large proportion of cases with more than 50 months of follow up were censored. The K-M curve also reflects this, with the horizontal lines being prominent in the curves after 50 months. The shape of the KM survival curve is has very large implications for the interpretation of the results. Figure 3 shows a very large

	discrepancy in survival curves up to 50 months. It could reasonably be suggested that the only reason the 10-year survival estimates are similar between the observed and predicted values is the large amount of censoring after 50 months of follow up. Re Table 1, were those groupings used to predict an individual woman's ten year survival, and then those predicted survival values averaged over the cohort? If so, this would seem to lose a lot of information. Would it be better to calculate the average NPI score over the whole cohort, then the final survival estimate would be derived from Table 1? Regardless, more information is needed as to the exact method used. Re Table 3, it would be expected that the predicted 10 year survival estimates have uncertainty associated with them, so 95% confidence intervals should be calculated and presented. The statement that this study assessed mortality during a 10 year follow up period (Discussion, 2nd paragraph) needs revision giving more than 50% of the cases were followed for less than 8 years. The paper could be suitable for publication if the authors focused on 5 year survival (better reflecting the characteristics of the study cohort), however if they did this then, based on Figure 3, the findings and conclusions would be substantially different.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name Dr. Zubair Ahmad
Institution and Country Aga Khan University Hospital, Karachi, Pakistan
Please state any competing interests or state 'None declared': None declared

No comments. Publication recommended

Reviewer 2

Reviewer Name Rajnish Gupta
Institution and Country Department of Medical Oncology
Mid-Western Cancer Centre
University Hospital Limerick
Dooradoyle
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Ireland
Please state any competing interests or state 'None declared': 'None declared'

Comments:

Comment: 'Will I live?' in my experience is rarely asked. More often, patients are concerned as to whether they may die as a consequence of the recent diagnosis.

Response: We agree with this comment and have changed the text to: 'what is my prognosis? This is the question that many patients directly or indirectly ask when given the diagnosis of breast cancer.' Our cohort is a young group often with a young family so we think prognosis is of upmost relevance to

this patient group.

Comment: Pag4 line 18: Why Belfast rather than incidence rate of the UK or England?

Response: We have updated the text to include the incidence rate in the UK with reference to 'Cancer Research UK' statistics. The text now reads as follows: Breast cancer is the most common cancer in women aged under 40. In the UK around 1,300 women are diagnosed with breast cancer between the ages of 35-39 each year.[1] The incidence of the disease in women <40 years of age varies from 4% in the UK, 6.2% in Italy, and 7% in the USA.

Comment: Page 5 line 11: Interesting that the authors used death from any cause and not disease-specific (breast-cancer related) death - especially given that this is a prospective and not a retrospective study.

Response: The reason that we used survival (all cause) as opposed to disease-specific survival is because it is a more applicable to a population and more useful in practice. Even at post mortem it is not easy to say why a patient actually died. Patients can live for years with image identified metastatic disease. Even if a post mortem was carried out, while it may confirm there is metastatic disease it cannot say whether the patient died of the cancer rather than with the disease. An example of the latter is a patient with breast cancer dying from pneumonia following surgery for a fractured femur with bone metastasis or from a road traffic accident.

Death from any cause was used because the Nottingham Prognostic Index 10-year survival figures quoted in table 1 relate to overall survival as opposed to 10-year breast cancer specific survival. The Adjuvant Online program gives both survival (all causes) and percentage risk of dying from breast cancer and from other causes.

Comment: Page 6 line 43: In Strengths and Limitations, page 2 bullet point 4 under Strengths the authors quote a median FU of 91 months!

Response: The survival data for the cohort of women was updated in September 2014 using the continuously updated hospital electronic records system. This has meant the follow-up figures have been changed appropriately. The paragraph on page 6 has been updated as follows: The average age of the 92 women involved in this study was 36.27 years. The median follow-up time was 113.5 months (range 11-120 months) and at the end of follow-up period 71 (77.2%) patients were alive.

Comments: Page 6 line 44: Why mean and median here and only median is quoted elsewhere in text?

Response: We agree that the mean is not quoted elsewhere in the text, therefore to be consistent we have updated the paragraph to only include the median follow-up times. It reads as follows: 'The median follow-up time for those patients that died was 40.0 months and for those that were alive at the end of follow-up it was 120.0 months.'

Comments: Page 7 line 50: Table 2. Is this seemingly low rate a reflection of the time period of the study, i.e. patients diagnosed between 1998 and 2007?

Response: The authors agree with the reviewers comments with regard to the low number of patients in the cohort who received neoadjuvant chemotherapy. We have added the following statement to the text: Neoadjuvant chemotherapy is now widely used and recognized as a treatment modality for locally invasive breast cancer especially in young patients. The Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) reports between 2000-2008 15.6% of young women

had neoadjuvant chemotherapy compared to 6.5% in the current study which demonstrates the increased acceptance of this form of treatment over the past decade.[2]

Comment: Page 8 line 32: road CI range, presumably due to low numbers (92 patients) in study.

Response: The confidence interval for the overall observed 10-year survival for the cohort of 92 women is 68.6-85.8. This confidence interval is comparable to similar studies investigating the 10-year overall survival of young women with breast cancer. In a similar study by Kee Seng Chia et al, a population-based cancer registry was used to analyse the observed 10-year survival rate for women <35 years of age. Their cohort consisted of 176 women with a 10-year survival rate of 62% with a confidence interval of 55-70.[3]

Comment: Page 9 line 13: Again find it interesting that the authors quote Northern Ireland as opposed to UK as a whole.

Response: We agree with the reviewer's comments and have updated the text to include reference to overall survival figures from the UK. We have also updated table 4 to include data from the Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) study, which has recently published results on the tumour characteristics and prognosis of its large cohort of young women between the ages of 18 to 40. The study sample consists of 2956 women and analysis has shown that our paper reports similar tumour characteristics and 5-year survival rates.[2]

Comment: Page 9 line 15: Data only collected at MDM - was it not validated against pathology reports, patient charts etc? Would not like to rely on MDM data only.

Response: In the MDT meetings the breast histology was reviewed by a breast histopathologist. In addition the patient charts were reviewed. If the patient had developed metastasis the imaging and pathology were discussed again from around 2009. Data from the MDT meetings was very consistent as a similar team of surgeons, histopathologists and oncologists reviewed all the patient data before making decisions on treatment and prognosis.

Comment: Page 9 line 52: typo - should read "caused"

Response: The text has been changed.

Comment: Page 10 line 13: "single-institue" -
"single institution" not a better term?

Response: We agree and the text has been updated.

Comment: Page 10 line 15: This seems incorrect as published experience is that Adjuvant Online overestimates not underestimates survival - as indicated in Table 3.

Response: The use of the Adjuvant Online outside the countries that it has been validated is still heavily discussed in the literature. The trend in the majority of studies is that Adjuvant! appears to overestimate the prognosis of women with invasive breast cancer.[4,5] However a recent study based in Ireland has demonstrated that the Adjuvant actually underestimates the 10-year survival in that population.[6] This highlights the need for more extensive testing of the adjuvant system in the populations it is being used.

We have updated the text to read: 'The accuracy of the Adjuvant! appears to be population specific as a recent study in Ireland demonstrated that the Adjuvant! actually underestimated the overall 10-year

survival of a cohort of 77 women.[6]'

Comment: Page 16 figure 3: Whilst the authors state that the overall 10y survival of the patients in this study demonstrate a survival rate similar to that predicted by NPI and slightly less than that predicted by AO, they omit to mention that their patients exhibit significantly worse survival from 2 to 7y than predicted by the clinical tools.

Response: We agree with the reviewer's comments that that the actual overall survival between 2 to 7 years is much lower compared to both the predicted NPI and Adjuvant! survival rate. This highlights the fact that both prognostic tools have only been validated for prediction for 10-year survival neither of them can be used to advice on 5-year survival rates. The Adjuvant only gives a 10-year survival figure and there have been no studies investigating the corresponding 5-year survival of NPI values. Figure 3 is a graphical representation of the predicted NPI and Adjuvant 10-year survival not the 5-year survival. The graph was created by assuming a constant hazard rate throughout the 10-year follow-up period. However, previous studies have shown that the hazard rate is significantly higher in the first 5-years after diagnosis especially in oestrogen-receptor negative breast cancer.[2] A larger sample size would also likely improve the correlation between the predicted and actual survival curves.

Comment: Thus the observed correlation of the 10y survival rate with NPI could have more to do with the poorer expected survival (death from all causes and not disease specific) due to the median age of the patients that the NPI and AO are based on (i.e. death due to old age, other co-morbidities etc.)

Response: The NPI was derived from The Nottingham Tenovus Primary Breast Cancer Study, which was set up in 1973 to investigate prognostic factors. Patients less than 71 years with primary operable breast cancer (clinically less than 5 cm) were included.[7] This cohort of women would have had a higher median age compared to the current study sample, it is likely that in the older cohort of patients the risk of dying from other causes, not breast cancer would have been higher. However, young age is associated with a higher incidence breast cancer with adverse biological features such as higher grade and lymph node involvement. The NPI makes no adjustment for the age of the patient. The Adjuvant has a correction factor for comorbidity status and applies a 1.5 fold increase in risk if the patient is less than 35 years old. All the patients in the current cohort were fit with no comorbidities. It is interesting that the NPI retains its accuracy despite being developed based on a group of women less than 71 years old with varying comorbidities. We agree with the reviewer's comments that the NPI may be more accurately predicting disease-specific survival in a young age group compared to overall survival in an older age group.

The manuscript appears acceptable once the comments have been addressed.

Reviewer 3

Reviewer Name Peter Baade
Institution and Country Cancer Council Queensland
Australia
Please state any competing interests or state 'None declared': None Declared

Comment: Given the purpose of this study is to determine how accurately the Nottingham Prognostic Index and Adjuvant Online predict actual survival, the small cohort size is a concern. Were power calculations conducted to ascertain what differences could be detected? This is particularly relevant when a null result (ie. no differences between the Indices and observed survival) is considered an ideal outcome.

Response: One of the reasons that there is a lack of information on young breast cancer and whether age is an independent maker of a poor prognosis is because there is a low incidence of the disease in people <40 years of age. Only 4% of breast cancer occurs in this age group. No power calculations were performed for this study, however as illustrated in table 4 the patient numbers in the current study are similar to the majority of previous studies investigating young breast cancer. It is encouraging that the current paper recorded similar tumour characteristics and survival rates to larger studies such as Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH) study. This means the results can be viewed with a higher degree of certainty despite no difference being demonstrated between the NPI and Adjuvant!

Comment: I'm not sure how this study is able to discuss the accuracy of the two Indices in relation to 10-year survival when the median follow up among the study cohort was 91 months (~7.5 years). Based on the details in Figure 2, a large proportion of cases with more than 50 months of follow up were censored. The K-M curve also reflects this, with the horizontal lines being prominent in the curves after 50 months.

Response: We agree with the reviewer's comments and have therefore completely updated the survival data for the cohort of women. The continuously updated hospital electronic record system was used to document the up to date survival information for the 92 women in September 2014. This increased the median follow-up time to 113.5 months (~9.5 years). This has meant that the majority of patients completed 10-year follow-up. Only 30 patients (32.6%) had censored data. The K-M curve has been updated to reflect these changes and therefore the results can be analysed with a higher degree of confidence.

Comment: The shape of the KM survival curve is has very large implications for the interpretation of the results. Figure 3 shows a very large discrepancy in survival curves up to 50 months. It could reasonably be suggested that the only reason the 10-year survival estimates are similar between the observed and predicted values is the large amount of censoring after 50 months of follow up.

Response: We have updated the survival data for the 92 women in our cohort which has reduced the amount of censoring and has improved the shape of the Kaplan-Meier curve in figure 2 and proportional survival curve in figure 3. This means that our results are more likely to indicate the true predictive quality of the NPI and Adjuvant when compared to the actual survival data.

Comment: Re Table 1, were those groupings used to predict an individual woman's ten year survival, and then those predicted survival values averaged over the cohort? If so, this would seem to lose a lot of information. Would it be better to calculate the average NPI score over the whole cohort, then the final survival estimate would be derived from Table 1? Regardless, more information is needed as to the exact method used.

Response: The numbers presented in Table 1 are those reported by Blamey et al 2007. For all NPI scores within each group only a single summary survival is reported. To calculate the overall survival of 77.3 for the NPI predicted survival in Table 3, we used the groupings in Table 1 to predict the 10 year survival for each woman, then those predicted survival times were averaged to get the value of 77.3. We felt that this method captured more detailed information than if we averaged the NPI scores and then looked up the corresponding survival for that group.

We have added detail to the methods section of the paper and have updated the text as follows: The NPI scores correspond to five groups ranging from a poor to excellent prognostic group. The numbers presented in Table 1 are those reported by Blamey et al. For all NPI scores within each group only a single summary 10-year survival figure is reported which has been validated by previous studies.[8]

Adjuvant! data is continuous, on a scale from zero to 100%. The mean of the Adjuvant! and NPI scores were then compared. The groupings in Table 1 were used to predict the 10-year survival for each women in the cohort and then those predicted survival times were averaged to calculate the mean NPI score.

Comment: Re Table 3, it would be expected that the predicted 10 year survival estimates have uncertainty associated with them, so 95% confidence intervals should be calculated and presented.

Response: We agree with the reviewer's comments and have updated table 3 with the 95% confidence intervals.

Comment: The statement that this study assessed mortality during a 10 year follow up period (Discussion, 2nd paragraph) needs revision giving more than 50% of the cases were followed for less than 8 years.

Response: The survival data for the study sample was updated in September 2014 which means that the majority of patients, 70% of them had completed survival data for 10-years of follow-up. The median follow-up time has increased to 9.5 years and therefore strengthens the analysis of the data and the conclusions made.

Comment: The paper could be suitable for publication if the authors focused on 5 year survival (better reflecting the characteristics of the study cohort), however if they did this then, based on Figure 3, the findings and conclusions would be substantially different.

Response: With the addition of 3 more years of survival data to the paper and the majority of patients being followed up to 10 years the papers analysis and conclusions have been validated and adds valuable information to the literature base on young breast cancer. Over the last decade limited research has been performed on this group and there are still many unanswered questions such as, is age an independent marker of poor prognosis and is young breast cancer a more biologically adverse disease? With the new survival data the study is valid as a 10-year follow-up study and it is not necessary to change this to focus on 5-year survival. In addition to this both the NPI and Adjuvant! do not report 5-year survival rates as they were designed to inform patients of their prognosis over a 10-year period from initial diagnosis.

References

1 Cancer Research UK. Breast cancer incidence statistics. Cancer Research UK. 2014.http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/uk-breast-cancer-incidence-statistics (accessed 30 Oct2014).

2 Copson E, Eccles B, Maishman T, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study. J Natl Cancer Inst 2013;105:978–88. doi:10.1093/jnci/djt134

3 Chia KS, Du WB, Sankaranarayanan R, et al. Do younger female breast cancer patients have a poorer prognosis? Results from a population-based survival analysis. Int J Cancer 2004;108:761–5. doi:10.1002/ijc.11632

4 Mook S, Schmidt MK, Rutgers EJ, et al. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study. Lancet Oncol 2009;10:1070–6. doi:10.1016/S1470-2045(09)70254-2

5 Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23:2716–25. doi:10.1200/JCO.2005.06.178

6 Quintyne KI, Woulfe B, Coffey JC, et al. Correlation Between Nottingham Prognostic Index and Adjuvant! Online Prognostic Tools in Patients With Early-Stage Breast Cancer in Mid-Western Ireland. Clinical Breast Cancer 2013;13:233–8. doi:10.1016/j.clbc.2013.02.011

7 Haybittle JL, Blamey RW, Elston CW, et al. A prognostic index in primary breast cancer. Br J Cancer 1982;45:361–6.

8 Blamey RW, Ellis IO, Pinder SE, et al. Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999. Eur J Cancer 2007;43:1548–55. doi:10.1016/j.ejca.2007.01.016

VERSION 2 – REVIEW

REVIEWER	Rajnish Gupta Mid-Western Cancer Centre University Hospital Limerick Limerick Ireland
REVIEW RETURNED	14-Nov-2014

GENERAL COMMENTS	Changes made and manuscript seems acceptable in my opinion.

REVIEWER	Peter Baade Cancer Council Queensland Australia
REVIEW RETURNED	25-Nov-2014

GENERAL COMMENTS	Under “Limitations”, the authors include a dot point saying “Relatively small sample size leading to low power, which meant a statistical difference between the NPI and Adjuvant was not demonstrated.” This seems to contradict the finding that the lack of statistical difference between the two Indices demonstrates the statistical robustness of the Indices. I acknowledge, as the authors note in their responses, the difficulty of getting large numbers of cases of breast cancer among this young age group. However, it would be very informative to know how different the survival measures would need to be for the difference to be statistically significant (as in Table 3). As per the STROBE statement, it would strengthen the paper considerably to include a comment about this limitation and its possible impact on the overall interpretation in the discussion section.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Reviewer Name: Rajnish Gupta
Institution and Country: Mid-Western Cancer Centre, University Hospital Limerick, Limerick, Ireland
Please state any competing interests or state 'None declared': 'None declared"

Comment: Changes made and manuscript seems acceptable in my opinion.

Reviewer 3

Reviewer Name: Peter Baade
Institution and Country: Cancer Council Queensland, Australia
Please state any competing interests or state 'None declared': None declared

Comment: Under "Limitations", the authors include a dot point saying "Relatively small sample size leading to low power, which meant a statistical difference between the NPI and Adjuvant was not demonstrated." This seems to contradict the finding that the lack of statistical difference between the two Indices demonstrates the statistical robustness of the Indices.

Response: We agree with the reviewers comment and have re-written the abstract conclusion removing the sentence stating that the prognostic tools have been shown to be 'statistically robust' when compared to the actual survival. The text has been updated as follows: 'The Nottingham Prognostic Index and Adjuvant! are widely used to predict survival in breast cancer patients. In this study no statistically significant difference was shown between the predicted prognosis and actual survival of a group of young breast cancer patients.'

Comment: I acknowledge, as the authors note in their responses, the difficulty of getting large numbers of cases of breast cancer among this young age group. However, it would be very informative to know how different the survival measures would need to be for the difference to be statistically significant (as in Table 3).

Response: The width of the 95% confidence interval for the overall survival figure with 92 patients was 17.2% as shown in table 3. We would need to study 273 patients (followed up for 10 years) if the true survival rate was 77.2% and we required the 95%CI to be of width 10%. Which would mean we could exclude the adjuvant predicted value of 82.1%. This has been further addressed in response to the next comment.

Comment: As per the STROBE statement, it would strengthen the paper considerably to include a comment about this limitation and its possible impact on the overall interpretation in the discussion section.

Response: We agree with the reviewer's comment and have added the following paragraph to the text: 'The main limitation of this study was the sample size was too small to demonstrate a statistically significant difference between the prognostic tools and the actual survival. If the Adjuvant! over prediction is a true result then a larger study will need to be performed to investigate this. A retrospective calculation using 77.2% as the true survival rate indicates that reducing the width of the 95% confidence interval to 10% would require a sample of 273 patients. This figure for the 95% confidence interval would exclude the adjuvant predicted value of 82.1%. The results emphasise the need for a national study to further scrutinise the accuracy of the Adjuvant! and NPI in young women with breast cancer.'

In the discussion section we have added a sentence on the overall interpretation of the results, the text has been updated as follows: ‘The current data should be interpreted as an establishment of information on this topic in a UK population.’