PSA density versus PSA as a selection biomarker before MRI for prostate cancer screening

A secondary analysis of the paired, screen-positive STHLM3-MRI trial

Andrea Discacciati*

2025-05-14

This document contains additional information on the secondary analysis in the manuscript entitled "*PSA density as a selection tool before MRI in prostate cancer screening: an analysis from the STHLM3-MRI randomized clinical trial*" (Björnebo et al., 2025). For more information on the STHLM3-MRI trial, see Nordström et al. (2021).

1 Notation and aim

Define the following events:

1. A: PSA$\geq$ 3 ng/ml;
2. $B(x)$: PSAd $> x$ ng/ml^2. This event depends on the PSAd cut-off $x > 0$;
3. C_i $(i = 1, ..., 7)$: positive *outcome*, where *outcome* refers to any of the 7 outcomes considered: {elevated PSA or PSAd, performed MRI scan, performed biopsy, benign biopsy, ISUP1, ISUP2+, ISUP3+}.

A bar above an event denotes its complement (e.g. $\bar{A}$).

The aim is to use **parametric models** to model the following target quantities:

1. The detection probability $P(A, B(x), C_i)$;
2. The Relative Positive Fraction $\text{RPF}_i(x) = \frac{P(A,B(x)|C_i)}{P(A|C_i)}$.

2 Identifiability

We expand $P(A, B(x), C_i)$ as the product of two probabilities:

$$P(A, B(x), C_i) = P(B(x)|A, C_i)P(A, C_i). \tag{1}$$

The probabilities $P(A, B(x), C_i)$ and $P(A, C_i)$ are identifiable in a study with a screen-positive design, such as the STHLM3-MRI trial (cfr. *detection probabilities*, Section 7.2.2,

*Karolinska Institutet, Stockholm, Sweden

in Pepe, 2003). $P(B(x)|A, C_i)$ is also identifiable, because of the conditioning on A. Table 1 will provide more intuition, if needed.

Table 1: Contingency table for a paired screen-positive study. Frequencies between brackets are not observed due to the screen-positive study design; $a + b + ... + h = N$.

	C_i			$\bar{C}_i$	
	A	$\bar{A}$		A	$\bar{A}$
$B(x)$	a	b	$B(x)$	e	f
$\bar{B}(x)$	c	$[d]$	$\bar{B}(x)$	g	$[h]$

3 Modelling

$P(A, C_i)$ is the probability of having PSA$\geq$ 3 ng/ml and positive outcome i. It is estimated as the ratio between the number of men satisfying the joint condition (A, C_i) and N. No modelling is required.

$P(B(x)|A, C_i)$ are probabilities from the survival function for PSAd, given PSA$\geq$ 3 ng/ml and positive outcome i: $P(B(x)|A, C_i) = P(\text{PSAd} > x|A, C_i) = S(x|A, C_i)$. This survival function can be modelled using parametric models. In particular, we propose to use flexible parametric models:

$$g(S(x|A, C_i)) = s(\ln x; \alpha),$$

where $g(S)$ is a suitable link function and $s(\ln x; \alpha)$ a flexible function having adjustable parameter vector α (e.g. natural splines) (Royston and Parmar, 2002; Liu et al., 2018; Bottai et al., 2021).

We now contrast the probabilities $P(A, B(x)|C_i)$ and $P(A|C_i)$ by taking their ratio. We refer to this ratio as the RPF, which generalises the relative true- and false-positive fractions for > 2 health or disease states (Karlsson et al., 2021)[1]. The RPF can be simplified as follows:

$$\begin{aligned} \text{RPF}_i(x) &= \frac{P(A, B(x)|C_i)}{P(A|C_i)} \\ &= \frac{P(B(x)|A, C_i)}{1} \\ &= S(x|A, C_i), \end{aligned} \tag{2}$$

where the first equality follows from multiplying and dividing by $P(A|C_i)$.

Of note, Equations (1) and (2) imply that modelling $P(B(x)|A, C_i)$ is sufficient to model both target quantities. Also, from Equation (1) it follows that $\text{RPF}_i(x) = P(A, B(x), C_i)/P(A, C_i)$.

[1]For example, if $\text{RPF}_6(0.10) = 0.8$, the probability of testing PSA$\geq$ 3 ng/ml and PSAd$>$ 0.10 ng/ml^2 is 20% lower than testing PSA$\geq$ 3 ng/ml, given an ISUP2+ cancer diagnosis.

4 Standard errors

The asymptotic standard error (ASE) for $P(A, B(x), C_i)$ is derived with the delta method:

$$ASE[P(A, B(x), C_i)] = \sqrt{P(B(x)|A, C_i)^2 ASE[P(A, C_i)]^2 + P(A, C_i)^2 ASE[P(B(x)|A, C_i)]^2}.$$

The formula for $ASE[P(B(x)|A, C_i)]$, which is also the ASE for the RPF, depends on the specific model for the survival function. The $ASE[P(A, C_i)]$ is equal to $\sqrt{P(A, C_i)(1 - P(A, C_i))/N)}$.

5 Heterogeneity of the Relative Positive Fractions

Outcome-specific heterogeneity of the RPF for all PSAd cut-offs with respect to a variable Z (e.g. age, previous benign biopsy,…) can be tested by including the variable in the model for the survival function:

$$g(S(x|A, C_i, Z = z)) = s(\ln x; \alpha) + \beta z.$$

Any statistical test for the regression coefficient $\beta \neq 0$ is a test for (overall) heterogeneity of the RPF. The interpretation of the regression coefficient β depends on the specific link function used in the analysis.

More complex models including interaction (product) terms between $s(\ln x; \alpha)$ and Z can be used to test for the heterogeneity of the RPF at specific PSAd cut-offs.

6 Application to the STHLM3-MRI trial data

In this secondary analysis of the STHLM3-MRI trial (Nordström et al., 2021), we fitted separate models with link $g(S) = -\text{logit}(S)$ for each event C_i. These models are known as proportional-odds models and provided a good fit to the the data while spending fewer degrees of freedom than proportional-hazards models. The number of degrees of freedom was selected based on the AIC. Models were fit using the `stpm2` function from the `rstpm2` R package. The ASEs for $S(x|A, C_i)$ were obtained using the delta method implemented in the `predict` function.

7 References

Björnebo, L., Discacciati, A., Abbadi, A., Falagario, U.G., Chandra Engel, J., Vigneswaran, H.T., Jäderling, F., Grönberg, H., Eklund, M., Lantz, A., Nordström, T. (2025). PSA Density as a selection tool before MRI in prostate cancer screening: an analysis from the STHLM3-MRI randomized clinical trial.

Bottai, M., Discacciati, A., & Santoni, G. (2021). Modeling the probability of occurrence of events. Statistical Methods in Medical Research, 30(8), 1976-1987.

Liu, X. R., Pawitan, Y., & Clements, M. (2018). Parametric and penalized generalized survival models. Statistical Methods in Medical Research, 27(5), 1531-1546.

Karlsson, A. A., Hao, S., Jauhiainen, A., Elfström, K. M., Egevad, L., Nordström, T., Heintz, E., & Clements, M. S. (2021). The cost-effectiveness of prostate cancer screening using the Stockholm3 test. PLoS One, 16(2), e0246674.

Nordström, T., Discacciati, A., Bergman, M., Clements, M., Aly, M., Annerstedt, M., Glaessgen, A., Carlsson, S., Jäderling, F., Eklund, M. and Grönberg, H. (2021). Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. The Lancet Oncology, 22(9), 1240-1249.

Pepe, M. S. (2003). The statistical evaluation of medical tests for classification and prediction. Oxford university press.

Royston, P., & Parmar, M. K. (2002). Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in Medicine, 21(15), 2175-2197.