Estimating sensitivity and specificity using Kaplan–Meier positive and negative predictive values

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1 Methods and formulas for `kmsenspec`

Our problem is estimating sensitivity and specificity of a predictive diagnostic test in a follow up study where not all participants have complete follow–up, because some have entered the study too recently. Under these conditions, positive and negative predictive values may be estimated on a cohort of patients tested on entry to the study, using Kaplan–Meier survival probabilities for time to a a disease diagnosis by a specified time (for instance a year) elapsed from a participant receiving the test. The survival probability $S(t)$ at a time t is the probability that a diagnosis has *not* been made at time t after the test is done. And the probability of a positive diagnosis by time t is $C(t) = 1 - S(t)$, the cumulative mortality probability at time t. Details of the formulas used for Kaplan–Meier analysis in the Stata statistical language can be found in the survival analysis sections of the manuals[1].

We might expect there to be separate conditional survival probabilities and cumulative diagnosis probabilities depending on whether the test at baseline was positive or negative, denoted as $S(t|\texttt{testpos})$) and $C(t|\texttt{testpos})$ for the case where the baseline test was positive, and as $S(t|\texttt{testneg})$) and $C(t|\texttt{testneg})$ for the case where the baseline test was negative. We can define positive and negative predictive values at time t as $\texttt{PPV}(t) = C(t|\texttt{testpos})$ and $\texttt{NPV}(t) = S(t|\texttt{testneg})$, respectively.

To estimate sensitivity and specificity at a time t from the cumulative mortality and survival at the same time, we use Bayes' theorem. We estimate sensitivity at follow up time t as the probability that a diagnosis has been made by time t given that the baseline test was positive, and specificity as the probability that a diagnostic test nas *not* been made by time t given that the baseline test was negative. So, sensitivity at t is estimated as

$$\texttt{sens}(t) = \frac{N_{\texttt{testpos}}\texttt{PPV}(t)}{N_{\texttt{testpos}}\texttt{PPV}(t) + N_{\texttt{testneg}}(1 - \texttt{NPV}(t))}, \quad (1)$$

and specificity at t is estimated as

$$\texttt{spec}(t) = \frac{N_{\texttt{testneg}}\texttt{NPV}(t)}{N_{\texttt{testneg}}\texttt{NPV}(t) + N_{\texttt{testpos}}(1 - \texttt{PPV}(t))}, \quad (2)$$

where $N_{\texttt{testpos}}$ and $N_{\texttt{testneg}}$ are the numbers testing positive and negative, respectively, at time zero. Conventionally, both of these expressions are set to 0 when the numerator is 0, in order to ensure continuity at the boundary when $\texttt{NPV}(t)$ is 1 and $\texttt{PPV}(t)$ is 0 or *vice versa*.

Note that the equations 1 and 2 for the sensitivity and specificity are of the form $\alpha X/(\alpha X + \beta Y)$, where X and Y are Kaplan–Meier parameters estimable with a Greenwood standard error and α and β are known constants, at least after the predictive tests at time zero have been done. These simple smooth functions enable the user to define delta–method standard errors for the sensitivity and specificity, at least if the user remembers their differential calculus. The derivative of $\alpha X/(\alpha X + \beta Y)$ with respect to X is

$$\frac{d}{dX}\frac{\alpha X}{\alpha X + \beta Y} = \frac{[\alpha X + \beta Y]\frac{d}{dX}\alpha X - \alpha X\frac{d}{dX}[\alpha X + \beta Y]}{[\alpha X + \beta Y]^2} = \frac{\alpha\beta Y}{[\alpha X + \beta Y]^2}, \quad (3)$$

and its derivative with respect to Y is

$$\frac{d}{dY}\frac{\alpha X}{\alpha X + \beta Y} = \frac{[\alpha X + \beta Y]\frac{d}{dY}\alpha X - \alpha X\frac{d}{dY}[\alpha X + \beta Y]}{[\alpha X + \beta Y]^2} = \frac{-\alpha\beta X}{[\alpha X + \beta Y]^2}. \quad (4)$$

The sample positive and negative predictive values are statistically independent, as they are computed from disjoint sets of participants, at least after the baseline tests have been done. It follows that an expression

of the asymptotic variances of the sensitivity in 1 and the specificity in 2 will contain only terms in the variances of the PPV and NPV, as their covariances are zero. So, given expressions and estimates for the variances of $\texttt{PPV}(t)$ and $\texttt{NPV}(t)$, which might be derived from the familiar Greenwood formula, we only need partial derivatives of $\texttt{sens}(t)$ and $\texttt{spec}(t)$ with respect to $\texttt{PPV}(t)$ and $\texttt{NPV}(t)$ to derive formulas for the whole covariance matrix of all 4 parameter estimates. We will denote by $\mathbf{A}(t)$ the vector $(\texttt{PPV}(t), \texttt{NPV}(t))$, and denote by $\mathbf{B}(t)$ the greater vector $(\texttt{sens}(t), \texttt{spec}(t), \texttt{PPV}(t), \texttt{NPV}(t))$. and denote by $\mathbf{D}(t)$ the 4×2 matrix of partial derivatives of $\mathbf{B}(t)$ with respect to $\mathbf{A}(t)$. The covariance matrix of $B(t)$ can then be approximated by

$$\texttt{Var}\left[\mathbf{B}(t)\right]] \approx \mathbf{D}(t)\texttt{Var}\left[\mathbf{A}(t)\right]\mathbf{D}(t)^T. \tag{5}$$

The matrix $\texttt{Var}[\mathbf{A}]$ is simply the diagonal matrix $\texttt{diag}(\texttt{Var}[\texttt{PPV}(t)], \texttt{Var}[\texttt{NPV}(t)])$. And the lower half of $\mathbf{D}$ is simply the 2×2 diagonal identity matrix. This leaves the partial derivatives of $\texttt{sens}(t)$ and $\texttt{spec}(t)$ with respect to $\texttt{PPV}(t)$ and $\texttt{NPV}(t)$, respectively. In (3) and (4), sensitivity represents the case where $X = \texttt{PPV}$, $Y = 1 - \texttt{NPV}$, $\alpha = N_{\texttt{testpos}}$, and $\beta = N_{\texttt{testneg}}$, whereas specificity represents the case where $X = \texttt{NPV}$, $Y = 1 - \texttt{PPV}$, $\alpha = N_{\texttt{testneg}}$, and $\beta = N_{\texttt{testpos}}$. The derivatives are therefore

$$\begin{aligned}
\frac{\partial \texttt{sens}(t)}{\partial \texttt{PPV}(t)} &= \frac{N_{\texttt{testpos}} N_{\texttt{testneg}} \left(1-\texttt{NPV}(t)\right)}{\left[N_{\texttt{testpos}} \texttt{PPV}(t) + N_{\texttt{testneg}} \left(1-\texttt{NPV}(t)\right)\right]^2}, \\
\frac{\partial \texttt{sens}(t)}{\partial \texttt{NPV}(t)} &= -\frac{\partial \texttt{sens}(t)}{\partial \left(1-\texttt{NPV}(t)\right)} = \frac{N_{\texttt{testpos}} N_{\texttt{testneg}} \texttt{PPV}(t)}{\left[N_{\texttt{testpos}} \texttt{PPV}(t) + N_{\texttt{testneg}} \left(1-\texttt{NPV}(t)\right)\right]^2}, \\
\frac{\partial \texttt{spec}(t)}{\partial \texttt{PPV}(t)} &= -\frac{\partial \texttt{spec}(t)}{\partial \left(1-\texttt{PPV}(t)\right)} = \frac{N_{\texttt{testpos}} N_{\texttt{testneg}} \texttt{NPV}(t)}{\left[N_{\texttt{testpos}} \left(1-\texttt{PPV}(t)\right) + N_{\texttt{testneg}} \texttt{NPV}(t)\right]^2}, \\
\frac{\partial \texttt{spec}(t)}{\partial \texttt{NPV}(t)} &= \frac{N_{\texttt{testpos}} N_{\texttt{testneg}} \left(1-\texttt{PPV}(t)\right)}{\left[N_{\texttt{testpos}} \left(1-\texttt{PPV}(t)\right) + N_{\texttt{testneg}} \texttt{NPV}(t)\right]^2}.
\end{aligned} \tag{6}$$

These formulas are also conventionally set to 0 when their numerators are 0, to ensure continuity at the boundaries where $\texttt{NPV}(t)$ and $\texttt{PPV}(t)$ are 1 and 0 respectively or 0 and 1 respectively. They give us all the information we need to complete the matrix $\mathbf{D}(t)$, which can be used to transform the 2×2 variance matrix $\texttt{Var}[\mathbf{A}(t)]$ to the 4×4 covariance matrix $\texttt{Var}[\mathbf{B}(t)]$. In Stata, we have therefore written an estimation command `kmsenspec`, using the SSC package `kmest` to compute the estimates and variances for the PPV and the NPV, and then use the formulas (1) and (2) to estimate the sensitivities and specificities, and the formulas 6 to complete the matrix $\mathbf{D}(t)$ and compute a covariance matrix to be saved as part of the estimation results.

Once estimates and standard errors have been computed for the PPV, NPV, sensitivity, and specificity, we can use them to compute symmetrical untransformed confidence limits. Alternatively, we can use a transformation (such as the log, the logit or the log–log) to define a transformed PPV and/or NPV and/or sensitivity and/or specificity and a transformed standard error, and then compute a confidence interval for the transformed parameter, and then back–transform the estimate and confidence limits to create an asymmetric confidence interval for the untransformed parameter. These asymmetric confidence intervals might be calculated using the SSC package `parmest` to save the estimates and confidence limits to a resultsset, and the SSC package `eseparm`, with the `parmcip` module of `parmest`, to compute the asymmetric confidence intervals. Multiple SSC packages can therefore be combined to do things that they could not do alone.

References

[1] StataCorp. *Stata: Release 19. Statistical Software.* College Station, TX: StataCorp LLC; 2025.