An original approach to evaluate the prognostic marker capacity using published survival curves

E. Dantan, C. Combescure, M. Lorent, J. Ashton-Chess, P. Daguin, JM. Classe, M. Giral & Y. Foucher

(Etienne.Dantan@univ-nantes.fr)

EA4275 Biostatistique, Pharmacoépidémiologie et Mesures Subjectives en Santé, Université de Nantes

3 Juin 2014

Context

- **Predicting health events** : a real challenge to improve long-term medical management of patients affected by chronic disease

- **Identification of prognostic markers/scores** : to early stratify patients according to their risk for future event

  - Adaptation of the therapy
  - Adaptation of the follow-up frequency
  - Information for patients, etc.

  $\Rightarrow$ Personalized medicine

- **In many medical papers**, lack of appropriate methodology to justify prognostic marker abilities

2 widespread confusions in medical papers

Usual statistical analysis to demonstrate a predictor

- Log-Rank statistic (small p-value)
- Kaplan-Meier estimator (high distance between survival curves)
- Cox model (high value of hazard ratio)

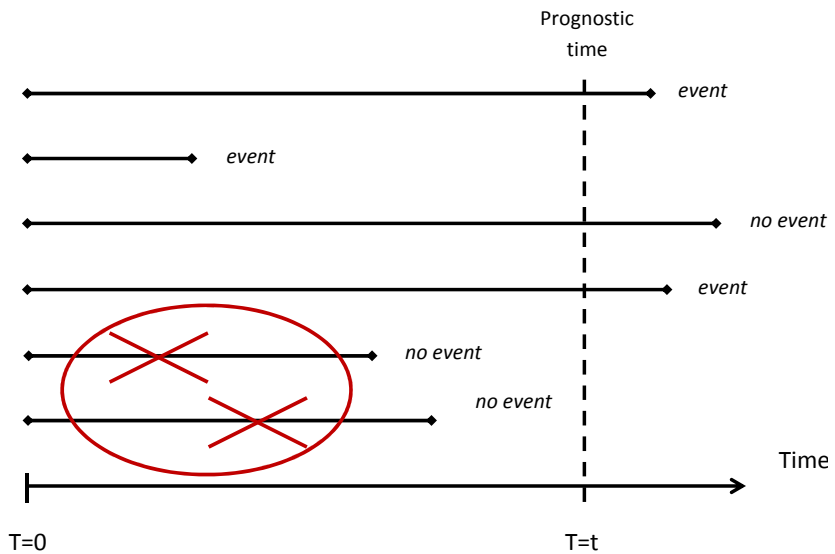
$\Rightarrow$ **Confusion between correlation and prediction**
A marker can be significantly correlated but poorly predictive

In practice, right censored patients often excluded

To calculate :

- Sensitivity $P(HR|D = 1)$
- Specificity $P(LR|D = 0)$
- ROC curve

$\Rightarrow$ **Confusion between diagnosis and prognosis**
Major selection bias



Objective

- To propose a simple tool for a better lecture of clinical research papers

  → to correctly interpret prognostic marker capacity

- using time-dependent sensitivity and specificity [1] and predictive values

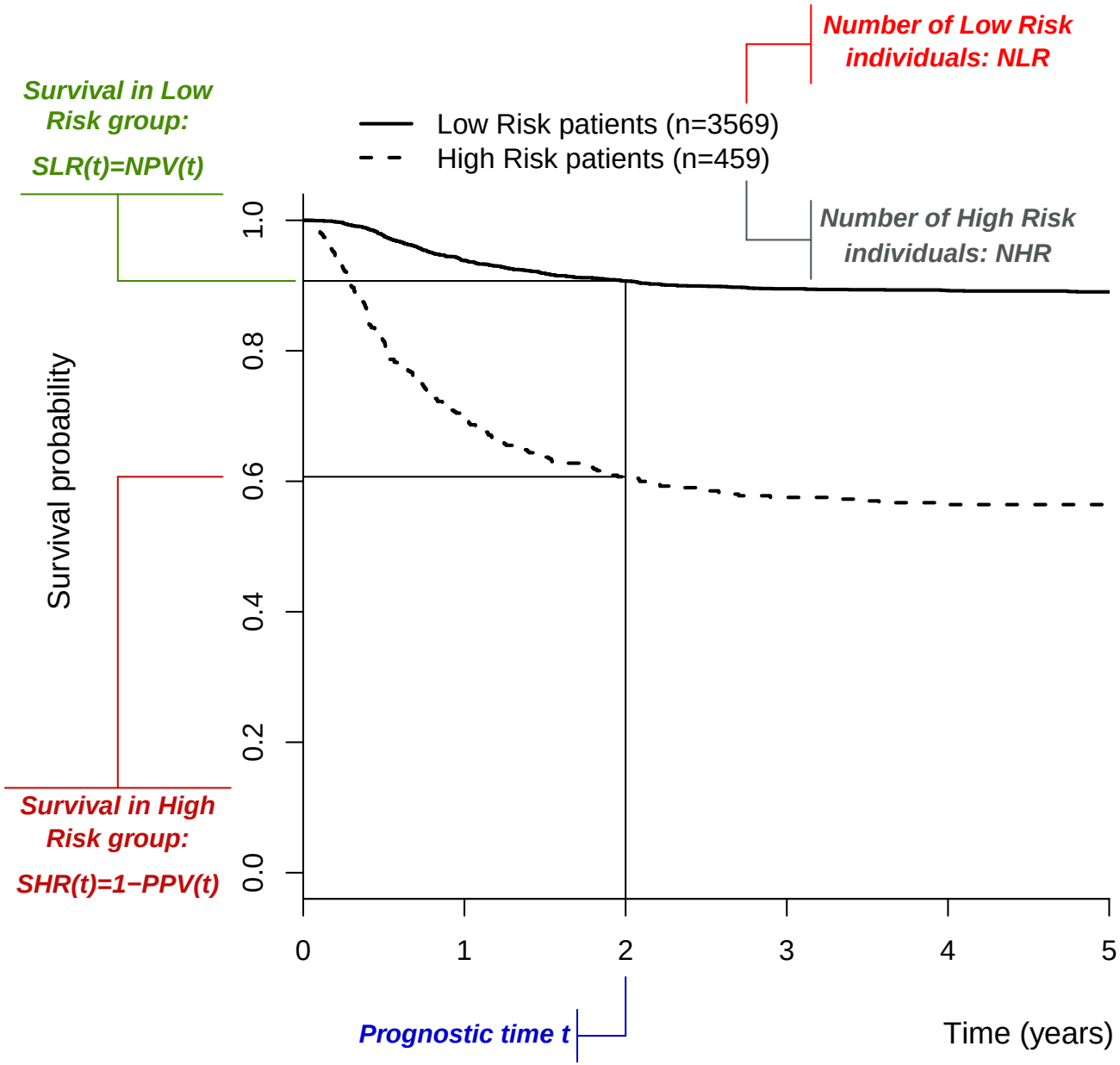
  → to correctly evaluate prognostic marker capacity

- from several published examples

  → based on survival curves

1. (Heagerty, 2000)

Available information in most of published papers



Time-dependent sensitivity and specificity

Time-dependent sensitivity

Proportion of patients who are correctly classified as HR among all the patients who experience event before time t

$$Se(t) = P(HR|D(t) = 1) = \frac{(1 - SHR(t)).NHR}{(1 - SHR(t)).NHR + (1 - SLR(t)).NLR}$$

Time-dependent specificity

Proportion of patients who are correctly classified as LR among all the patients who do not experience the event before time t

$$Sp(t) = P(LR|D(t) = 0) = \frac{SLR(t).NLR}{SHR(t).NHR + SLR(t).NLR}$$

with $D(t) = \mathbb{1}_{T^* < t}$, T^* event time

Time-dependent predictive values

Time-dependent positive predictive value

Proportion of HR patients who experience event before prognosis time t

$$PPV(t) = P(D(t) = 1|HR) = 1 - P(D(t) = 0|HR) = 1 - SHR(t)$$
$$= \frac{Se(t).P(D(t) = 1)}{Se(t).P(D(t) = 1) + (1 - Sp(t)) . (1 - P(D(t) = 1))}$$

Time-dependent negative predictive value

Proportion of LR patients who do not experience event before prognosis time t

$$NPV(t) = P(D(t) = 0|LR) = SLR(t)$$
$$= \frac{Sp(t) * (1 - P(D(t) = 1))}{Sp(t) * (1 - P(D(t) = 1)) + (1 - Se(t)) * P(D(t) = 1)}$$

$$P(D(t) = 1) = 1 - \frac{SHR(t) * NHR + SLR(t) * NLR}{NHR + NLR}$$

Metastatic potential of T1 breast cancer can be predicted by the 70-gene Mammaprint signature (Mook, *Ann Surg Oncol.*, 2010)

ABSTRACT

Background. Mammographic screening and increased awareness has led to an increase in the detection of T1 breast tumors that are generally estimated as having low risk of recurrence after locoregional treatment. However, even small tumors can metastasize, which leaves us with the question for the necessity of adjuvant treatment. Therefore, additional prognostic markers are needed to tailor adjuvant systemic treatment for these relatively low-risk patients. The aim of our study was to evaluate the accuracy of the 70-gene MammaPrint signature in T1 breast cancer.

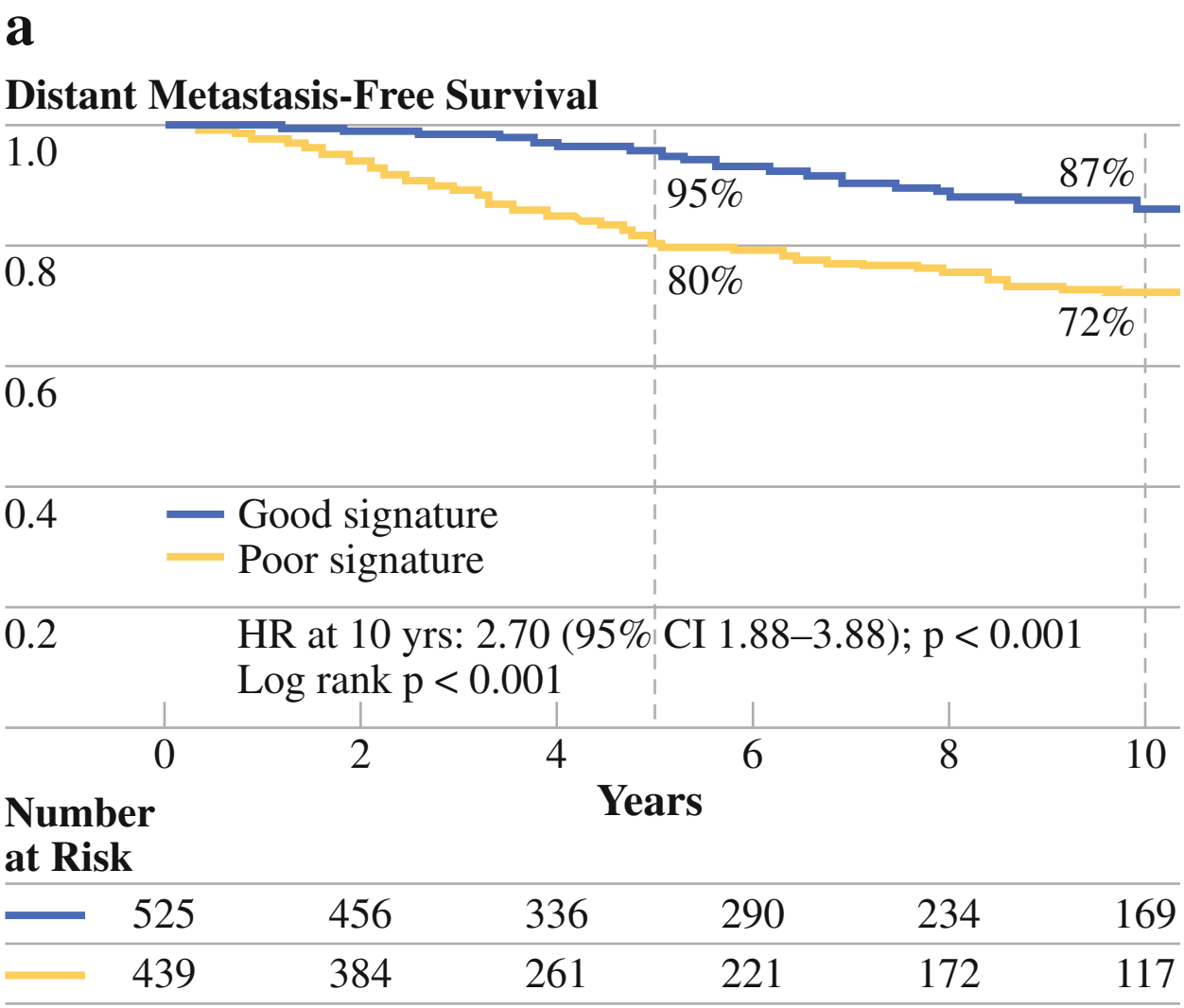
Materials and Methods. We selected 964 patients from previously reported studies with pT1 tumors (≤2 cm). Frozen tumor samples were hybridized on the 70-gene signature array at the time of the initial study and classified as having good prognosis or poor prognosis.

Results. The median follow-up was 7.1 years (range 0.2–25.2). The 10-year distant metastasis-free (DMFS) and breast cancer specific survival (BCSS) probabilities were 87% (SE 2%) and 91% (SE 2%), respectively, for the good prognosis-signature group ($n = 525$), and 72% (SE 3%) and 72% (SE 3%), respectively, for the poor prognosis-signature group ($n = 439$). The signature was an independent prognostic factor for BCSS at 10 years (multivariate hazard ratio [HR] 3.25 [95% confidence interval, CI, 1.92–5.51; $P < .001$]). Moreover, the 70-gene MammaPrint signature predicted DMFS at 10 years for 139 patients with pT1ab cancers (HR 3.45 [95% CI 1.04–11.50, $P = .04$]).

Conclusions. The 70-gene MammaPrint signature is an independent prognostic factor in patients with pT1 tumors and can help to individualize adjuvant treatment recommendation in this increasing breast cancer population.

Primary tumor size, in addition to axillary lymph node status, is considered to be one of the most important prognostic factors in breast cancer, with small tumor size being an indicator of good prognosis.[1–5] However, even small tumors can metastasize, suggesting that the ability to metastasize is an early and inherent genetic property.[6,7] Adjuvant treatment decisions based on tumor size alone are only moderately accurate and could result in undertreatment of T1ab and overtreatment of T1c tumors. The need for adjuvant systemic therapy after locoregional therapy for patients with small tumors is unresolved.[8,9] Currently used

Metastatic potential of T1 breast cancer can be predicted by the 70-gene Mammaprint signature (Mook, *Ann Surg Oncol.*, 2010)



Prognostic biomarker abilities at 5 years
(Mook, *Ann Surg Oncol.*, 2010)

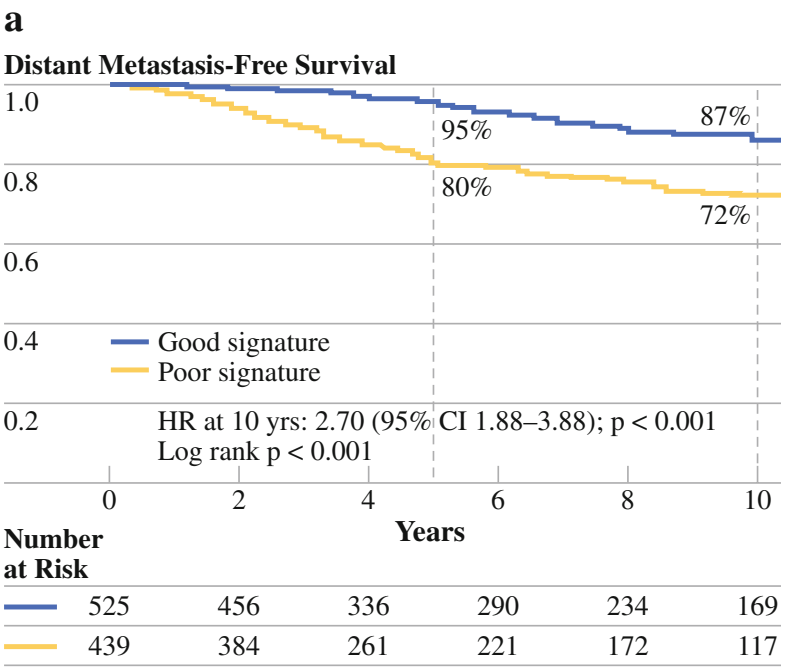
Parameters	Values
Sensitivity	77 %
Specifity	58.7 %

At $t = 5$ years, prognostic biomarker abilities can lead to the following error rates :

$\Rightarrow$ among the patients who should suffer the event, $P(LR|D(t) = 1) = 23\%$ may be incorrectly classified as low risk.

$\Rightarrow$ among the patients who should not suffer the event, $P(HR|D(t) = 0) = 41.3\%$ may be incorrectly classified as high risk.

Prognostic biomarker abilities for 11.8% of events at 5 years
(Mook, *Ann Surg Oncol.*, 2010)



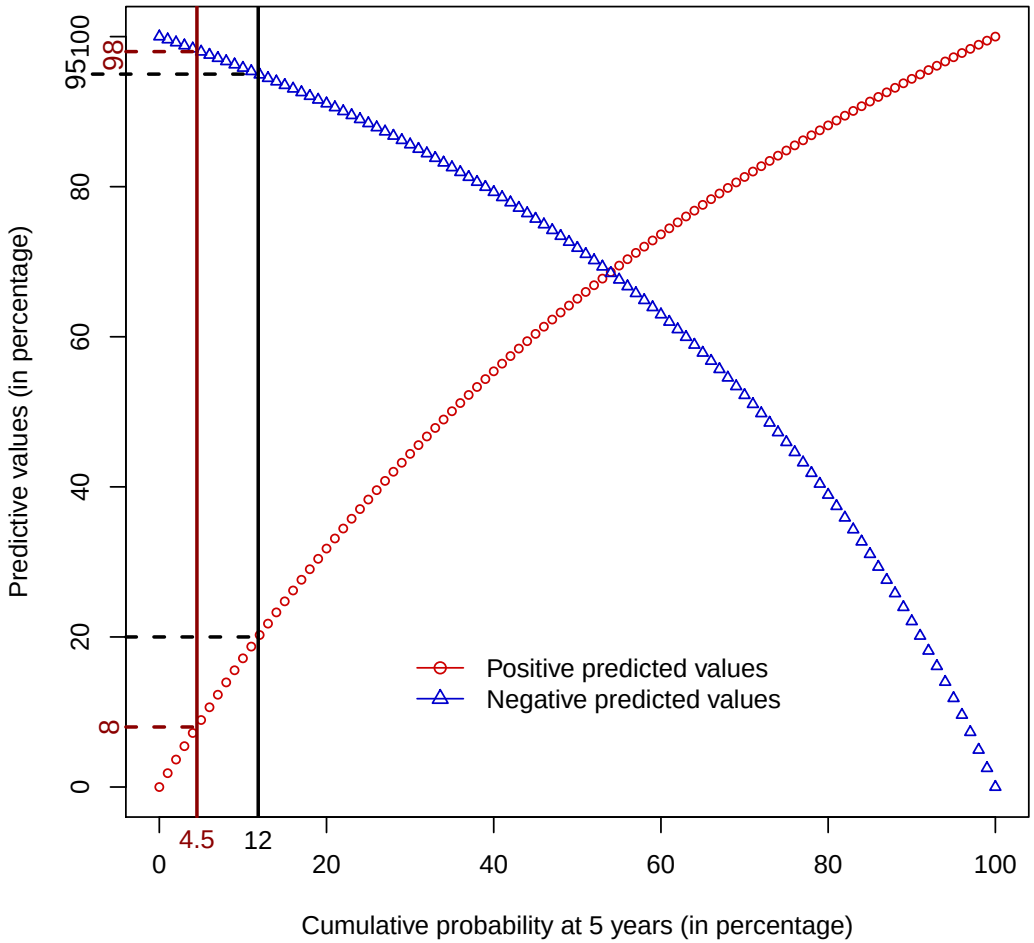
Parameters	Values
Positive predicted value	20 %
Negative predicted value	95 %

With 11.8% of events before 5 years, i.e. $P(D(5) = 1) = 11.8\%$, one can expect that the following error rates :

$\Rightarrow$ HR-classified patients have $P(D(t) = 0|HR) = 80\%$ of risk to not suffer the event.

$\Rightarrow$ LR-classified patients have $P(D(t) = 1|LR) = 5\%$ of risk to suffer the event.

Expected predicted values (in %) according to the population frailty



In France, $P(D(5) = 1) = 4.5\%$ [2]

$\Rightarrow PPV(5) = 8\%$ et $NPV(5) = 98\%$

2. (Data from BERENIS cohort, ICO, Nantes)

Conclusion

- In a prognostic context, time-dependent indicators calculated from published survival curves

  $\Rightarrow$ helps to improve the accuracy of interpretations

- Online calculator available at

  http ://www.divat.fr/en/online-calculators/evalbiom

- Dantan et al. (*JCE*, 2014) introduce :
  - Time-dependent likelihood ratios
  - Time-dependent post-test probability ratio

Time-dependent likelihood ratios

- Well-known indicators in diagnostic context $\Rightarrow$ in prognostic :

Time-dependent positive likelihood ratio

$$LikR^{+}(t) = \frac{P(HR|D(t)=1)}{P(HR|D(t)=0)} = \frac{Se(t)}{1-Sp(t)}$$

Time-dependent negative likelihood ratio

$$LikR^{-}(t) = \frac{P(LR|D(t)=1)}{P(LR|D(t)=0)} = \frac{1-Se(t)}{Sp(t)}$$

- High $LikR^{+}(t) \Rightarrow$ HR group probability associated with the occurrence of the event before time t
- Low $LikR^{-}(t) \Rightarrow$ LR group probability associated with the absence of the event before time t

Time-dependent post-test probability ratios

Time-dependent positive post-test probability ratio

$$PT^{+}(t) = \frac{P(D(t)=1|HR)}{P(D(t)=0|HR)} = \frac{P(D(t)=1)}{P(D(t)=0)} LikR^{+}(t)$$

Time-dependent negative post-test probability ratio

$$PT^{-}(t) = \frac{P(D(t)=1|LR)}{P(D(t)=0|LR)} = \frac{P(D(t)=1)}{P(D(t)=0)} LikR^{-}(t)$$

- Multiplicative coefficient between pre-test probability ratio and post-test probability ratio

$\Rightarrow$ A HR patient has a $PT^{+}(t)$ times greater risk of presenting the event before time t than after t

$\Rightarrow$ A LR patient has a $\frac{1}{PT^{-}(t)}$ times greater risk of presenting the event after time t than before t

Conclusion

- Sensitivity and Specificity (and Likelihood Ratio) :
  - intrinsic quality of the marker
  - independent to probability of survival event

$\Rightarrow$ Robust indicators

- PPV and NPV (and Post-test probability ratios) :
  - attractive indicators regarding the clinical interpretation and the marker-based decision making
  - depends on the population frailty

$\Rightarrow$ Leading to wrong therapeutic decisions, if the cumulative probability of the event differs from the initial one

Conclusion

- Proposed approach : *a posteriori* evaluation of prognostic ability when inadequate/incomplete methodology in published paper

$\Rightarrow$ Better to evaluate *a priori* prognostic ability from individual data :

  - time-dependent sensitivity and specificity from Heagerty et al.
  - time-dependent ROC curves
  - etc.

References

Dantan E, Combescure C, Lorent M, Ashton-Chess J, Daguin P, Classe JM, Giral M and Foucher Y. An original approach was used to better evaluate the capacity of a prognostic marker using published survival curves. *Journal of Clinical Epidemiology*. 2014 ;67(4) :441-8.

Foucher Y, Combescure C, Ashton-Chess J, Giral M. Prognostic markers : data misinterpretation often leads to overoptimistic conclusions. *Am. J. Transplant.* 2012 ;12(4) :1060-1.

Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics.* 2001 ;56(2) :337-44.

Mook S, Knauer M, Bueno-de-Mesquita JM, et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. *Ann Surg Oncol.* 2010 ;17 :1406-13.

Thanks for your attention