External validation of prediction models for breast cancer with different outcomes done with individual patient data from the Netherlands Cancer Registry

Author
Name: Lotte Knollema
Bachelor program: Health science
Educational institute: University of Twente

Supervisors
First: Prof. Dr. S. Siesling, University of Twente
Second: Dr. Ir. H. Koffijberg, University of Twente
External: T. Hueting, MSc, Evidencio

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L.M. Knollema

Abstract

Objectives

The aim of this study is to validate existing prediction models for breast cancer for the Dutch breast cancer population using available data from the Netherlands cancer registry.

Study design

This study is done by analysing retrospective data from the "Nederlandse Kankerregistratie" (Netherlands cancer registry, NCR). To validate the prediction models, the validation module of Evidencio was used. The validation module of Evidencio assesses the validations on discrimination and calibration. Discrimination is visualized using a ROC-curve and it is quantified using the C-index. Calibration is visualized using a calibration plot and a histogram and it is quantified with the calibration slope and intercept.

Results

A total of 250915 patients, between 2003 and 2018, were included in the general data selection. While 145 prediction models were identified only 13 models from 7 different articles could be validated due to various reasons, including mis-matching between available and needed data.

Model Werkhoven Rouzier (10-year) and Rouzier (pCR) have a poor discrimination with a 95% confidence interval that is below or includes 0.7. Model Guo, Rouzier (5-year), Vila, Liu (1-year, deceased married), Liu (3-year, deceased married), Liu (5-year, deceased married) and Wen (2016, 10-year) have an acceptable discrimination with C-index between 0.7 and 0.8. Wen (2016, 5-year), Wen (2016, 10-year), Wen (2017, 5-year) and Liu (1-year, survivors married) have an excellent discrimination with C-index between 0.8 and 0.9. Model Liu (3-year, survivors married) and Liu (5-year, survivors married) have an outstanding discrimination with C-index higher than 0.9.

The calibrations of the models are not that good. A perfect calibration has a slope of 1.0 and an intercept of 0.0. Model Wen (2017, 10-year) has the best calibration of all the models validated with a slope of 1.0316 and an intercept of 0.072. After that comes model Rouzier (pCR) with a slope of 0.7186 and an intercept of 0.0464. Liu (1-year, deceased married) has the worst calibration with a slope of 0.0580 and an intercept of 0.9423

Conclusion

The NCR included only a limited amount of the predictors and outcomes needed for the validations and because of this, 82 models could not be validated. The models that could be validated in this study show, on average, an acceptable discrimination for the Dutch population but the calibration of the models require improvement.

Introduction

Breast cancer is, among females, the most commonly diagnosed cancer with 2 million new cases worldwide each year [1]. In the Netherlands breast cancer concerns 28% of all cancers, with 17,000 women who get diagnosed each year [2]. But while the incidence of breast cancer is high, the mortality from breast cancer is relatively low. Only 7% of all deaths from cancer in the Netherlands are related to breast cancer [2]. This relatively low mortality is due to the early detection through population screening, better staging and providing personalized care in recent years [2]. To further minimize the mortality rates, an optimization of the treatment per patient is necessary. To optimize the treatment per patient information about the tumour and the background of the patient is required. By making a distinction between the types of breast cancer, their classified cancer stages, background information of the patient and the patient's preferences, it can be determined which care path is desired [3].

A care path contains many decision moments. To make the best decision it is helpful to have a prediction of the outcome for each of the possible choices. Clinical prediction models support physicians in making these decisions and adjusting the treatment to the needs of an individual patient [4]. They are used to discover the relationship between the predictors (baseline health states) and the future or unknown outcomes. The models should give an accurate prediction of a specific event, otherwise the outcome of the prediction might mislead the physicians and can lead to insufficient management of patient or resources by healthcare professionals. Besides, for a model to be commonly used, the model should be easy to apply, relevant, and should not be costly nor time-consuming. A balance between predictability and simplicity is important for a good clinical prediction model, so the use of a web-based application can enhance implementation. [5]

It is preferred to validate prediction models on the target population before structurally implementing the model for that population. A good example of a predicting model used in practice is PREDICT [6]. PREDICT is a model to predict overall and breast cancer specific survival for women who will be treated for early breast cancer in the United Kingdom [6]. This model is validated and made into a web-based application [7]. This model keeps being updated with extensions, re-fittings and corrections [8]. The online tool PREDICT version 2.0 is also validated on the Dutch population and deemed reliable [9]. It is used by doctors to predict the survival rate of surgery only and the additional benefit of chemotherapy, hormonal therapy and/or trastuzumab [9]. In version 2.1 of PREDICT the additional benefit of bisphosphonates is also predicted but this is not yet validated in the Dutch population [7]. PREDICT can be used by medical professionals to decide if an additional treatment with for example chemotherapy may be beneficial for that specific patient based on several patient and tumour characteristics. These predictors are age at diagnosis, menopausal status, ER status, HER2 status, Ki-67 status, tumour size (mm), tumour grade, detection method, number of positive nodes and micrometastases [7]. It can also be used by patients if they want more information on the choices they can make, but it is not recommended to use it without consultation with a medical professional.

In earlier study, a literature study was performed to identify prediction models for breast cancer. The objective of that study was to identify as many breast cancer prediction models as possible and to assess the models on transparency, reproducibility and clinical applicability. In the study it was concluded that many of the publications of the prediction models did not have the necessary information to reproduce the models. [10]

The aim of the present study is to validate existing prediction models for breast cancer for the Dutch breast cancer population using available data from the Netherlands cancer registry.

Methods

Study design

This study is done by analysing retrospective data from the "Nederlandse Kankerregistratie" (Netherlands cancer registry, NCR). The NCR is a database with information about every patient with cancer in the Netherlands and is hosted by the Netherlands comprehensive cancer organisation ("Integraal kankercentrum Nederland", IKNL). [11]

This study is performed to validate existing prediction models for breast cancer for the Dutch breast cancer population [10]. This means that the original models are based on a different population than the validation population, with maybe other specific demographics. The study population of this study exists of breast cancer patients selected from the NCR who were diagnosed and treated between 2003 and 2018. For each validation done, only the patients with complete information on the predictors and outcome for that specific validation were used. So, each model can have a different validation population because the models can have different conditions, predictors and/or outcomes and that means that it is possible that different patients are used.

To validate models, the validation module of Evidencio was used. Evidencio is a platform that enables users to use, create, validate and integrate clinical prediction models [12]. The previously performed review identified 145 prediction models [10]. Of these models 109 models were made available on the Evidencio platform for validation on www.evidencio.org. Data on predictors and outcomes required to validate the models were collected from the NCR. Models with predictors or outcomes that were unavailable in the NCR were excluded for the analysis.

The validation module of Evidencio assesses the validations on discrimination and calibration. Discrimination is visualized using a ROC-curve and it is quantified using the C-index. Calibration is visualized using a calibration plot and a histogram and it is quantified with the calibration slope and intercept. With these data combined, the validated models are examined. [13]

The model with the highest C-index has the best discrimination, if the C-index is 1.0 the discrimination is 100%. The discrimination refers to the ability of the model to distinguish patients with different outcomes [14]. As a general rule a model has no discrimination when the C-index is 0.5, an acceptable discrimination if the C-index is between 0.7 and 0.8, an excellent discrimination if the C-index is between 0.8 and 0.9 and if the C-index is higher than 0.9 the discrimination is considered outstanding [15].

Calibration refers to the agreement between observed outcomes and predictions. The calibration is the best if the calibration slope is 1.0 and the intercept is 0.0. If the slope is smaller than 1.0 than the predictions are too extreme and if the slope is bigger than 1.0 the predictions are too moderate. [14]

Missing data

The patients used in the validation are the patients from the NCR database with complete information on the predictors and outcome for that specific model. So, the patients with missing data items were excluded from the validation. Besides, there were two predictors

from the models validated missing in the data: disease specific survival (DSS) and marital status.

In the NCR no information on the cause of death is available, so in case the outcome of a model was breast cancer specific survival the assumption was made that the patient died from breast cancer in case a distant metastasis was diagnosed. If the patient died while there were no distant metastases the death was not due to breast cancer.

The models with the variable marital status got two validation, one validation where there is assumed that only the survivors were married and one validation where there is assumed that only the deceased were married.

Ethical considerations

This study was not subjected to the "Wet Medisch Wetenschappelijk Onderzoek met mensen" (Law Medical Scientific Research with people, WMO), because one of the two conditions was not met [16]. There were no persons subjected to actions or rules of conduct.

But, the privacy and safety of the patients stayed important. The data in this study was collected and delivered by IKNL. The collection of this data by IKNL is a standard procedure in the Netherlands so the patients had no additional burden because of this study. Beside that the data was delivered completely anonymous by IKNL, so even the researcher did not know which person was connected to which details.

Results

Patients characteristics

A total of 250915 patients, collected between 2003 and 2018, were included in the general data selection, with 1524 (0.6%) men and 249391 (99.4%) women. The mean age was 61, with a standard deviation of 13.7. Table 1 shows the characteristics of the population. However, as population size varied between validated models, the population used for each model differs. The size of each population is noted in Table 2 and the patient characteristics per model can be found in the supplementary materials.

Predictors

While 145 prediction models were identified only 13 models from 7 different articles could be validated (see Figure 1). There are 82 models excluded because of missing data in the NCR. The most important predictors missing in the NCR are: Ki67, stromal overgrowth, lymphovascular invasion, the type of metastases and the type of lymph nodes. The most important outcomes missing are risk on breast cancer, bone-only metastases, (non-)sentinel lymph node metastases and arm lymphedema.

The 13 validated models were sorted in 5 groups based on the outcome: Human epidermal growth factor receptor 2 (HER2), DSS, metastases-free survival, pathologic complete response (pCR) and ipsilateral breast relapse (IBR). The model in the HER2 outcome group predicts the results of the fluorescence in situ hybridization (FISH) assay for patients with HER2-borderline disease as determined via immunohistochemistry (IHC) [17]. The outcomes and the outcome groups per model are noted in Table 3.

Combined, the validated models included 23 predictors, as shown in Table 4. The six most used predictors were Oestrogen Receptor (ER) (12), grade (9), pathologic Nodes (pN) stage (8), count of positive lymph nodes (7), HER2 (6) and clinical Tumour (cT) stage (6).

Model performance

For each validation the population, the Concordance-index (C-index), the 95% Confidence Interval (CI), the slope and the intercept are noted in Table 2. The C-index and the 95% CI tell the discrimination and the calibration is described by the slope and the intercept. The ROC plots, calibration plots and histograms from all the models can be found in the supplementary materials.

HER2 and IBR

Model Guo en model Werkhoven are the only models with respectively HER2 and IBR as outcome [17][18]. Model Werkhoven is the model with the poorest discrimination of all the models validated with a C-index of 0.5844 (0.5524-0.6163) (Figure 2) [18]. The calibration of the model is also not that good with a slope of 0.5577 and an intercept of 0.4006. It is notable that most of the observed and predicted outcomes are higher than 0.8. It is also notable that most of the predicted outcomes are a bit lower than the observed outcomes but the group with the lowest outcome had a predicted outcome higher that the observed outcome. This influences the calibration so that most of the predicted outcomes give an underestimation.

The discrimination of Model Guo is, with 0.7233 (0.7162-0.7304), higher than 0.7 so acceptable [17]. The calibration has a slope of 0.5193 and an intercept of 0.1137. The difference is the most extreme for the patients with a low chance on positive HER2, there is a group with a predicted value of 0.7 and an observed risk of 0.35.

Metastases-free survival

The outcome group metastases-free survival exists of Rouzier (5-year) and Rouzier (10-year) [19]. Model Rouzier (5-year) has an acceptable discrimination with a C-index of 0.7378 (0.7291 - 0.7464) and has a calibration of a slope of 0.4669 and an intercept of 0.5451. The discrimination of model Rouzier (10-year) is on the edge of acceptable with a C-index of 0.6947 (0.6828 - 0.7066) and has a calibration of a slope of 0.3978 and an intercept of 0.6085.

Pathologic complete response

The models Rouzier (pCR) and Vila make up the outcome group pCR [19] [20]. The discrimination of model Rouzier (pCR) is on the edge of acceptable with a C-index of 0.7291 (0.6443 – 0.814) and the calibration exists of a slope of 0.7186 and an intercept of 0.0464 [19].

Model Vila has an acceptable discrimination with an C-index of 0.7577 (0.7431 - 0.7723) [20]. The calibration has a slope of 1.7155 and intercept of 0.0889.

Disease specific survival

Models Liu (1-year), Liu (3-year), Liu (5-year), Wen (2016, 5-year), Wen (2016, 10-year), Wen (2017, 5-year) and Wen (2017, 10-year) are all in the outcome group DSS.

The model Liu (5-year, survivors married) has the best discrimination of this group, an outstanding discrimination (Figure 3) with a C-index of 0.9362 (0.928-0.9445) [21]. The Liu models have a good discrimination, the three validations with deceased married have all an acceptable discrimination and the three validations with survivors married have all an outstanding discrimination. The calibrations of the Liu models are not that good. The highest slope is 0.1679 from Liu (1-year, survivors married), while 1.0 is the goal. The lowest intercept is 0.8337 from Liu (1-year, survivors married), while 0.0 is the goal. Liu (1-year, deceased married) has the worst calibration of the group with a slope of 0.0580 and an intercept of 0.9423 (Figure 4).

Model Wen (2016, 10-year) has the poorest discrimination of this group but is still on the edge of excellent with a C-index of 0.8098 (0.7826-0.837) [22]. The earlier validations of the two Wen models (2016 and 2017) have both an excellent discrimination. Wen (2017, 10-year) model (Figure 5) has the best calibration of all the models validated with a slope of 1.0316 and an intercept of 0.072 [23].

Discussion

This study aimed to validate 145 models for breast cancer. The NCR database was used for the validations. Although this is within the world a cancer registry which contains details on treatment and tumour characteristics, it still included only a limited amount of the predictors and outcomes needed for the validations. Because of this, 82 models could not be validated. The NCR might consider incorporating these missing predictors into their registry because it looks like these are items that can predict certain outcomes and may therefore be of interest to the clinical policy. If these items were known, not only the models could be validated but also the clinical decision-making policy to predict the outcomes for certain treatments and thus decide on an individual level for the most favourable outcome.

For each validation the patients with incomplete data were excluded. It is possible that this exclusion caused a bias. It could be that the validation population excludes a specific group, while the original population includes that group. This is possible because not all countries measure the same variables of the same patients. For example, model Werkhoven had the poorest discrimination, one of the reasons for this poor discrimination could be that in the data used for this validation there were no patients with ductal carcinoma in situ (DCIS). The population of this validation was 5277 and there were no DCIS patients while the study population was 1603 with 905 DCIS patients. The study was a trial so maybe that attracted a specific group, but it is something that is notable and should be looked at further. Model Werkhoven was the only model that had an exclusion this clear, but it could be that in other models less obvious groups are excluded.

Besides that, assumptions were necessary to validate 7 of the 13 models. There was no data for DSS, so the assumption was made that the death was disease specific if the patient had a metastasis and is deceased. The fact that model Liu, Wen (2016) and Wen (2017) seem to underestimate the DSS probability could be partly explained by this assumption. It is plausible that a few of the deaths from people without metastases were also disease specific which could have influenced the validation.

This study was preformed because a good prediction model for the Dutch population can help medical professionals to make the best decision. For this it is helpful to have a prediction of the outcome for each of the choices possible. The models validated in this study were only in 5 different outcome groups. The models excluded could have predict 32 outcome groups. With the most models in the groups: Overall survival (19), recurrence free survival (7), locoregional recurrence (6), risk on breast cancer (6) and non-sentinel lymph node metastasis (5).

The models included predict the outcome on five different decision moments. If the IHC determines HER2-borderline Model Guo can predict the HER2 instead of doing a FISH assay [17]. The models Liu predicts the (additional) DSS benefit of preoperative radiotherapy [21]. The models Rouzier and model Vila predict the (additional) benefit of preoperative chemotherapy on the metastasis free survival and the pCR [19] [20]. The models Wen can be used at the time of surgery to predict the disease specific survival [22] [23]. Model Werkhoven can be used before breast conserving therapy to predict the best boost dose [18].

Model Wen (2017) predicts the same as model Wen (2016) but has a better calibration and a better discrimination so if the decision moment is the 5- or 10-year DSS in the Dutch population the best model is Wen (2017). This could be expected because model Wen (2017) is an update from model Wen (2016) but it was possible that the original model (Wen 2016) worked better in the Dutch population.

From the 13 models validated 12 models had an external validation within the study of the development of the model, mostly the articles only tell the C-index of this validation. Only Model Werkhoven had no external validation within the article and there is no other external validation found for this model [18].

Model Guo had a C-index of 0.749 in the validation in the original article, while in this study the C-index was 0.7233 (0.7162-0.7304) [17]. This difference could be explained because the validation cohort in the earlier study was small with only 139 patients while this study had a cohort of 27870 patients.

For model Liu the C-indices were 0.817 (1-year), 0.816 (3-year) and 0.810 (5-year) in the earlier validation [21]. Models Liu is difficult to compare to the earlier validation because of the two validations. The C-indices in this study surround the C-indices of the earlier validation with the C-index of the models with all the deceased married lower and the C-index of the models with all the survivors married higher. Thus, there is no direct difference to see in the C-indices, but it is noticeable that the discrimination of the validation is quite good even with the missing variable. So, it would be beneficial if a next study would do another validation of model Liu (1-year), Liu (3-year) and Liu (5-year) with different data, where the marital status is known.

Model Rouzier had C-indices of 0.79 (pCR), 0.72 (5-year) and there was no validation for the 10-year metastasis-free survival [19]. The C-index of the pCR of the earlier validation falls with 0.79 in the 95% CI of this study with 0.7291 (0.6443-0.814). The 5-year metastasis-free survival in this study was, with 0.7378 (0.7291-0.7464), a bit higher. The population of the validation in this study was small, with only 214 patients, and the population in the earlier validation was also quite small, with 377 (pCR) and 308 (5-year) patients, and the patient characteristics also differed so it is possible that that is partly the reason for the difference.

Model Vila had a C-index of 0.794 while in this study the C-index was 0.7577 [20]. But, the 95% CI of the earlier validation is relatively big, with 0.746-0.843, and almost the whole 95% CI of this study (0.7431-0.7723) falls in that interval. So, the validation in this study gives a lower C-index but is still within the confidence interval.

The validation of model Wen (2016) gives only one C-index, 0.796 (0.756-0.860), because they combined the 5- and the 10-year model into one model [22]. The C-indices in this study are both a bit higher, with 0.8388 (0.8132-0.8644) for the 5-year model and 0.8098 (0.7826-0.837) for the 10-year model, but the 95% CI's of the validation overlap almost completely.

Model Wen (2017) has also only one C-index 0.789 (0.711-0.868) [23]. This is quite a bit lower than the C-indices in this study, with 0.8748 (0.8529-0.8967) for the 5-year and 0.8632 (0.8408-0.8856) for the 10-year. So, the 95% CI's of the validation overlap.

If the assumption is made that to be implemented in the clinical practice in the Netherlands the C-index must be at least 0.7, the intercept must be between -0.1 and 0.1 and the slope must be between 0.9 and 1.1, there can be looked at which models already can be implemented. Models Guo, Liu (1-year), Liu (3-year), Liu (5-year), Rouzier (5-year), Vila, Wen (2016, 5-year), Wen (2016, 10-year), Wen (2017, 5-year) and Wen (2017, 10-year) all have a C-index higher than 0.7. The 95% CI's of models Rouzier (pCR) and Rouzier (10-year) both start

below the 0.7. The C-index of model Werkhoven, 0.5844 (0.5524-0.6163), is complete below 0.7. Only the intercepts of models Rouzier (pCR), Vila and Wen (2017, 10-year) are between 0.1 and -0.1. There is only one model with a slope between 0.9 and 1.1 and that is model Wen (2017, 10-year). So, the only model with an accepted C-index, slope and intercept is model Wen (2017, 10-year). This means that with this assumption only model Wen (2017, 10-year) could be directly implemented in the clinical practice in the Netherlands. Models Guo, Rouzier (5-year), Vila, Wen (2016, 5-year), Wen (2016, 10-year) and Wen (2017, 5-year) would need a re-calibration to be eligible for implementation. For models Liu (1-year), Liu (3-year) and Liu (5-year) it could be beneficial to do a new validation with data including the variable marital status but based on the validations in this study a re-calibration is recommended. Models Rouzier (pCR), Rouzier (10-year) and Werkhoven have to improve on discrimination and calibration so it would be beneficial to make a model revision for the Dutch population [24].

Conclusion

This study shows that there are possibly more usable models but there was a mis-match of the needed data with the available data in the NCR database. The NCR included only a limited amount of the predictors and outcomes needed for the validations and because of this, 82 models could not be validated. These excluded models could improve the clinical practice by predicting different outcomes or on different decision moments.

The models that could be validated in this study show, on average, an acceptable discrimination for the Dutch population with only three models with a 95% confidence interval that is below or includes 0.7. The calibration of the validated models require improvement. A perfect calibration has a slope of 1.0 and an intercept of 0.0. The best calibration, Model Wen (2017, 10-year), has a slope of 1.0316 and an intercept of 0.072 but after that comes model Rouzier (pCR) with a slope of 0.7186 and an intercept of 0.0464.

Figures and tables

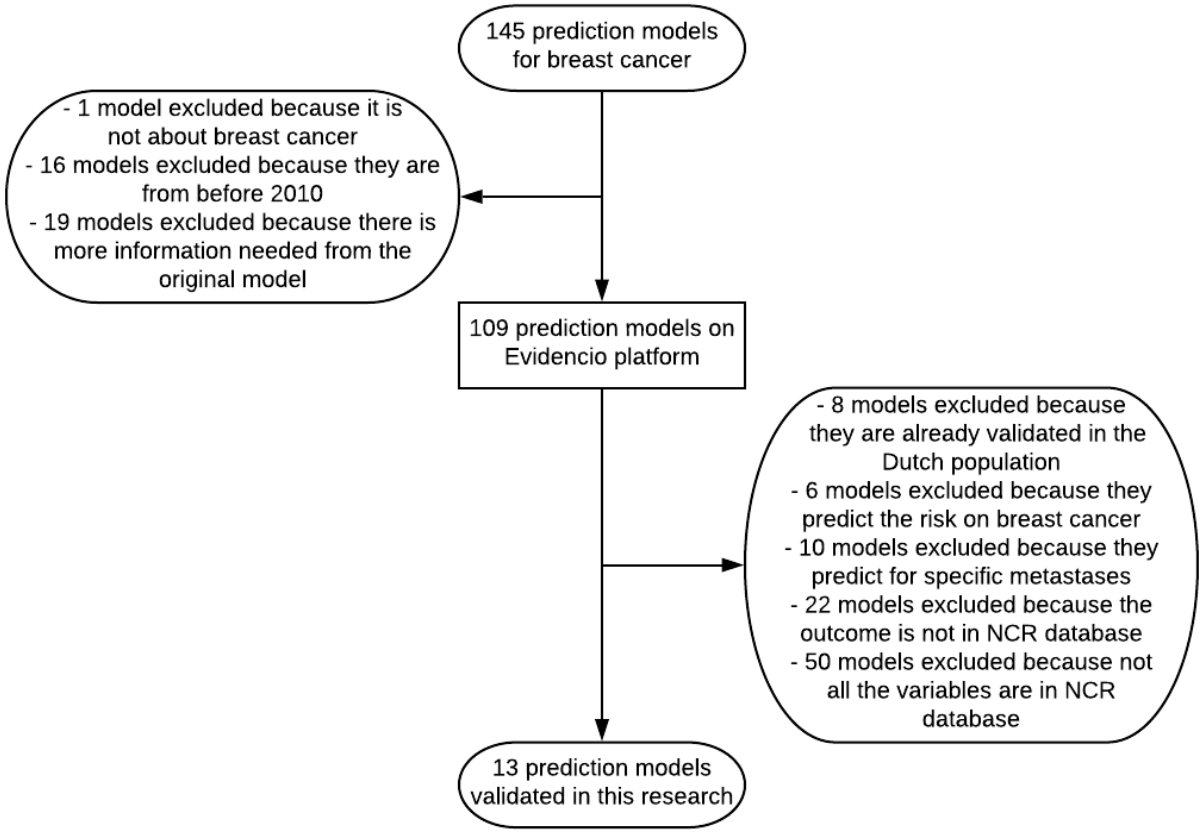

Figure 1 Chart flow prediction models

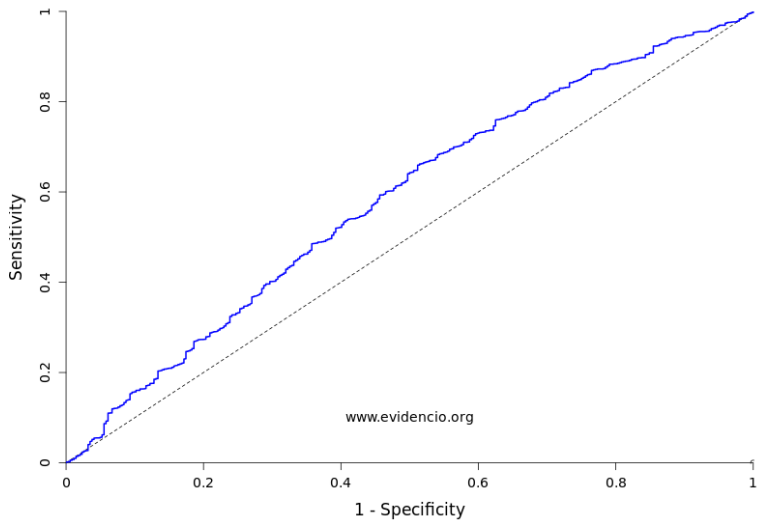

Figure 2 ROC plot model Werkhoven

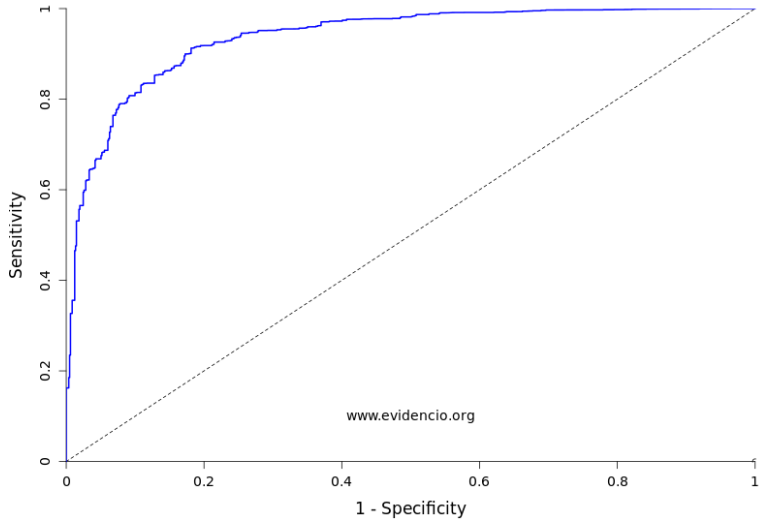

Figure 3 ROC plot model Liu (5-year, survivors married)

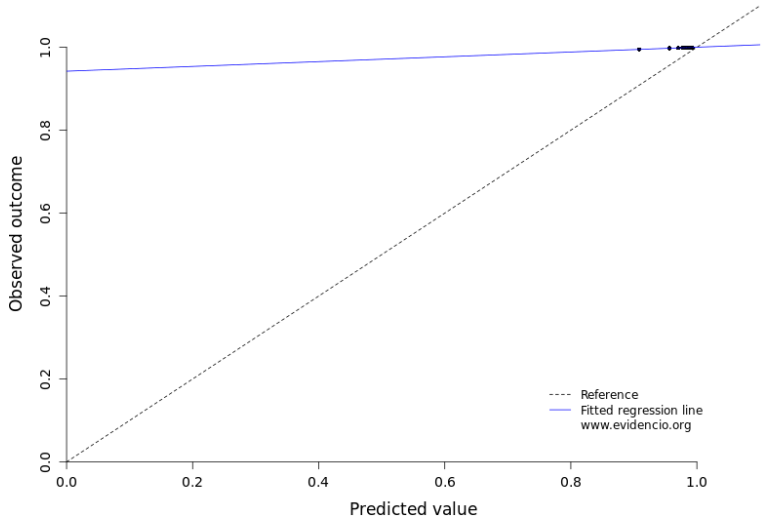

Figure 4 Calibration plot model Liu (1-year, deceased married)

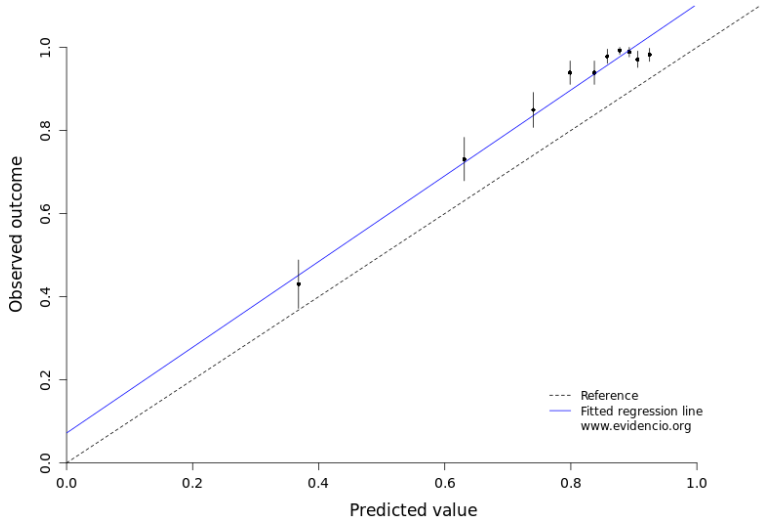

Figure 5 Calibration plot model Wen (2017, 10-year)

Table 1 Characteristics

		NCR cohort (250915)	
		Amount	*%*
Age		250915	100%
	Mean (SD)	61.3 (13.7)	
Gender	*Male*	1524	0.6%
	Female	249391	99.4%
ER	*Negative*	35293	14.1%
	Positive	176045	70.2%
	Missing	39577	15.8%
PR	*Negative*	67879	27.1%
	Positive	139469	55.6%
	Missing	43567	17.4%
HER2	*Negative*	158570	63.2%
	Positive	25745	10.3%
	Missing	63593	25.3%
cT stage	*0*	1362	0.5%
	1	119546	47.6%
	2	65518	26.1%
	3	10049	4.0%
	4	9607	3.8%
	Missing	44833	17.9%
pT stage	*0*	4702	1.9%
	1	123086	49.1%
	2	58666	23.4%
	3	6525	2.6%
	4	1993	0.8%
	Missing	55943	22.3%
pN stage	*0*	145859	58.1%
	1	50026	19.9%
	2	11589	4.6%
	3	6931	2.8%
	Missing	36414	14.5%
Grade	*1*	48888	19.5%
	2	95955	38.2%
	3	67534	26.9%
	4	51	0.0%
	Missing	38487	15.3%
Lymph nodes	*Negative*	148709	59.3%
	Positive	75704	30.2%
	Missing	26502	10.6%

Table 2 Results

Model	Addition	Population	Events	C-index	95% CI	Slope	Intercept	Reference
Guo		27870	6668	0.7233	0.7162 - 0.7304	0.5193	0.1137	[17]
Liu (1-year)	Deceased married	150871	196	0.7464	0.7093 - 0.7835	0.0580	0.9423	[21]
	Survivors married	150871	196	0.9087	0.8885 - 0.9289	0.1679	0.8337	[21]
Liu (3-year)	Deceased married	120551	603	0.7897	0.7706 - 0.8087	0.0608	0.9426	[21]
	Survivors married	120551	603	0.9298	0.9195 - 0.9401	0.1373	0.8708	[21]
Liu (5-year)	Deceased married	92478	811	0.7996	0.7836 - 0.8155	0.0798	0.9279	[21]
	Survivors married	92478	811	0.9362	0.928 - 0.9445	0.1672	0.8485	[21]
Rouzier (5-year)		41235	3748	0.7378	0.7291 - 0.7464	0.4669	0.5451	[19]
Rouzier (10-year)		15767	2293	0.6947	0.6828 - 0.7066	0.3978	0.6085	[19]
Rouzier (pCR)		208	184	0.7291	0.6443 - 0.814	0.7186	0.0464	[19]
Vila		4740	3156	0.7577	0.7431 - 0.7723	1.7155	0.0889	[20]
Wen (2016, 5-year)		21669	298	0.8388	0.8132 - 0.8644	0.1857	0.8356	[22]
Wen (2016, 10-year)		2789	413	0.8098	0.7826 - 0.837	0.7017	0.436	[22]
Wen (2017, 5-year)		21669	298	0.8748	0.8529 - 0.8967	0.2828	0.7375	[23]
Wen (2017, 10-year)		2789	413	0.8632	0.8408 - 0.8856	1.0316	0.072	[23]
Werkhoven		5277	382	0.5844	0.5524 - 0.6163	0.5577	0.4006	[18]

Table 3 List of models

Model	Article title	Outcome	Outcome group	Decision moment	Reference
Guo	A nomogram to predict HER2 status in breast cancer patients with HER2-borderline disease as determined via immunohistochemistry	Probability of positive HER2	HER2	After HER2-borderline on IHC	[17]
Liu (1-year)	Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study	1-year disease specific survival	Disease specific survival	Before preoperative radiotherapy	[21]
Liu (3-year)	Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study	3-year disease specific survival	Disease specific survival	Before preoperative radiotherapy	[21]
Liu (5-year)	Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study	5-year disease specific survival	Disease specific survival	Before preoperative radiotherapy	[21]
Rouzier (5-year)	Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer	5- year metastases-free survival	Metastases-free survival	Before preoperative chemotherapy	[19]
Rouzier (10-year)	Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer	10-year metastases-free survival	Metastases-free survival	Before preoperative chemotherapy	[19]
Rouzier (pCR)	Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer	Pathologic complete response	Pathologic complete response	Before preoperative chemotherapy	[19]
Vila	Nomograms for Predicting Axillary Response to Neoadjuvant Chemotherapy in Clinically Node-Positive Patients with Breast Cancer	Axillary Response to neoadjuvant chemotherapy	Pathologic complete response	Before preoperative chemotherapy	[20]
Wen (2016, 5-year)	Development and validation of a prognostic nomogram based on the log odds of positive lymph nodes (LODDS) for breast cancer	5-year disease specific survival	Disease specific survival	At the time of surgery	[22]
Wen (2016, 10-year)	Development and validation of a prognostic nomogram based on the log odds of positive lymph nodes (LODDS) for breast cancer	10-year disease specific survival	Disease specific survival	At the time of surgery	[22]
Wen (2017, 5-year)	Development and validation of a nomogram for predicting survival on the base of modified lymph node ration in breast cancer patients	5-year disease specific survival	Disease specific survival	At the time of surgery	[23]
Wen (2017, 10-year)	Development and validation of a nomogram for predicting survival on the base of modified lymph node ration in breast cancer patients	10-year disease specific survival	Disease specific survival	At the time of surgery	[23]
Werkhoven	Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial	10- year proportion IBR-free	Ipsilateral breast relapse	Before breast conserving therapy	[18]

Table 4 Predictors

	Guo	Liu (1-year)	Liu (3-year)	Liu (5-year)	Rouzier (5-year)	Rouzier (10-year)	Rouzier (pCR)	Vila	Wen (2016, 5-year)	Wen (2016, 10-year)	Wen (2017, 5-year)	Wen (2017, 10-year)	Werkhoven	**Total**
Age		x	x	x			x						x	5
Boost													x	1
Chemotherapy													x	1
Count of courses neo-adjuvant chemotherapy							x							1
Count of lymph nodes examined									x	x	x	x		4
Count of positive lymph nodes					x	x		x	x	x	x	x		7
cT stage							x	x	x	x	x	x		6
DCIS													x	1
ER	x	x	x	x	x	x	x	x	x	x	x	x		12
Grade	x	x	x	x	x	x	x	x					x	9
HER2	x							x	x	x	x	x		6
Marital status		x	x	x										3
Menopausal status									x	x	x	x		4
Morphology					x	x								2
Multifocal tumour								x						1
pN stage		x	x	x				x	x	x	x	x		8
PR	x							x						2
pT stage		x	x	x										3
Received breast conservation surgery		x	x	x										3
Tamoxifen													x	1
Topography		x	x	x										3
Tumour size					x	x							x	3
Total	4	8	8	8	5	5	5	8	7	7	7	7	7	

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Supplement

Model Guo

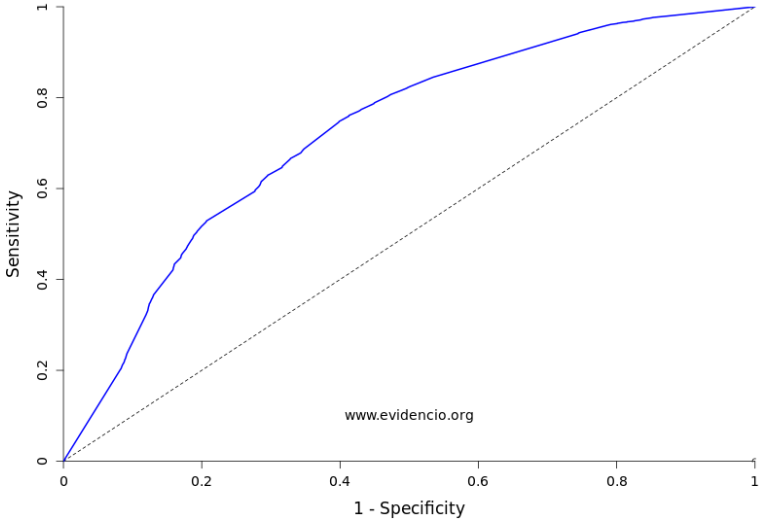
Name: A nomogram to predict HER2 status in breast cancer patients with HER2-borderline disease as determined via immunohistochemistry
Authors: Guo Q., Chen K., Lin X., Su Y., Xu R., Dai Y., Qiu C., Song X., Mao S. & Chen Q.
Outcome: Probability of positive HER2[1]
Variables: ER[2], grade and PR[3]

Characteristics:

		Study cohort (n=1482)		Validation cohort (n=27870)	
		Number	*%*	*Number*	*%*
ER	*Negative*	415	28.0%	4276	15.3%
	Positive	1067	72.0%	23594	84.7%
PR	*Negative*	449	30.3%	8923	32.0%
	Positive	1033	69.7%	18947	68.0%
Grade	*1*	70	4.7%	6216	22.3%
	2	1058	71.4%	13513	48.5%
	3	354	23.9%	8141	29.2%
HER2	*Negative*	Unknown		22392	80.3%
	Positive	Unknown		5478	19.7%

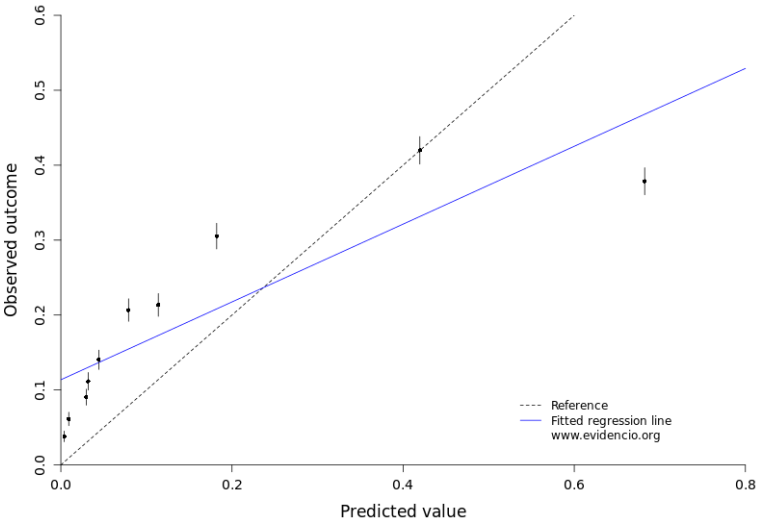
Discrimination: C-index: 0.7233 | 95% CI: 0.7162 - 0.7304
Calibration: Slope: 0.5193 | Intercept: 0.1137

ROC plot:

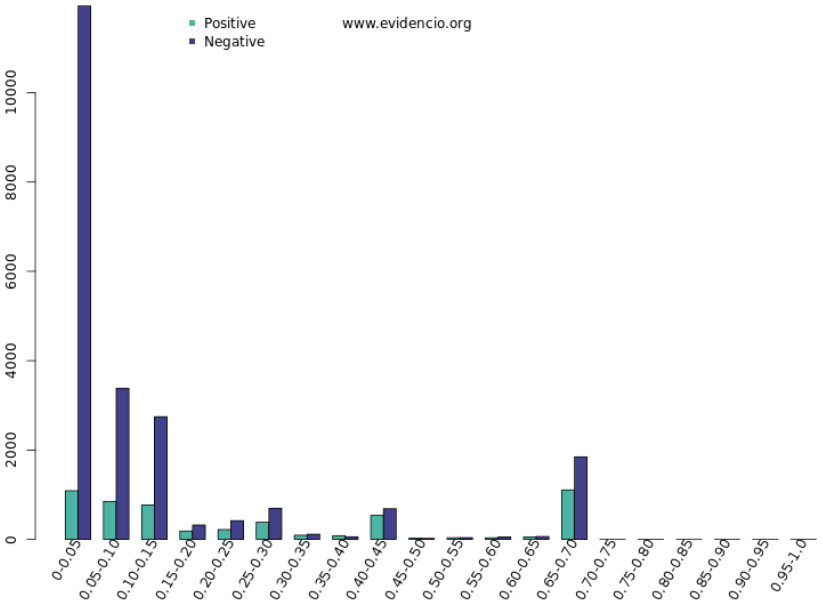


[1] Human epidermal growth factor receptor 2
[2] Oestrogen receptor
[3] Progesterone receptor

Calibration plot:



Histogram:



Model Liu (1-year, deceased married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 1-year disease specific survival
Variables: age, ER, grade, marital status, pN stage[4], pT stage[5], received breast conservation surgery and topography
Assumptions:

- All deceased are married, all survivors are not married
- Disease-specific death is if the patient had a metastasis and is deceased

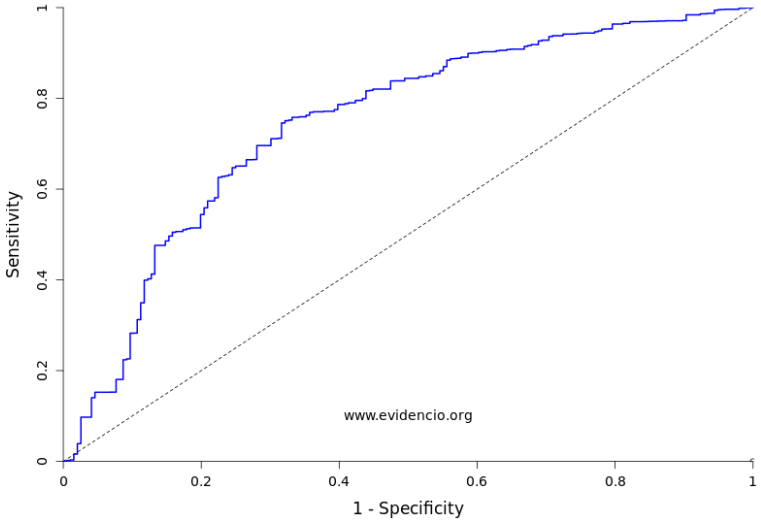
Characteristics:

		Training set (n = 1692)		**Validation cohort (n=150871)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		60.12 (12.65)	
Marital	*Yes*	1250	73.9%	196	0.1%
	No	442	26.1%	150675	99.9%
Tumour location	*Centre/Nipple*	92	5.4%	12217	8.1%
	Upper-outer	771	45.6%	18799	12.5%
	Upper-inner	200	11.8%	58545	38.8%
	Lower-outer	138	8.2%	12756	8.5%
	Lower-inner	112	6.6%	11175	7.4%
	Overlapping lesion	379	22.4%	37379	24.8%
Grade	*Well*	290	17.1%	36703	24.3%
	Moderately	768	45.4%	70422	46.7%
	Poorly	606	35.8%	43729	29.0%
	Undifferentiated	28	1.7%	17	0.0%
pT stage	*1*	1020	60.3%	97648	64.7%
	2	462	27.3%	47524	31.5%
	3	106	6.3%	4565	3.0%
	4	104	6.1%	1134	0.8%
pN stage	*0*	1091	64.5%	97563	64.7%
	1	340	20.1%	39405	26.1%
	2	167	9.9%	8782	5.8%
	3	94	5.6%	5073	3.4%
ER status	*Negative*	408	24.1%	23596	15.6%
	Positive	1284	75.9%	127275	84.4%
Breast conservation surgery	*Yes*	1219	72.0%	28	0.0%
	No	473	28.0%	150843	100.0%
1-year disease specific survival	*Yes*	Unknown		150675	99.9%
	No	Unknown		196	0.1%

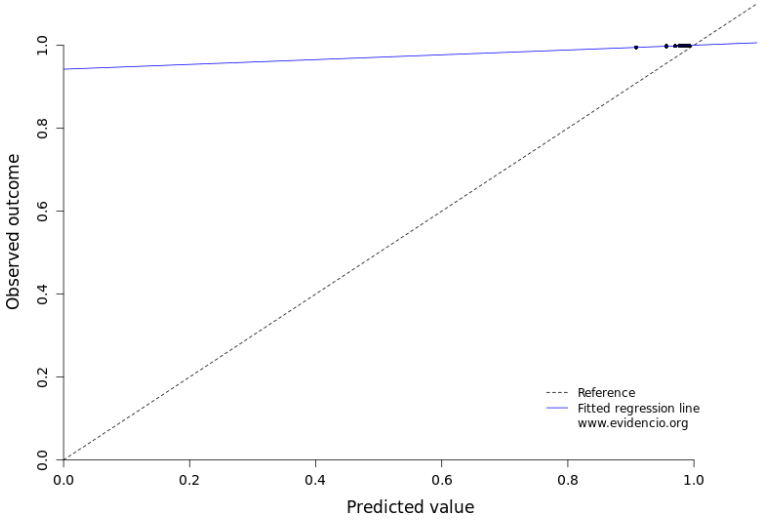
Discrimination: C-index: 0.7464 | 95% CI: 0.7093 - 0.7835
Calibration: Slope: 0.058 | Intercept: 0.9423

[4] Pathologic Nodes stage
[5] Pathologic Tumour stage

ROC plot:



Calibration plot:



Histogram:

Model Liu (1-year, survivors married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 1-year disease specific survival
Variables: age, ER, grade, marital status, pN stage, pT stage, received breast conservation surgery and topography
Assumptions:

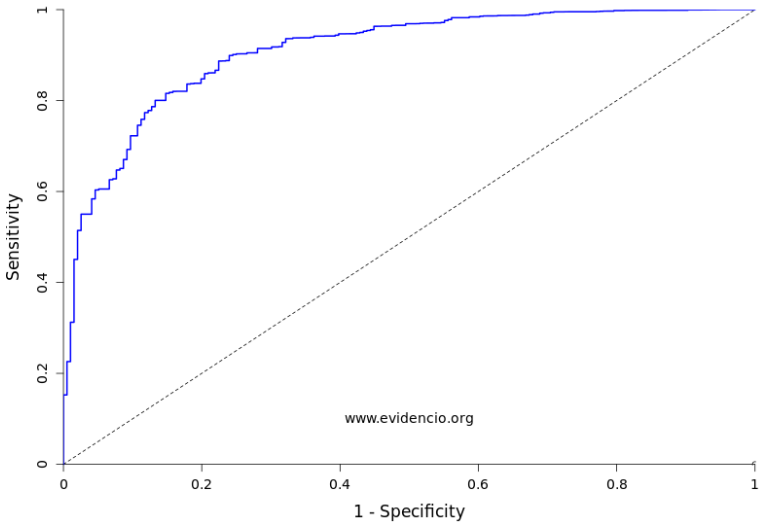
- All survivors are married, all deceased are not married
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

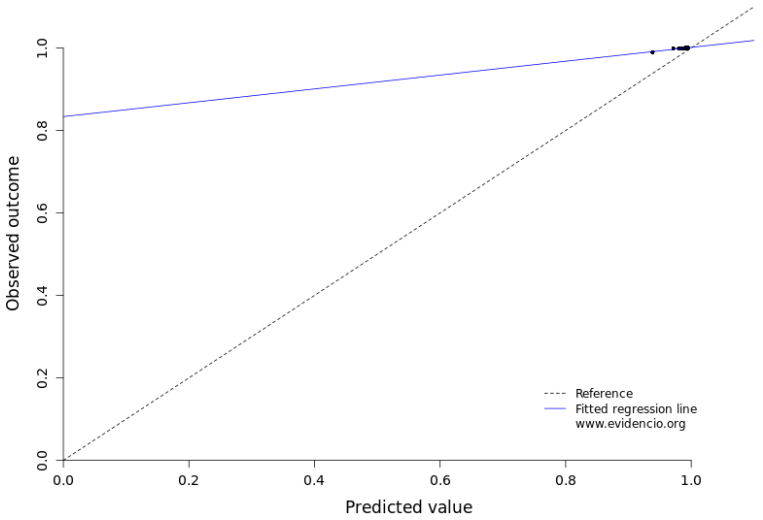
		Training set (n = 1692)		**Validation cohort (n=150871)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		60.12 (12.65)	
Marital	*Yes*	1250	73.9%	150675	99.9%
	No	442	26.1%	196	0.1%
Tumour location	*Centre/Nipple*	92	5.4%	12217	8.1%
	Upper-outer	771	45.6%	18799	12.5%
	Upper-inner	200	11.8%	58545	38.8%
	Lower-outer	138	8.2%	12756	8.5%
	Lower-inner	112	6.6%	11175	7.4%
	Overlapping lesion	379	22.4%	37379	24.8%
Grade	*Well*	290	17.1%	36703	24.3%
	Moderately	768	45.4%	70422	46.7%
	Poorly	606	35.8%	43729	29.0%
	Undifferentiated	28	1.7%	17	0.0%
pT stage	*1*	1020	60.3%	97648	64.7%
	2	462	27.3%	47524	31.5%
	3	106	6.3%	4565	3.0%
	4	104	6.1%	1134	0.8%
pN stage	*0*	1091	64.5%	97563	64.7%
	1	340	20.1%	39405	26.1%
	2	167	9.9%	8782	5.8%
	3	94	5.6%	5073	3.4%
ER status	*Negative*	408	24.1%	23596	15.6%
	Positive	1284	75.9%	127275	84.4%
Breast conservation surgery	*Yes*	1219	72.0%	28	0.0%
	No	473	28.0%	150843	100.0%
1-year disease specific survival	*Yes*	Unknown		150675	99.9%
	No	Unknown		196	0.1%

Discrimination: C-index: 0.9087 | 95% CI: 0.8885 - 0.9289
Calibration: Slope: 0.1679 | Intercept: 0.8337

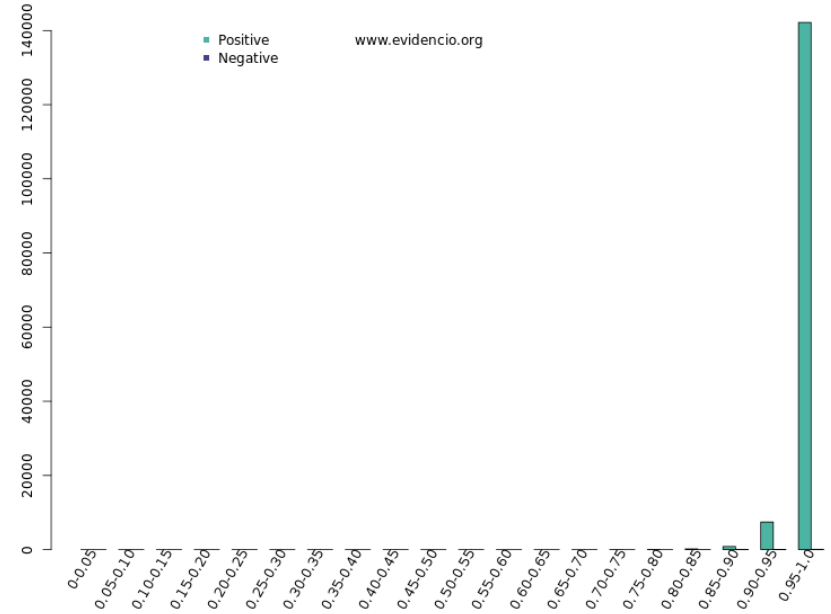
ROC plot:



Calibration plot:



Histogram:



Model Liu (3-year, deceased married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 3-year disease specific survival
Variables: age, ER, grade, marital status, pN stage, pT stage, received breast conservation surgery and topography
Assumptions:

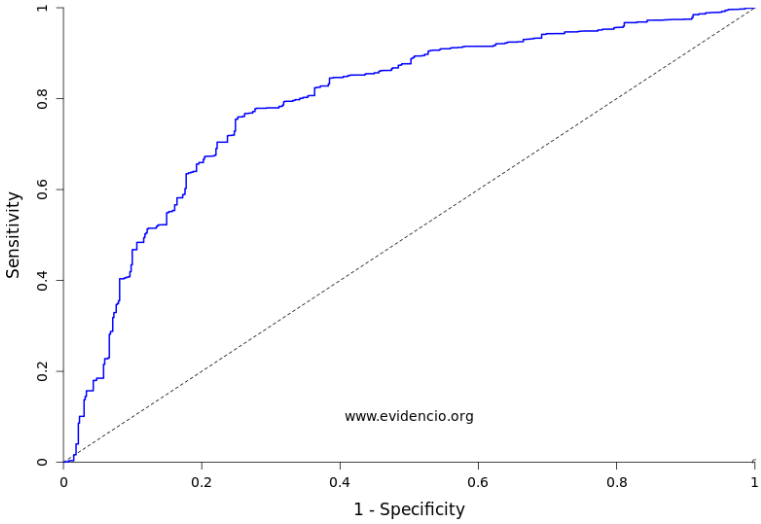
- All deceased are married, all survivors are not married
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

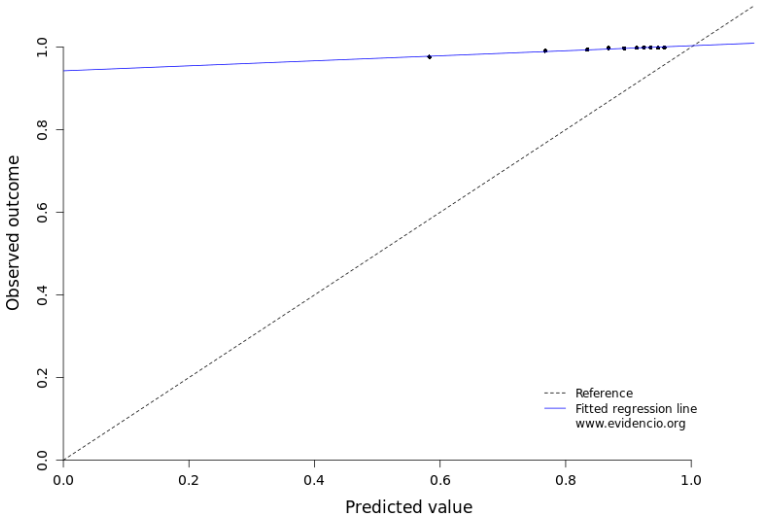
		Training set (n = 1692)		**Validation cohort (n=120551)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		59.53 (12.46)	
Marital	*Yes*	1250	73.9%	603	0.5%
	No	442	26.1%	119948	99.5%
Tumour location	*Centre/Nipple*	92	5.4%	9488	7.9%
	Upper-outer	771	45.6%	15001	12.4%
	Upper-inner	200	11.8%	47172	39.1%
	Lower-outer	138	8.2%	10107	8.4%
	Lower-inner	112	6.6%	8958	7.4%
	Overlapping lesion	379	22.4%	29825	24.7%
Grade	*Well*	290	17.1%	29683	24.6%
	Moderately	768	45.4%	56020	46.5%
	Poorly	606	35.8%	34834	28.9%
	Undifferentiated	28	1.7%	14	0.0%
pT stage	*1*	1020	60.3%	78693	65.3%
	2	462	27.3%	37799	31.4%
	3	106	6.3%	3297	2.7%
	4	104	6.1%	762	0.6%
pN stage	*0*	1091	64.5%	78215	64.9%
	1	340	20.1%	31375	26.0%
	2	167	9.9%	7145	5.9%
	3	94	5.6%	3814	3.2%
ER status	*Negative*	408	24.1%	18322	15.2%
	Positive	1284	75.9%	102229	84.8%
Breast conservation surgery	*Yes*	1219	72.0%	28	0.0%
	No	473	28.0%	120523	100.0%
3-year disease specific survival	*Yes*	Unknown		119948	99.5%
	No	Unknown		603	0.5%

Discrimination: C-index: 0.7897 | 95% CI: 0.7706 - 0.8087
Calibration: Slope: 0.0608 | Intercept: 0.9426

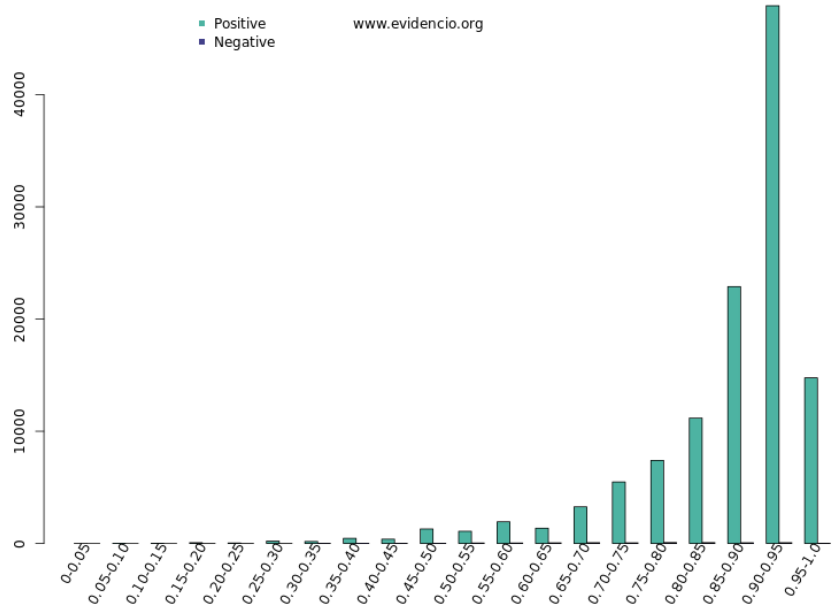
ROC plot:



Calibration plot:



Histogram:



Model Liu (3-year, survivors married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 3-year disease specific survival
Variables: age, ER, grade, marital status, pN stage, pT stage, received breast conservation surgery and topography
Assumptions:

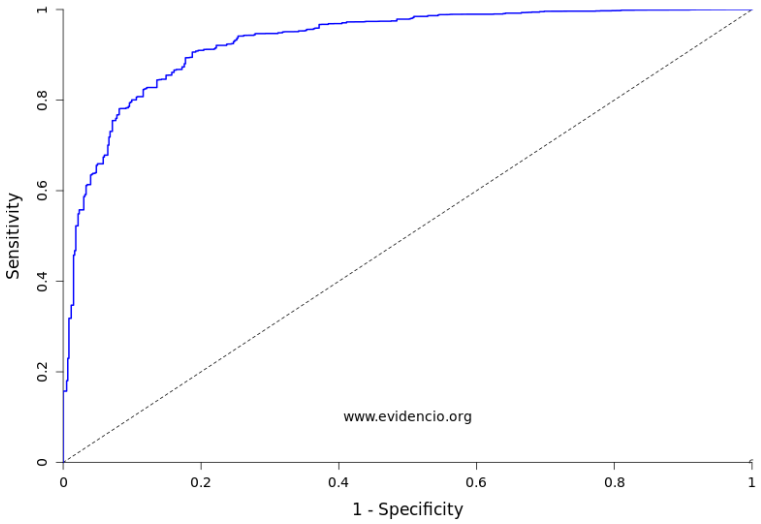
- All survivors are married, all deceased are not married
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

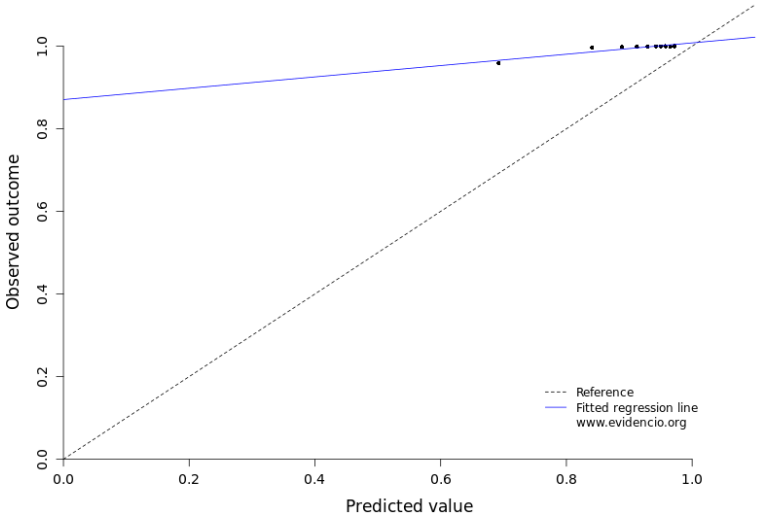
		Training set (n = 1692)		**Validation cohort (n=120551)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		59.53 (12.46)	
Marital	*Yes*	1250	73.9%	119948	99.5%
	No	442	26.1%	603	0.5%
Tumour location	*Centre/Nipple*	92	5.4%	9488	7.9%
	Upper-outer	771	45.6%	15001	12.4%
	Upper-inner	200	11.8%	47172	39.1%
	Lower-outer	138	8.2%	10107	8.4%
	Lower-inner	112	6.6%	8958	7.4%
	Overlapping lesion	379	22.4%	29825	24.7%
Grade	*Well*	290	17.1%	29683	24.6%
	Moderately	768	45.4%	56020	46.5%
	Poorly	606	35.8%	34834	28.9%
	Undifferentiated	28	1.7%	14	0.0%
pT stage	*1*	1020	60.3%	78693	65.3%
	2	462	27.3%	37799	31.4%
	3	106	6.3%	3297	2.7%
	4	104	6.1%	762	0.6%
pN stage	*0*	1091	64.5%	78215	64.9%
	1	340	20.1%	31375	26.0%
	2	167	9.9%	7145	5.9%
	3	94	5.6%	3814	3.2%
ER status	*Negative*	408	24.1%	18322	15.2%
	Positive	1284	75.9%	102229	84.8%
Breast conservation surgery	*Yes*	1219	72.0%	28	0.0%
	No	473	28.0%	120523	100.0%
3-year disease specific survival	*Yes*	Unknown		119948	99.5%
	No	Unknown		603	0.5%

Discrimination: C-index: 0.9298 | 95% CI: 0.9195 - 0.9401
Calibration: Slope: 0.1373 | Intercept: 0.8708

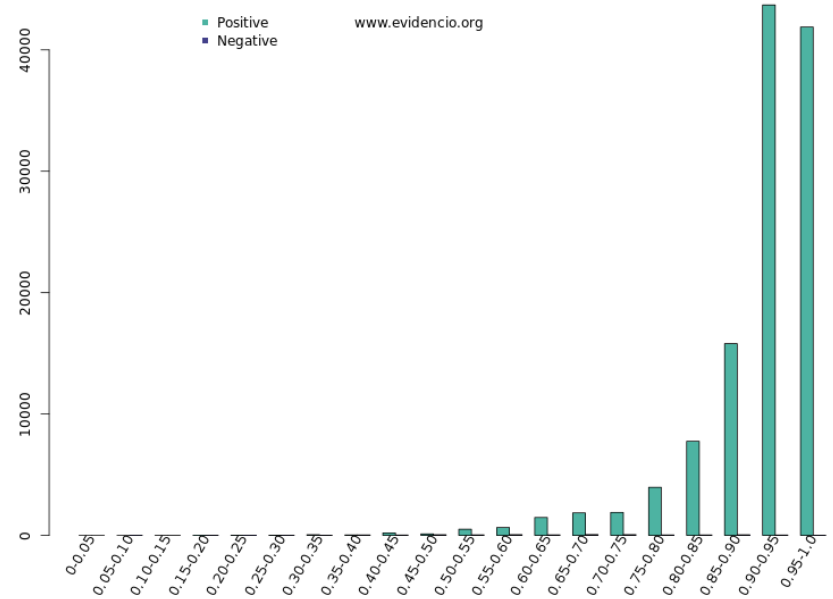
ROC plot:



Calibration plot:



Histogram:



Model Liu (5-year, deceased married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 5-year disease specific survival
Variables: age, ER, grade, marital status, pN stage, pT stage, received breast conservation surgery and topography
Assumptions:

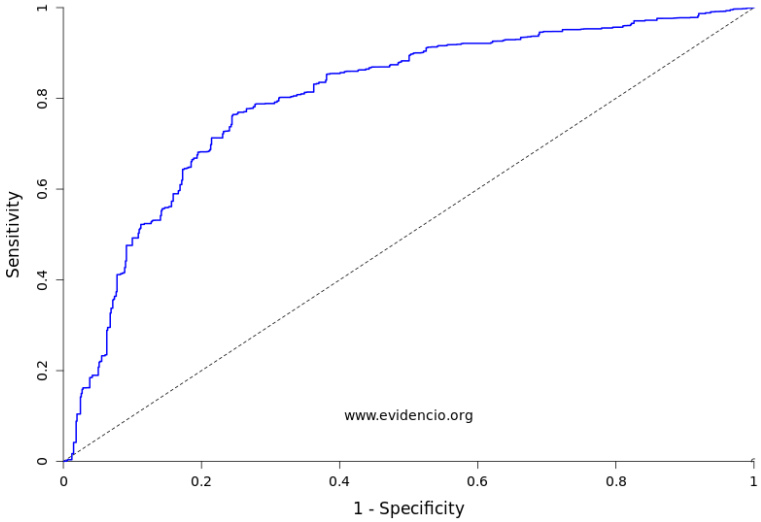
- All deceased are married, all survivors are not married
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

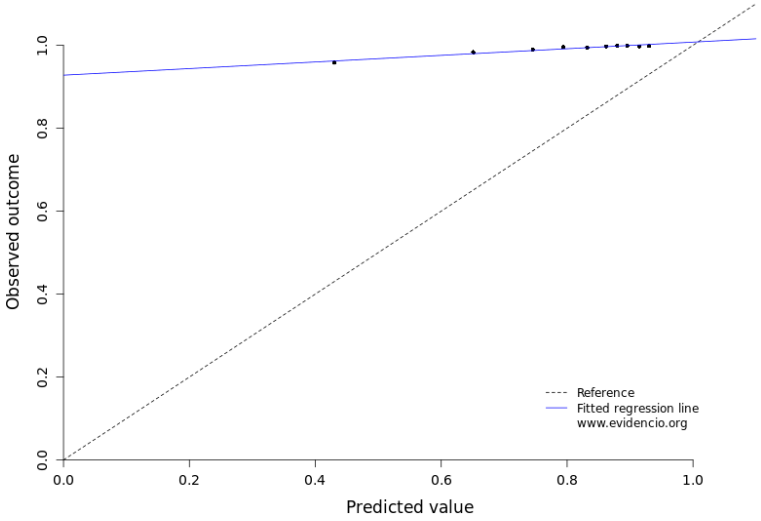
		Training set (n = 1692)		**Validation cohort (n=92478)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		58.79 (12.25)	
Marital	*Yes*	1250	73.9%	811	0.9%
	No	442	26.1%	91667	99.1%
Tumour location	*Centre/Nipple*	92	5.4%	7135	7.7%
	Upper-outer	771	45.6%	11387	12.3%
	Upper-inner	200	11.8%	36557	39.5%
	Lower-outer	138	8.2%	7608	8.2%
	Lower-inner	112	6.6%	6930	7.5%
	Overlapping lesion	379	22.4%	22861	24.7%
Grade	*Well*	290	17.1%	22952	24.8%
	Moderately	768	45.4%	42754	46.2%
	Poorly	606	35.8%	26761	28.9%
	Undifferentiated	28	1.7%	11	0.0%
pT stage	*1*	1020	60.3%	60760	65.7%
	2	462	27.3%	28853	31.2%
	3	106	6.3%	2320	2.5%
	4	104	6.1%	545	0.6%
pN stage	*0*	1091	64.5%	59981	64.9%
	1	340	20.1%	24051	26.0%
	2	167	9.9%	5624	6.1%
	3	94	5.6%	2821	3.1%
ER status	*Negative*	408	24.1%	14144	15.3%
	Positive	1284	75.9%	78334	84.7%
Breast conservation surgery	*Yes*	1219	72.0%	26	0.0%
	No	473	28.0%	92452	100.0%
5-year disease specific survival	*Yes*	Unknown		91667	99.1%
	No	Unknown		811	0.9%

Discrimination: 0.7996 | 95% CI: 0.7836 - 0.8155
Calibration: Slope: 0.0798 | Intercept: 0.9279

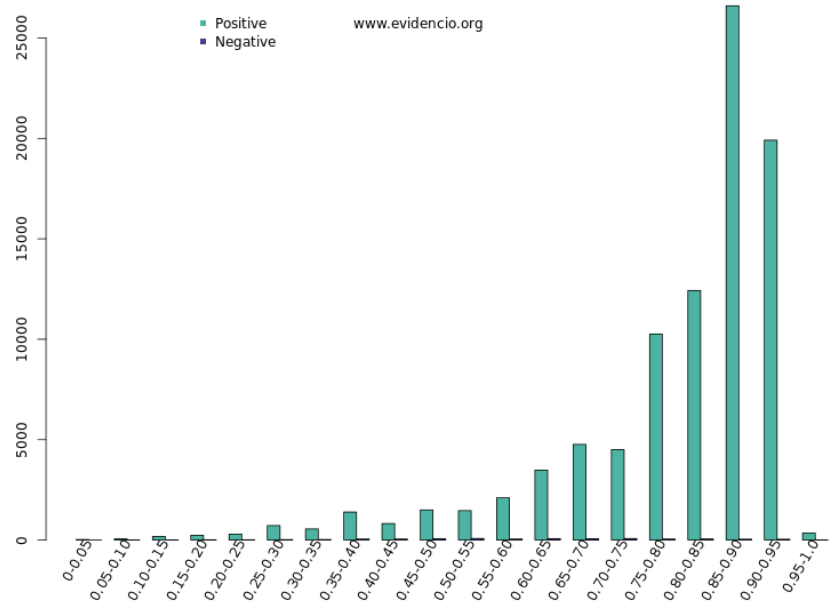
ROC plot:



Calibration plot:



Histogram:



Model Liu (5-year, survivors married)

Name: Nomogram predicts survival benefit from preoperative radiotherapy for non-metastatic breast cancer: A SEER-based study
Authors: Liu J., Su M., Hong S., Hong G., Zheng X. & Wang S.
Outcome: 5-year disease specific survival
Variables: age, ER, grade, marital status, pN stage, pT stage, received breast conservation surgery and topography
Assumptions:

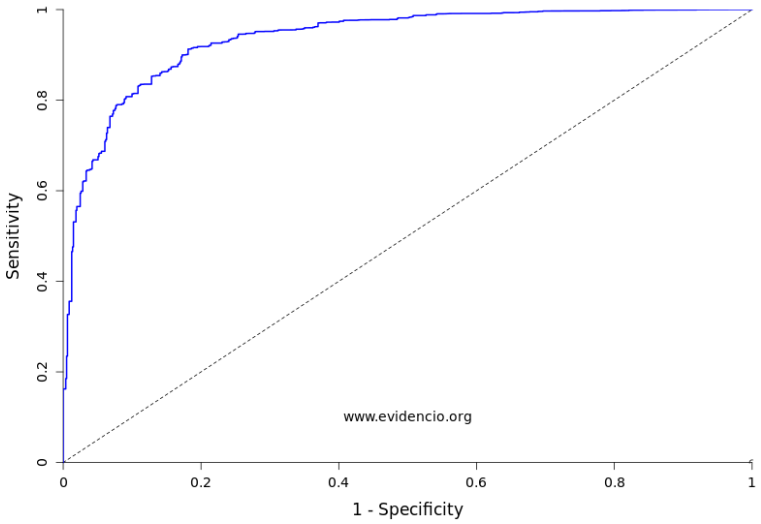
- All survivors are married, all deceased are not married
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

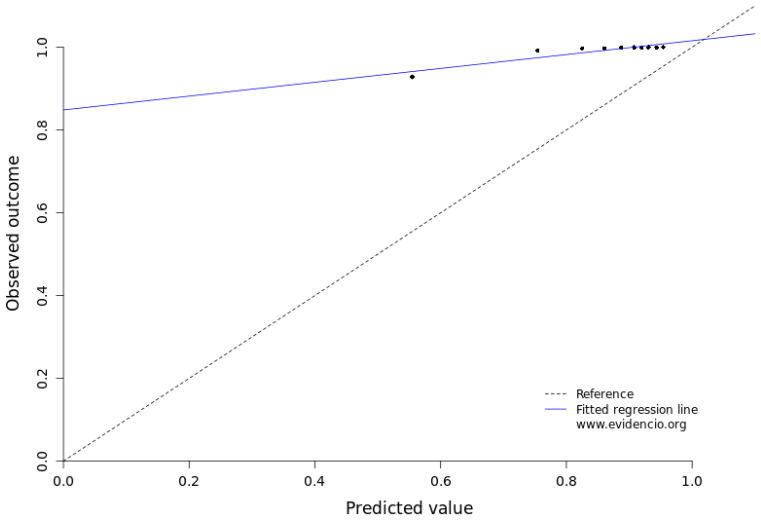
		Training set (n = 1692)		**Validation cohort (n=92478)**	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	58.0 (13.3)		58.79 (12.25)	
Marital	*Yes*	1250	73.9%	91667	99.1%
	No	442	26.1%	811	0.9%
Tumour location	*Centre/Nipple*	92	5.4%	7135	7.7%
	Upper-outer	771	45.6%	11387	12.3%
	Upper-inner	200	11.8%	36557	39.5%
	Lower-outer	138	8.2%	7608	8.2%
	Lower-inner	112	6.6%	6930	7.5%
	Overlapping lesion	379	22.4%	22861	24.7%
Grade	*Well*	290	17.1%	22952	24.8%
	Moderately	768	45.4%	42754	46.2%
	Poorly	606	35.8%	26761	28.9%
	Undifferentiated	28	1.7%	11	0.0%
pT stage	*1*	1020	60.3%	60760	65.7%
	2	462	27.3%	28853	31.2%
	3	106	6.3%	2320	2.5%
	4	104	6.1%	545	0.6%
pN stage	*0*	1091	64.5%	59981	64.9%
	1	340	20.1%	24051	26.0%
	2	167	9.9%	5624	6.1%
	3	94	5.6%	2821	3.1%
ER status	*Negative*	408	24.1%	14144	15.3%
	Positive	1284	75.9%	78334	84.7%
Breast conservation surgery	*Yes*	1219	72.0%	26	0.0%
	No	473	28.0%	92452	100.0%
5-year disease specific survival	*Yes*	Unknown		91667	99.1%
	No	Unknown		811	0.9%

Discrimination: C-index: 0.9362 | 95% CI: 0.928 - 0.9445
Calibration: Slope: 0.1672 | Intercept: 0.8485

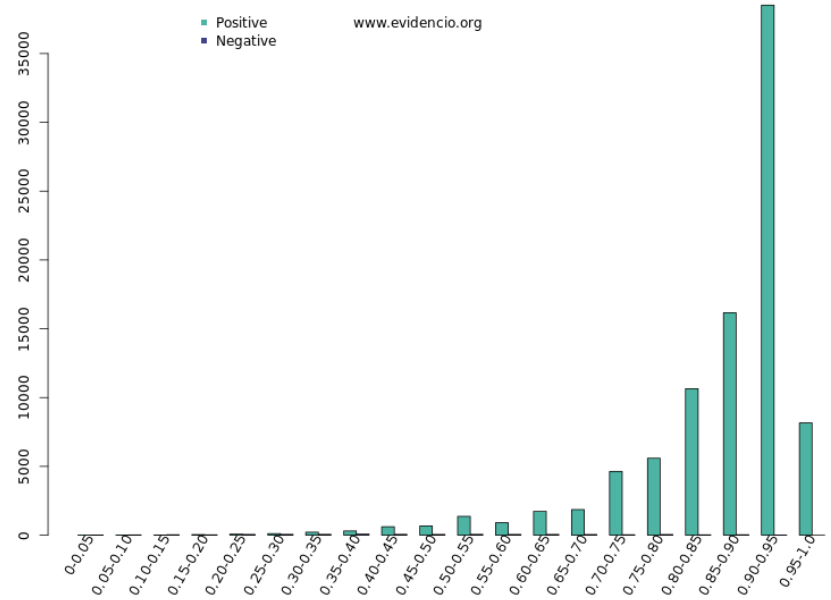
ROC plot:



Calibration plot:



Histogram:



Model Rouzier (5-year)

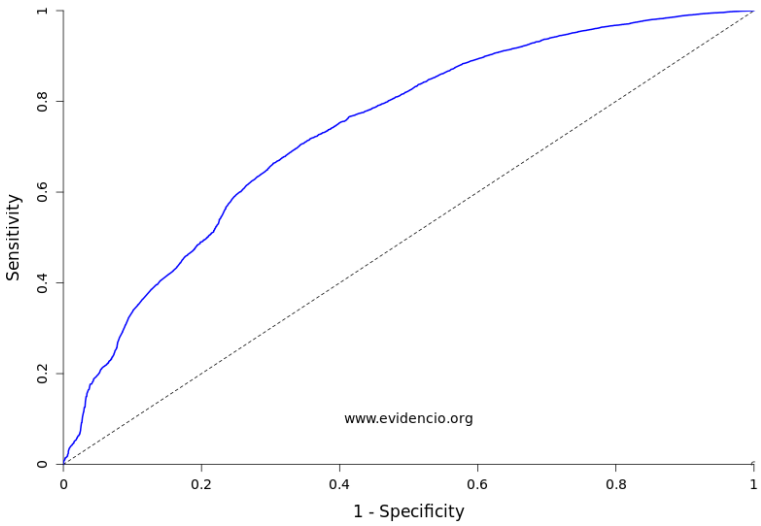
Name: Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer
Authors: Rouzier R., Pusztai L., Delaloge S., Gonzalez-Angulo A.M., Andre F., Hess K.R., Buzdar A.U., Garbay J.R., Spielmann M., Mathieu M.C., Symmans W.F., Wagner P., Atallah D., Valero V., Berry D.A. & Hortobagyi G.N.
Outcome: 5- year metastases-free survival
Variables: count of positive lymph nodes, ER, grade, morphology and tumour size

Characteristics:

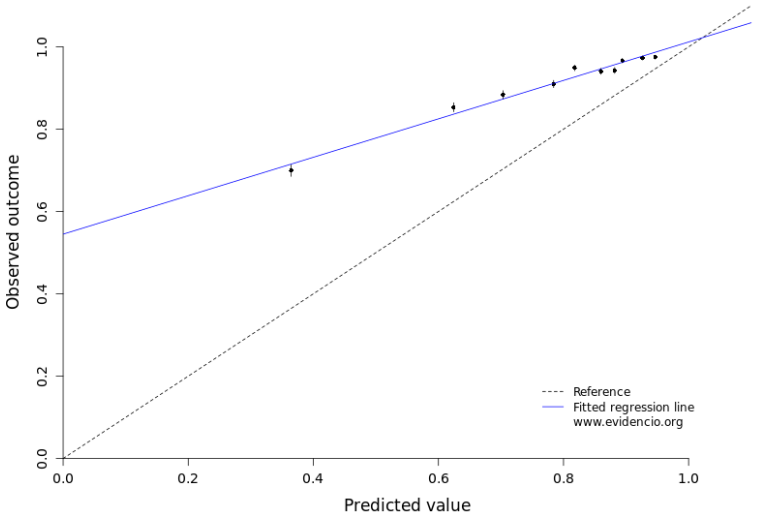
		Study cohort (n=496)		**Validation cohort (n=41253)**	
		Number	*%*	*Number*	*%*
Grade	*1*	37	6.3%	8918	21.6%
	2	282	48.3%	18671	45.3%
	3	177	30.3%	13664	33.1%
ER	*Negative*	144	24.7%	7607	18.4%
	Positive	353	60.4%	33646	81.6%
Tumour size	*Mean (SD)*	Unknown		20.13 (12.87)	
Lymph nodes	*Negative*	Unknown		24739	60.0%
	Positive	Unknown		16514	40.0%
Morphology	*Lobular*	56	9.6%	4696	11.4%
	Ductal	440	75.3%	36557	88.6%
5-year metastases free survival	*No*	Unknown		3748	9.1%
	Yes	Unknown		37505	90.9%

Discrimination: C-index: 0.7378 | 95% CI: 0.7291 - 0.7464
Calibration: Slope: 0.4669 | Intercept: 0.5451

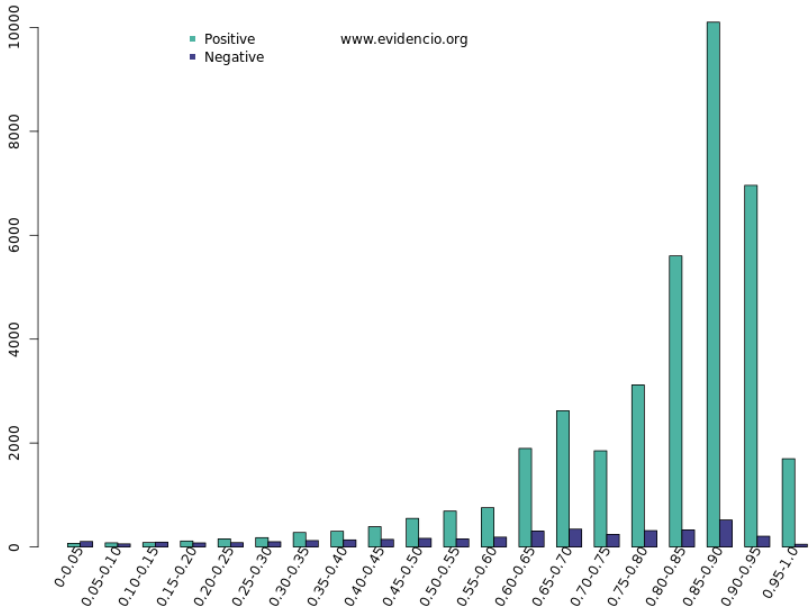
ROC plot:



Calibration plot:



Histogram:



Model Rouzier (10-year)

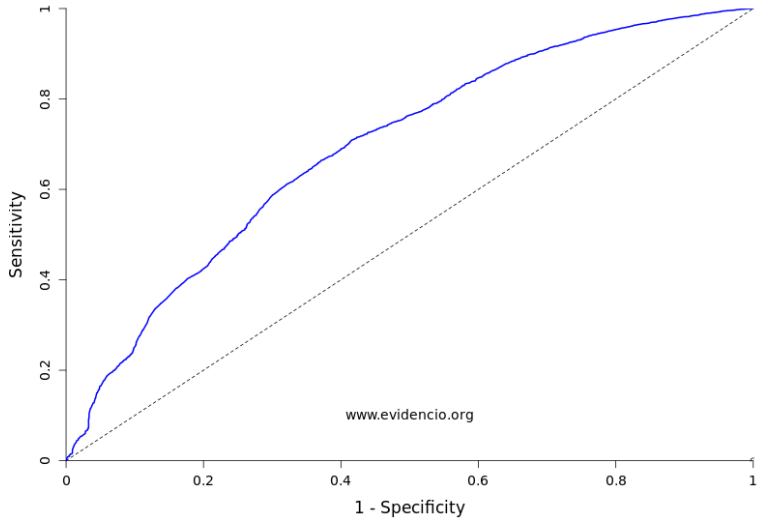
Name: Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer
Authors: Rouzier R., Pusztai L., Delaloge S., Gonzalez-Angulo A.M., Andre F., Hess K.R., Buzdar A.U., Garbay J.R., Spielmann M., Mathieu M.C., Symmans W.F., Wagner P., Atallah D., Valero V., Berry D.A. & Hortobagyi G.N.
Outcome: 10-year metastases-free survival
Variables: count of positive lymph nodes, ER, grade, morphology and tumour size

Characteristics:

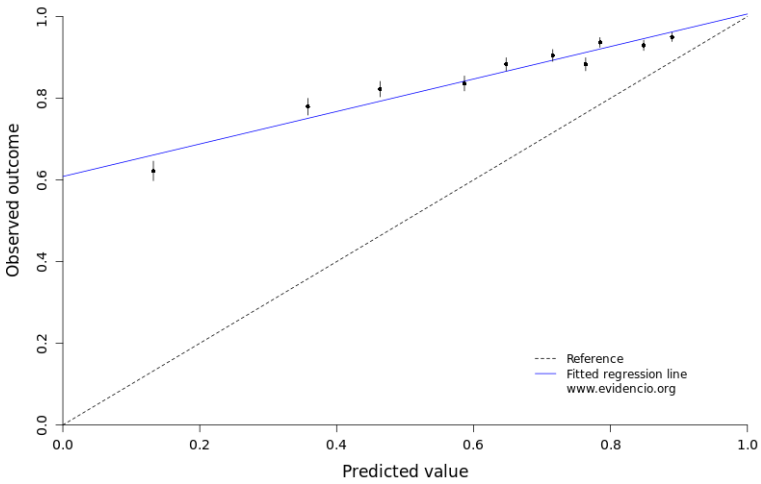
		Study cohort (n=496)		Validation cohort (n=15770)	
		Number	*%*	*Number*	*%*
Grade	*1*	37	6.3%	3307	21.0%
	2	282	48.3%	7063	44.8%
	3	177	30.3%	5400	34.2%
ER	*Negative*	144	24.7%	3022	19.2%
	Positive	353	60.4%	12748	80.8%
Tumour size	*Mean (SD)*	Unknown		20.49 (13.21)	
Lymph nodes	*Negative*	Unknown		9400	22.8%
	Positive	Unknown		6370	15.4%
Morphology	*Lobular*	56	9.6%	1762	11.2%
	Ductal	440	75.3%	14008	88.8%
10-year metastases free survival	*No*	Unknown		2293	14.5%
	Yes	Unknown		13477	85.5%

Discrimination: C-index: 0.6947 | 95% CI: 0.6828 - 0.7066
Calibration: Slope: 0.3978 | Intercept: 0.6085

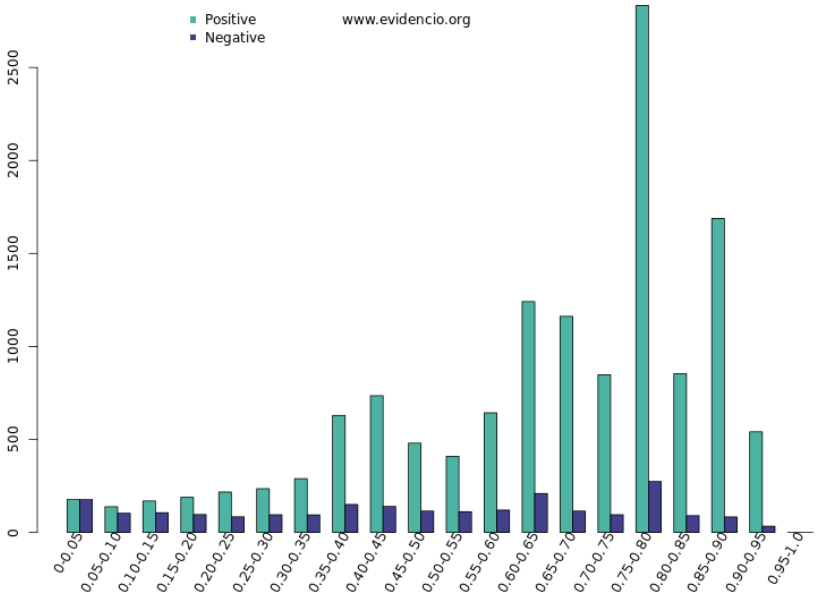
ROC plot:



Calibration plot:



Histogram:



Model Rouzier (pCR)

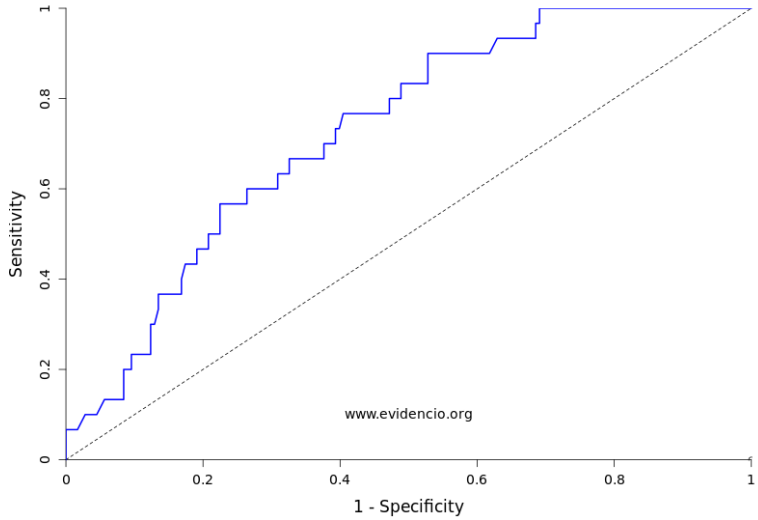
Name: Nomograms to Predict Pathologic Complete Response and Metastasis-Free Survival After Preoperative Chemotherapy for Breast Cancer
Authors: Rouzier R., Pusztai L., Delaloge S., Gonzalez-Angulo A.M., Andre F., Hess K.R., Buzdar A.U., Garbay J.R., Spielmann M., Mathieu M.C., Symmans W.F., Wagner P., Atallah D., Valero V., Berry D.A. & Hortobagyi G.N.
Outcome: Pathologic complete response
Variables: age, count of courses neo-adjuvant chemotherapy, cT stage[6], ER and grade

Characteristics:

		Training set (n=496)		Validation cohort (n=214)	
		Number	*%*	*Number*	*%*
Age	*Mean (SD)*	52 (10)		53.72 (11.36)	
cT stage	*0-1*	3	0.6%	28	13.1%
	2	293	59.1%	126	58.9%
	3	161	32.5%	40	18.7%
	4	39	7.9%	20	9.3%
Grade	*1*	37	7.5%	23	10.7%
	2	282	56.9%	87	40.7%
	3	177	35.7%	104	48.6%
ER status	*Negative*	144	29.0%	94	43.9%
	Positive	353	71.2%	120	56.1%
Number of courses	*3*	229	46.2%	67	31.3%
	4	267	53.8%	147	68.7%
Pathologic complete response	*Yes*	45	9.1%	30	14.0%
	No	451	90.9%	184	86.0%

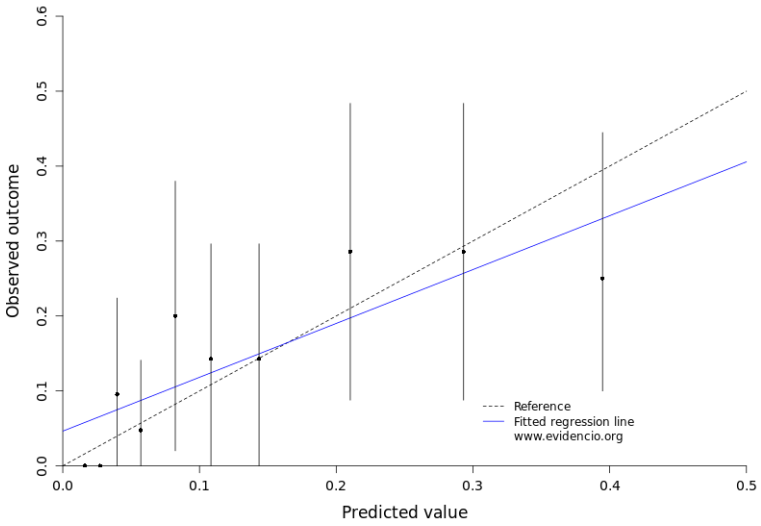
Discrimination: C-index: 0.7291 | 95% CI: 0.6443 - 0.814
Calibration: Slope: 0.7186 | Intercept: 0.0464

ROC plot:

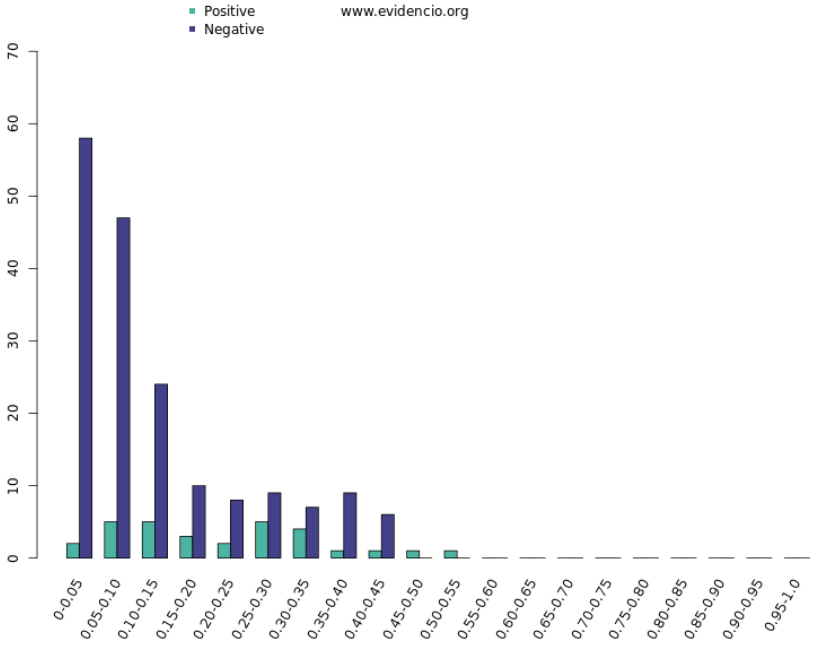


[6] Clinical Tumour stage

Calibration plot:



Histogram:



Model Vila

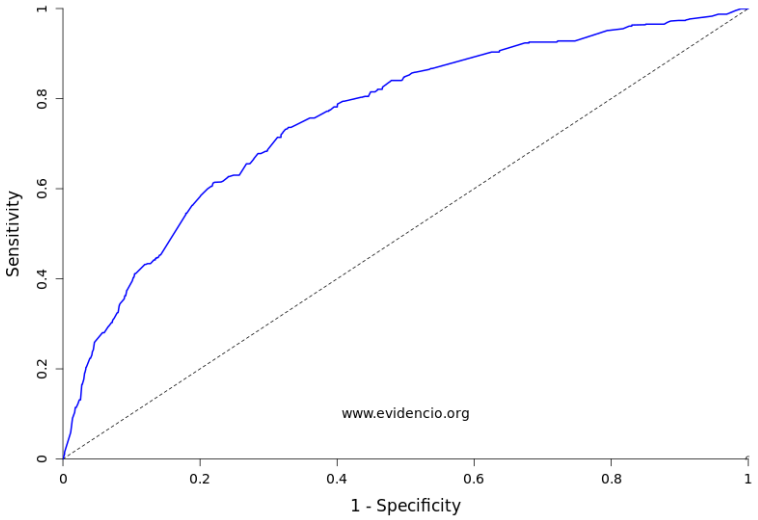
Name: Nomograms for Predicting Axillary Response to Neoadjuvant Chemotherapy in Clinically Node-Positive Patients with Breast Cancer
Authors: Vila J., Mittendorf E.A., Farante G., Bassett R.L., Veronesi P., Galimberti V., Peradze N., Stauder M.C., Chavez-MacGregor M., Litton J.F., Huo L., Kuerer H.M., Hunt K.K. & Caudle A.S.
Outcome: Axillary response to neoadjuvant chemotherapy
Variables: count of positive lymph nodes, cT stage, ER, grade, HER2. multifocal tumour, pN stage and PR

Characteristics:

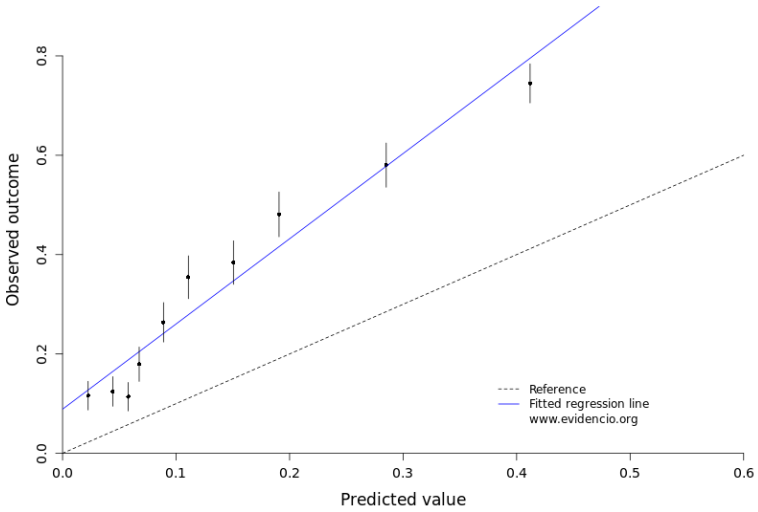
		Study cohort (n=584)		Validation cohort (n=4740)	
		Number	*%*	*Number*	*%*
cT stage	*1*	88	15.1%	697	14.7%
	2	354	60.6%	2489	52.5%
	3	100	17.1%	1082	22.8%
	4	42	7.2%	472	10.0%
Positive lymph nodes	*<4*	429	73.5%	3821	80.6%
	≥4	155	26.5%	919	19.4%
Multifocal	*No*	444	76.0%	3190	67.3%
	Yes	139	23.8%	1550	32.7%
Grade	*1*	28	4.8%	482	10.2%
	2	251	43.0%	2373	50.1%
	3	301	51.5%	1885	39.8%
HER2	*Negative*	467	80.0%	3511	74.1%
	Positive	117	20.0%	1229	25.9%
ER	*Negative*	436	74.7%	1459	30.8%
	Positive	148	25.3%	3281	69.2%
PR	*Negative*	375	64.2%	2142	45.2%
	Positive	207	35.4%	2598	54.8%
pCR	*Negative*	367	62.8%	3156	66.6%
	Positive	217	37.2%	1584	33.4%

Discrimination: C-index: 0.7577 | 95% CI: 0.7431 - 0.7723
Calibration: Slope: 1.7155 | Intercept: 0.0889

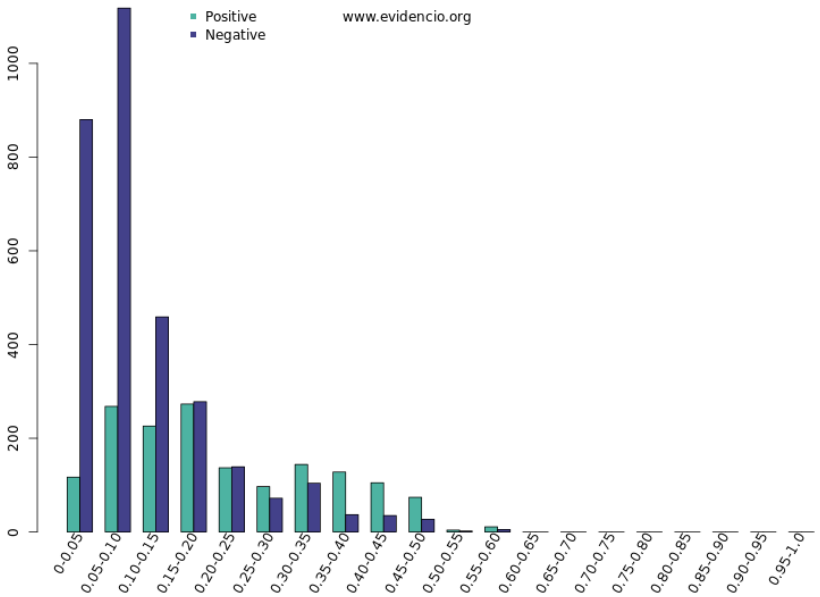
ROC plot:



Calibration plot:



Histogram:



Model Wen (2016, 5-year)

Name: Development and validation of a prognostic nomogram based on the log odds of positive lymph nodes (LODDS) for breast cancer
Authors: Wen J., Feng Y., He X., Li S., Huang X., Xiao X., & Xie X.
Outcome: 5-year disease specific survival
Variables: count of lymph nodes examined, count of positive lymph nodes, cT stage, ER, HER2. menopausal status and pN stage
Assumptions:

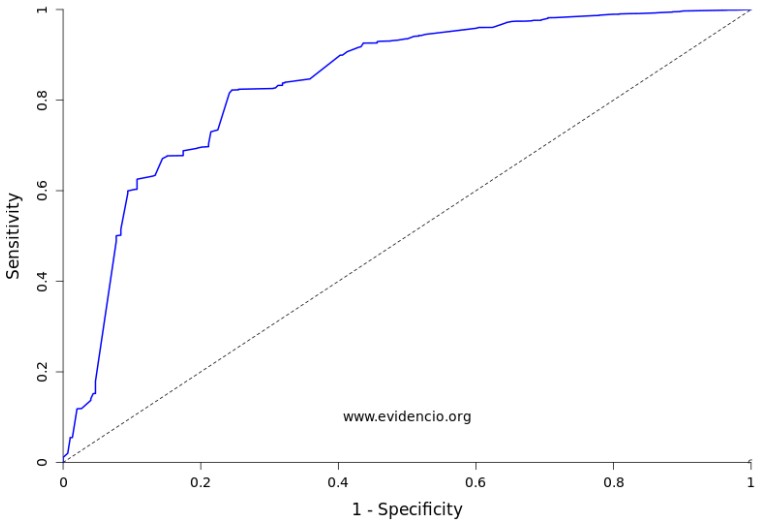
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

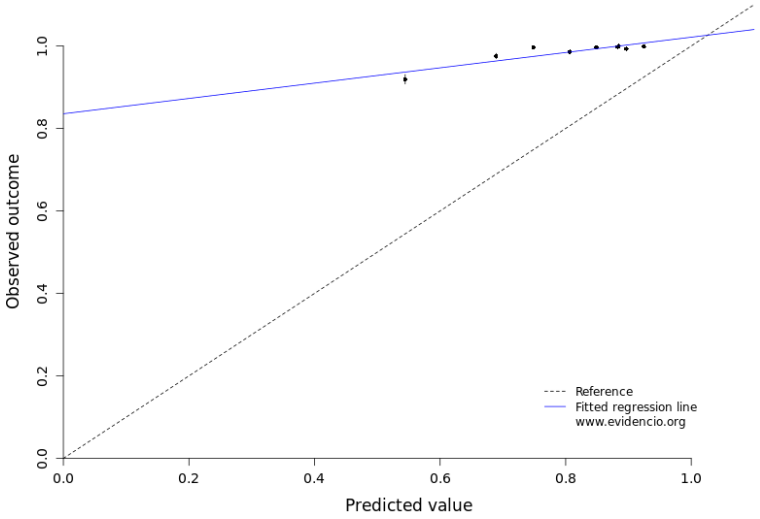
		Study cohort (n=1504)		Validation cohort (n=21671)	
		Number	*%*	*Number*	*%*
Menstrual status	*Menopause*	395	26.3%	16010	73.9%
	Premenopause	1109	73.7%	5661	26.1%
cT stage	*1*	633	42.1%	13751	63.5%
	2	793	52.7%	6967	32.1%
	3	78	5.2%	953	4.4%
pN stage	*0*	712	47.3%	13735	63.4%
	1	411	27.3%	5864	27.1%
	2	215	14.3%	1373	6.3%
	3	166	11.0%	699	3.2%
Retrieved lymph nodes	*<10*	232	15.4%	15209	70.2%
	≥10	1272	84.6%	6462	29.8%
Lymph nodes	*Negative*	Unknown		13586	62.7%
	Positive	Unknown		8085	37.3%
ER	*Negative*	554	36.8%	3324	15.3%
	Positive	950	63.2%	18347	84.7%
HER2	*Negative*	1111	73.9%	18625	85.9%
	Positive	393	26.1%	3046	14.1%
5-year disease specific survival	*Yes*	Unknown		21373	98.6%
	No	Unknown		298	1.4%

Discrimination: C-index: 0.8388 | 95% CI: 0.8132 - 0.8644
Calibration: Slope: 0.1857 | Intercept: 0.8356

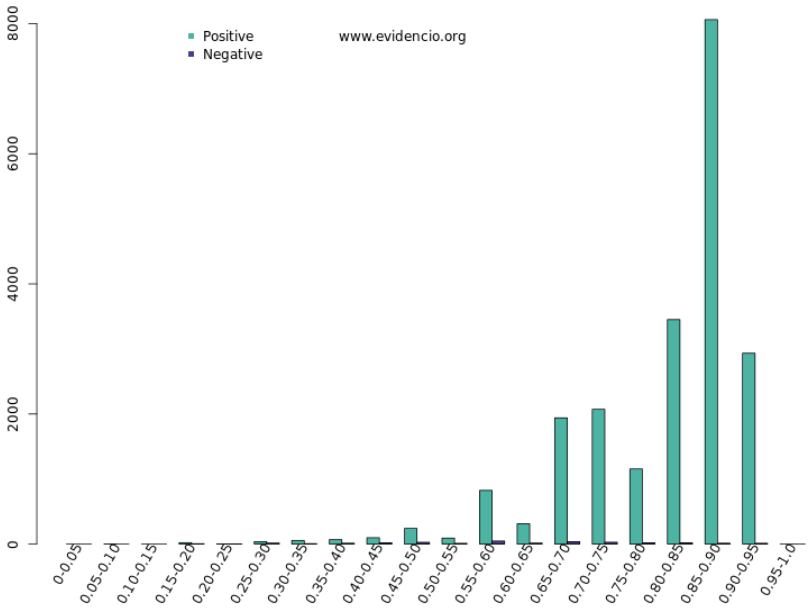
ROC plot:



Calibration plot:



Histogram:



Model Wen (2016, 10-year)

Name: Development and validation of a prognostic nomogram based on the log odds of positive lymph nodes (LODDS) for breast cancer
Authors: Wen J., Feng Y., He X., Li S., Huang X., Xiao X., & Xie X.
Outcome: 10-year disease specific survival
Variables: count of lymph nodes examined, count of positive lymph nodes, cT stage, ER, HER2. menopausal status and pN stage
Assumptions:

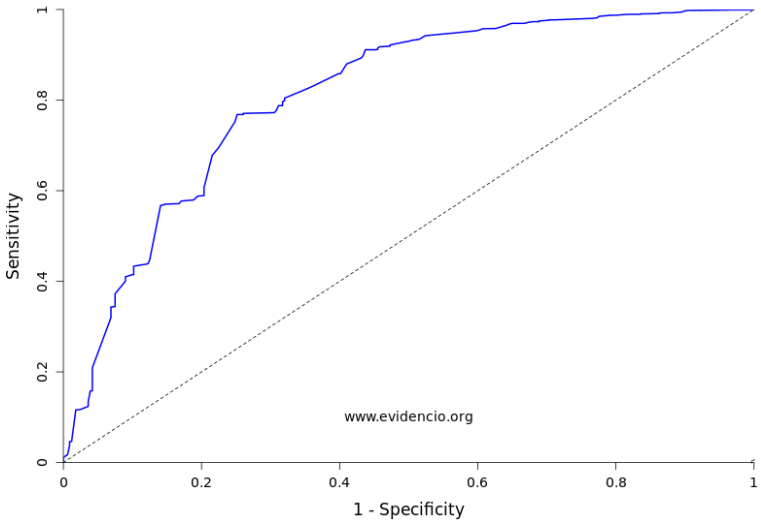
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

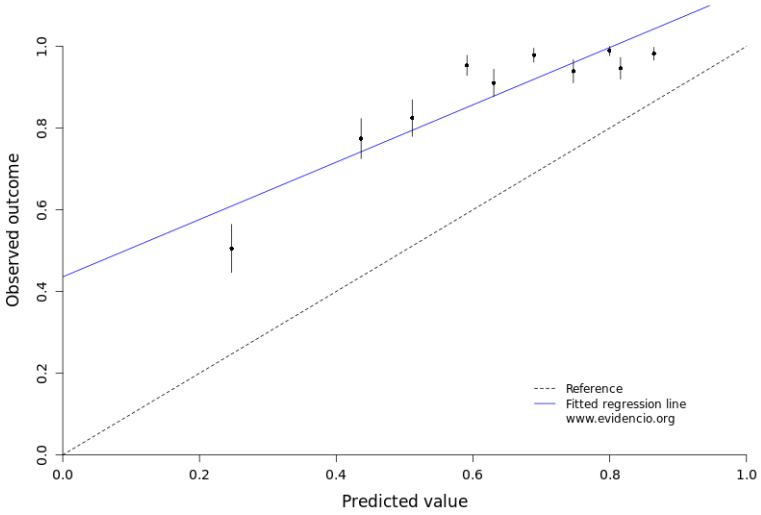
		Study cohort (n=1504)		Validation cohort (n=2789)	
		Number	*%*	*Number*	*%*
Menstrual status	*Menopause*	395	26.3%	1335	47.9%
	Premenopause	1109	73.7%	1454	52.1%
cT stage	*1*	633	42.1%	1531	54.9%
	2	793	52.7%	1084	38.9%
	3	78	5.2%	174	6.2%
pN stage	*0*	712	47.3%	1101	39.5%
	1	411	27.3%	1058	37.9%
	2	215	14.3%	392	14.1%
	3	166	11.0%	238	8.5%
Retrieved lymph nodes	*<10*	232	15.4%	1212	43.5%
	≥10	1272	84.6%	1577	56.5%
Lymph nodes	*Negative*	Unknown		1089	39.0%
	Positive	Unknown		1700	61.0%
ER	*Negative*	554	36.8%	641	23.0%
	Positive	950	63.2%	2148	77.0%
HER2	*Negative*	1111	73.9%	2065	74.0%
	Positive	393	26.1%	724	26.0%
10-year disease specific survival	*Yes*	Unknown		2455	88.0%
	No	Unknown		334	12.0%

Discrimination: C-index: 0.8098 | 95% CI: 0.7826 - 0.837
Calibration: Slope: 0.7017 | Intercept: 0.436

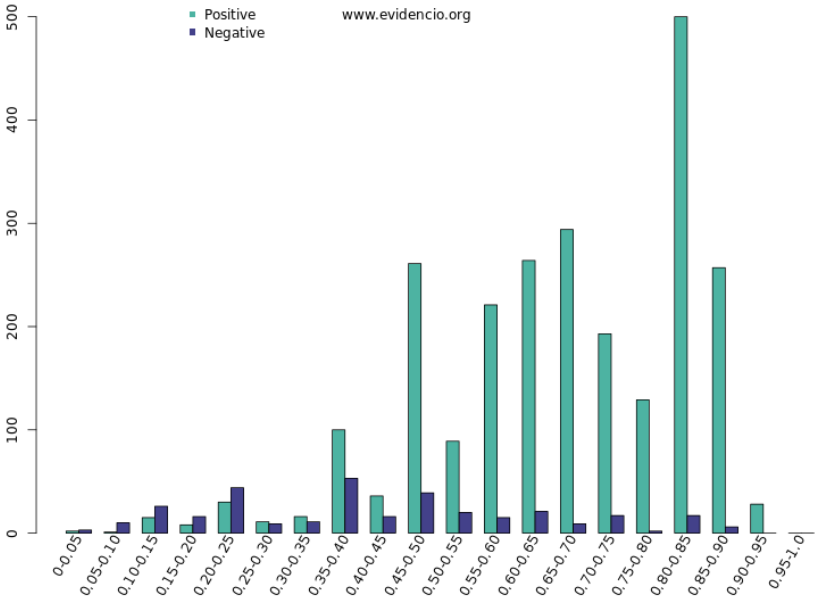
ROC plot:



Calibration plot:



Histogram:



Model Wen (2017, 5-year)

Name: Development and validation of a nomogram for predicting survival on the base of modified lymph node ration in breast cancer patients
Authors: Wen J., Yang T., Liu P., Ye P., Tang H., Huang X., Zhong S. & Xie X.
Outcome: 5-year disease specific survival
Variables: count of lymph nodes examined, count of positive lymph nodes, cT stage, ER, HER2. menopausal status and pN stage
Assumptions:

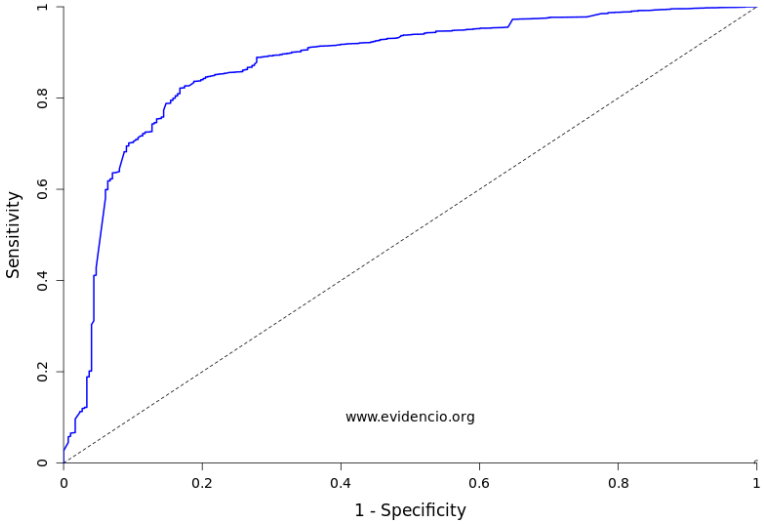
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

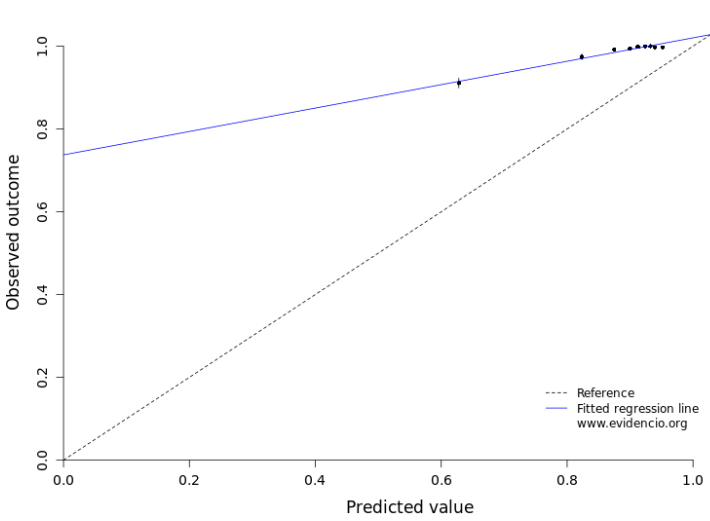
		Study cohort (n=2502)		Validation cohort (n=21671)	
		Number	*%*	*Number*	*%*
Menstrual status	*Menopause*	935	37.4%	16010	73.9%
	Premenopause	1567	62.6%	5661	26.1%
cT stage	*1*	1019	40.7%	13751	63.5%
	2	1320	52.8%	6967	32.1%
	3	163	6.5%	953	4.4%
pN stage	*0*	1290	51.6%	13735	63.4%
	1	639	25.5%	5864	27.1%
	2	324	12.9%	1373	6.3%
	3	249	10.0%	699	3.2%
ER	*Negative*	969	38.7%	3324	15.3%
	Positive	1533	61.3%	18347	84.7%
HER2	*Negative*	1901	76.0%	18625	85.9%
	Positive	602	24.1%	3046	14.1%
Retrieved lymph nodes	*<10*	236	15.7%	15209	70.2%
	≥10	2266	150.7%	6462	29.8%
Lymph nodes	*Negative*	Unknown		13586	62.7%
	Positive	Unknown		8085	37.3%
5-year disease specific survival	*Yes*	Unknown		21373	98.6%
	No	Unknown		298	1.4%

Discrimination: C-index: 0.8748 | 95% CI: 0.8529 - 0.8967
Calibration: Slope: 0.2828 | Intercept: 0.7375

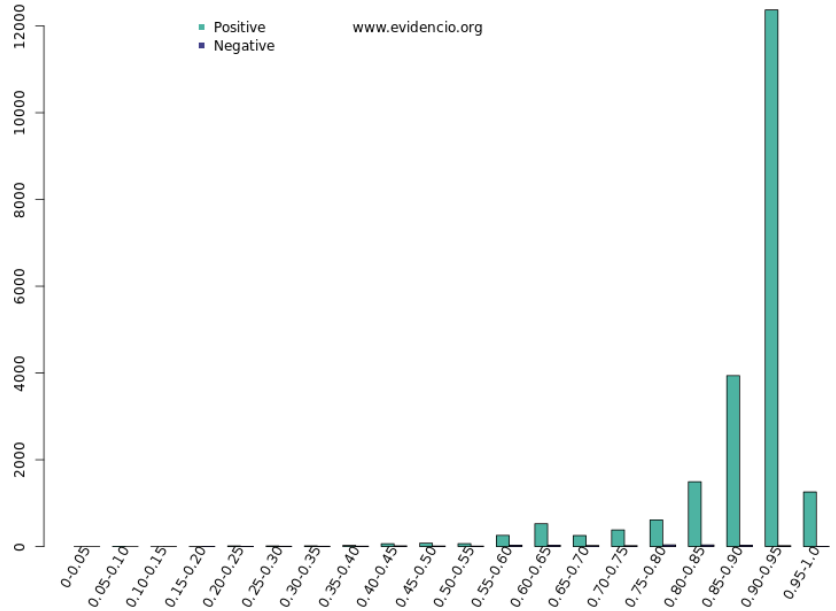
ROC plot:



Calibration plot:



Histogram:



Model Wen (2017, 10-year)

Name: Development and validation of a nomogram for predicting survival on the base of modified lymph node ration in breast cancer patients
Authors: Wen J., Yang T., Liu P., Ye P., Tang H., Huang X., Zhong S. & Xie X.
Outcome: 10-year disease specific survival
Variables: count of lymph nodes examined, count of positive lymph nodes, cT stage, ER, HER2. menopausal status and pN stage
Assumptions:

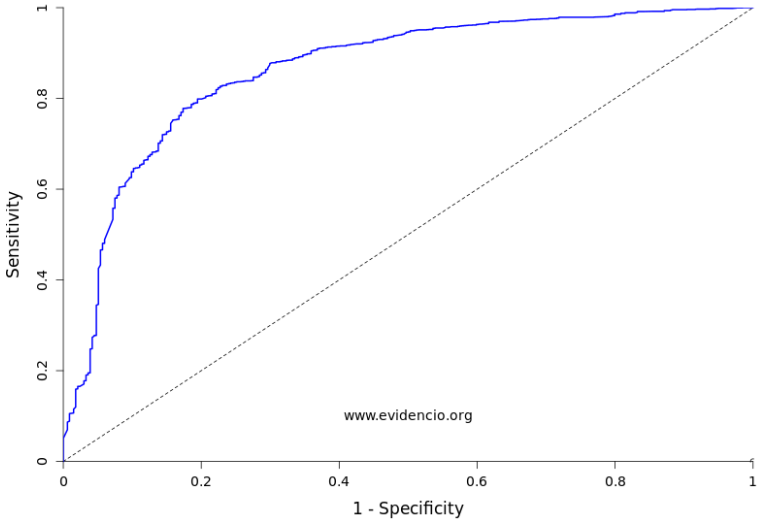
- Disease-specific death is if the patient had a metastasis and is deceased

Characteristics:

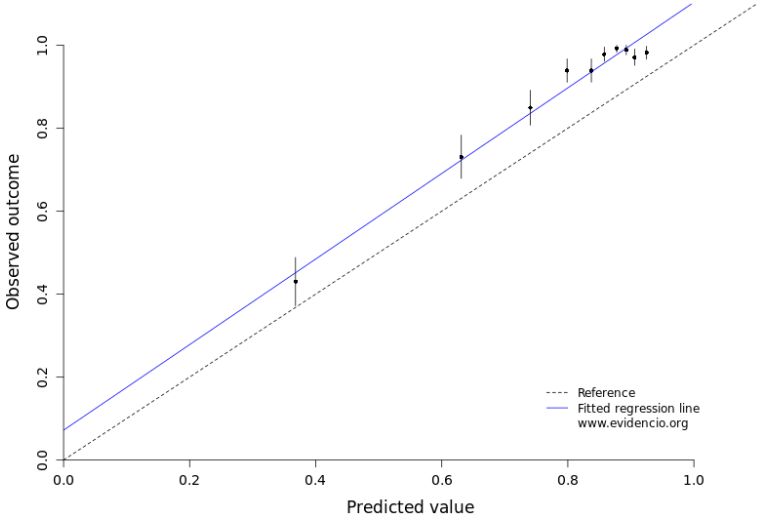
		Study cohort (n=2502)		Validation cohort (n=2789)	
		Number	*%*	*Number*	*%*
Menstrual status	*Menopause*	935	37.4%	1335	47.9%
	Premenopause	1567	62.6%	1454	52.1%
cT stage	*1*	1019	40.7%	1531	54.9%
	2	1320	52.8%	1084	38.9%
	3	163	6.5%	174	6.2%
pN stage	*0*	1290	51.6%	1101	39.5%
	1	639	25.5%	1058	37.9%
	2	324	12.9%	392	14.1%
	3	249	10.0%	238	8.5%
ER	*Negative*	969	38.7%	641	23.0%
	Positive	1533	61.3%	2148	77.0%
HER2	*Negative*	1901	76.0%	2065	74.0%
	Positive	602	24.1%	724	26.0%
Retrieved lymph nodes	*<10*	236	15.7%	1212	43.5%
	≥10	2266	150.7%	1577	56.5%
Lymph nodes	*Negative*	Unknown		1089	39.0%
	Positive	Unknown		1700	61.0%
10-year disease specific survival	*Yes*	Unknown		2455	88.0%
	No	Unknown		334	12.0%

Discrimination: C-index: 0.8632 | 95% CI: 0.8408 - 0.8856
Calibration: Slope: 1.0316 | Intercept: 0.072

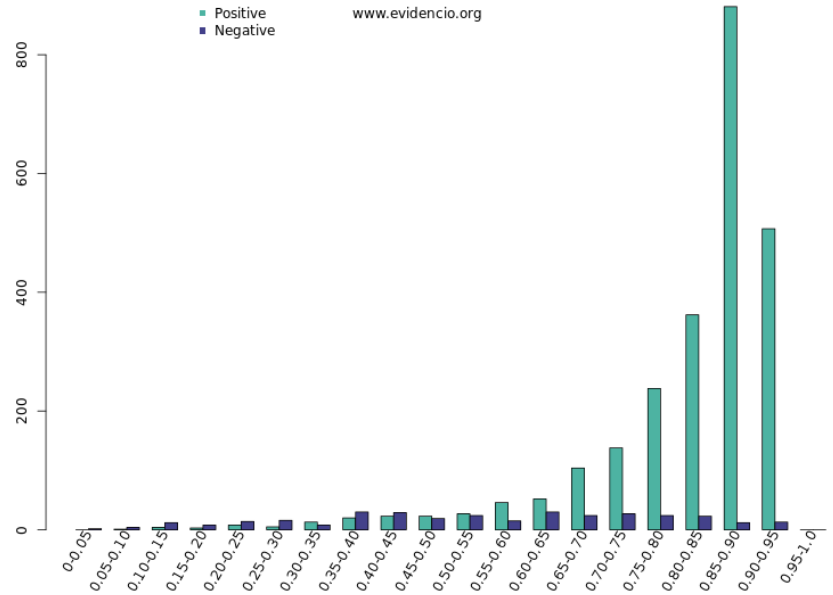
ROC plot:



Calibration plot:



Histogram:



Model Werkhoven

Name: Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial
Authors: Werkhoven E. van, Hart G., Tinteren H. van, Elkhuizen P., Collette L., Poortmans P. & Bartelink H.
Outcome: 10- year proportion IBR-free
Variables: age, boost, chemotherapy, DCIS[7], grade, tamoxifen and tumour size
Particularities: No patients with DCIS

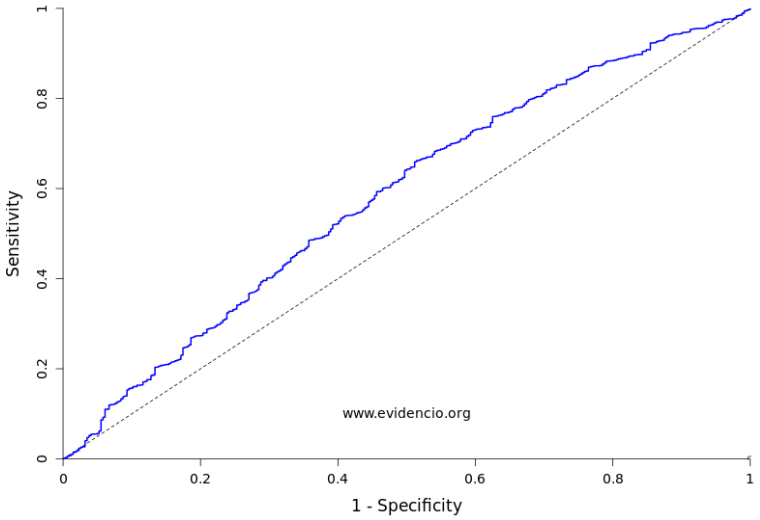
Characteristics:

		Study cohort (n=1603)		Validation cohort (n=5722)	
		Number	*%*	*Number*	*%*
Tumour size	*Mean (SD)*	Unknown		19.96 (13.75)	
Age	*Mean (SD)*	Unknown		56.31 (11.70)	
	≤50	622	38.8%	1946	34.0%
	>50	981	61.2%	3776	66.0%
Tamoxifen	*Yes*	369	23.0%	3794	66.3%
	No	1234	77.0%	1929	33.7%
Chemotherapy	*Yes*	252	15.7%	187	3.3%
	No	1351	84.3%	5536	96.7%
Boost	*Yes*	808	50.4%	3714	64.9%
	No	795	49.6%	2009	35.1%
DCIS	*Yes*	905	56.5%	0	0.0%
	No	660	41.2%	5722	100.0%
	Missing	38	2.4%	0	0.0%
Grade	*1*	778	48.5%	1350	23.6%
	2	392	24.5%	2432	42.5%
	3	359	22.4%	1940	33.9%
	Missing	74	4.6%	0	0.0%
Ipsilateral breast relapse	*Negative*	1012	63.1%	5340	93.3%
	Positive	120	7.5%	382	6.7%
	Censored	471	29.4%	0	0.0%

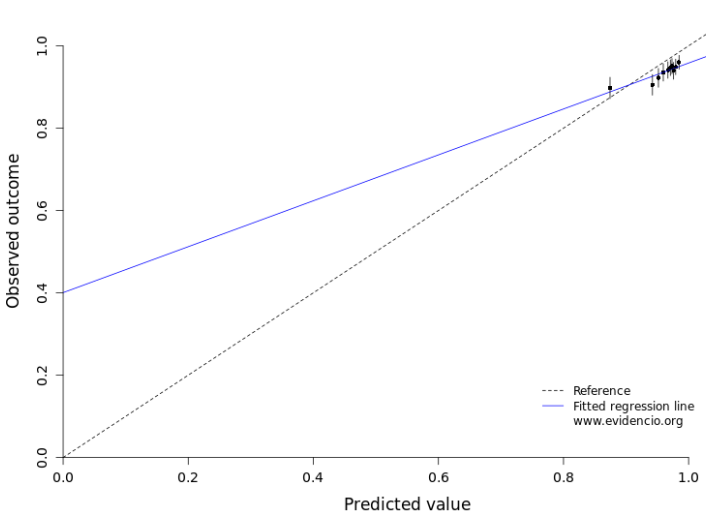
Discrimination: C-index: 0.5844 | 95% CI: 0.5524 - 0.6163
Calibration: Slope: 0.5577 | Intercept: 0.4006

[7] Ductal Carcinoma in Situ

ROC plot:



Calibration plot:



Histogram: