**ABSTRACT**

**Objective** Multichotomous tests have three or more outcome or risk categories, and can provide richer information and a better fit with clinical decision-making than dichotomous tests. Our objective is to present a fully developed approach to the meta-analysis of multichotomous clinical prediction rules (CPRs) and tests, including meta-analysis of stratum specific likelihood ratios.

**Study design** We have developed a novel approach to the meta-analysis of likelihood ratios for multichotomous tests that avoids the need to dichotomise outcome categories, and demonstrate its application to a sample CPR. We also review previously reported approaches to the meta-analysis of the area under the receiver operating characteristic curve (AUROCC) and meta-analysis of a measure of calibration (observed:expected) for multichotomous tests or CPRs.

**Results** Using data from 10 studies of the Cancer of the Prostate Risk Assessment (CAPRA) risk score for prostate cancer recurrence, we calculated summary estimates of the likelihood ratios for low, moderate and high risk groups of 0.40 (95% CI 0.32 to 0.49), 1.24 (95% CI 0.99 to 1.55) and 4.47 (95% CI 3.21 to 6.23), respectively. Applying the summary estimates of the likelihood ratios for each risk group to the overall prevalence of cancer recurrence in a population allows one to estimate the likelihood of recurrence for each risk group in that population.

**Conclusion** An approach to meta-analysis of multichotomous tests or CPRs is presented. A spreadsheet for data preparation and code for R and Stata are provided for other researchers to download and use. Combined with summary estimates of the AUROCC and calibration, this is a comprehensive strategy for meta-analysis of multichotomous tests and CPRs.

**INTRODUCTION**

Multichotomous clinical prediction rules (CPRs) and diagnostic tests classify patients into three or more risk categories or risk groups for an outcome. Examples include the Strep score, the Wells score for diagnosis of deep vein thrombosis, the Asymmetry Border Color Diameter (ABCD) rule for the evaluation of skin lesions and the Good Outcome Following Attempted Resuscitation (GO-FAR) score to predict the outcome of in-hospital cardiopulmonary resuscitation. An important advantage of multichotomous test interpretation is that it provides more information than simply dichotomising, and offers greater coherence with recommended strategies for clinical decision-making. Therefore, the authors identified low, moderate and high risk groups to rule out the diagnosis, and the high-risk group may not be high enough to initiate therapy. Thereafter, the authors identified low, moderate and high risk groups based on a single cut-off that maximises the sum of sensitivity and specificity creates two risk groups with 11% and 68% probabilities of developing RA. The low risk group is arguably not low risk enough to rule out the diagnosis, and the high-risk group may not be high enough to initiate therapy. Therefore, the authors identified low, moderate and high risk groups (<5, 5 to 9 and >9 points) to identify groups with 3%, 46% and 84% probabilities of subsequent RA. The low risk group now has the disease almost entirely ruled out, patients in the moderate risk group might...
be designated for close follow-up and repeat testing, and the high risk group is high enough in risk that one could consider for initiation of a disease modifying anti-rheumatic drug. Thus, the additional information from having more than two outcome categories proves very useful clinically.

While one can calculate positive and negative likelihood ratios for a dichotomous CPR, multichotomous CPRs do not have a single cut-off. Instead, the preferred measure of diagnostic accuracy for multichotomous tests and CPRs is the stratum specific likelihood ratio, that is, the likelihood ratio associated with each risk group. Because likelihood ratios are a characteristic of the test, in theory they should not vary with changes in disease prevalence (and assuming a generally similar spectrum of disease). Previous meta-analyses have taken one or more of the following five approaches to meta-analysis of a multichotomous CPRs, but all have limitations:

1. Calculating the area under a summary receiver operating characteristic (ROC) curve, with each study contributing a single sensitivity/specificity pair to the plot; 8,9
2. Reporting calibration as a risk ratio (RR), where a RR >1.0 represents overprediction of the diagnosis, and a RR <1.0 underprediction; 10,11
3. Performing meta-analysis of ROC curves; 12
4. Dichotomising the test, by combining groups until there are only two dichotomous categories with a single cut-off, and then calculating summary measures of sensitivity, specificity and positive and negative likelihood ratio; and
5. Combining the predictive values of an outcome for a risk group using meta-analysis. 13

As noted, all of these methods have limitations that affect their interpretability and usefulness. Summary ROC curves are useful for determining discrimination, but do not provide summary estimates of accuracy or calibration. Calibration (the ratio of observed to expected or O:E) is important for evaluating whether a rule is consistent with the performance in the original study, but does not provide an estimate of the likelihood of an outcome for patients in a particular risk group. Meta-analysis of predictive values (the likelihood of disease in a risk group) is inappropriate because predictive values may vary greatly with the underlying prevalence of disease, even if the CPR has the same accuracy as measured by stratum specific likelihood ratios across studies. 13 Finally, dichotomising CPRs that have three or more risk groups into two groups in order to calculate summary estimates of accuracy loses information as noted above, and is inconsistent with how the CPR was intended to be used or interpreted. For example, a clinician might ask: how much does having an ABCD score of 4 points increase the likelihood of melanoma, compared with scores of 2 points or 3 points? If scores of 2, 3 and 4 are combined into a single high risk group to dichotomise the risk score, that information is lost.

In this article, we describe a comprehensive approach to the meta-analysis of multichotomous tests and CPRs. First, we propose a novel approach to the calculation of a summary estimate of the stratum specific likelihood ratio (SSLR) for each risk group of a multichotomous test or CPR. We will also review methods, described in detail by Debray and colleagues, 14,15 for the meta-analysis of the area under the receiver operating characteristic curve (AUROCC) to calculate a summary estimate of discrimination and meta-analysis of the ratio of observed to expected outcomes to calculate a summary estimate of calibration. Finally, we apply our approach to meta-analysis of SSLRs to the Cancer of the Prostate Risk Assessment (CAPRA) score for prostate cancer prognosis.

METHODS
Calculating summary estimates of stratum specific likelihood ratios

A likelihood ratio (LR) is the likelihood of a test result in patients with the disease divided by the likelihood of the test result in patients without the disease. 16 When calculated for a dichotomous test, positive and negative LRs are commonly reported. For a multichotomous test or CPR with more three or more risk categories, each risk category has its own LR, called the SSLR. This section describes development and implementation of a novel approach to the calculation of SSLRs for multichotomous tests.

To calculate summary estimates of the SSLR, we will treat the likelihood ratio as a type of risk ratio, making it possible to adapt methods already developed for meta-analysis of risk ratios in randomised trials. By determining SSLRs, we can then apply them to the overall prevalence of disease in the population and calculate the post-test probability of disease for each risk category using Bayes’ formula. It is important to note that when calculating summary estimates of multichotomous (or dichotomous) tests, it is important that the same cut-offs are used across studies. For example, consistently defining low risk as 0 points, moderate risk as 1 to 2 points and high risk as 3 to 4 points. It would be inappropriate to perform meta-analysis when risk groups are defined differently by different studies.

For a dichotomous test, the LR is calculated as follows, where Pr is probability, T+ = positive test result, T− = negative test result, D+ is patients with disease and D− is patients without disease (note that ‘disease’ could represent any outcome predicted by a test or CPR, including death vs survival or treatment benefit vs treatment harm):

\[
LR_+ = \frac{Pr(T+ | D+)}{Pr(T+ | D−)}
\]

\[
LR_- = \frac{Pr(T− | D+)}{Pr(T− | D−)}
\]

For a multichotomous test or CPR, each risk category has its own SSLR; there is no longer a positive and negative LR. For example, if a CPR places patients into low, moderate and high risk groups, the SSLRs are calculated as follows. Note that Tlow risk, Tmoderate risk and Thigh risk are patients classified as low risk, moderate risk or high risk, while D+ is the total number of patients with the outcome and D− is the total without the outcome (for...
CPRs the outcome being predicted is often the likelihood of disease, hence use of D):

\[ LR_{low} = \frac{Pr(T_{low \ risk} \mid D+)}{Pr(T_{low \ risk} \mid D-)} \]

\[ LR_{moderate} = \frac{Pr(T_{moderate \ risk} \mid D+)}{Pr(T_{moderate \ risk} \mid D-)} \]

\[ LR_{high} = \frac{Pr(T_{high \ risk} \mid D+)}{Pr(T_{high \ risk} \mid D-)} \]

The CAPRA score is a CPR that assigns men with prostate cancer to low (0 to 2 points), moderate (3 to 5 points) or high risk (6 or more points) groups for biochemical recurrence after some period, typically 5 years from the time of initial treatment. Several validation studies of the CAPRA score have been conducted; the calculation of SSLRs for a single study is shown in Table 1.

For any multichotomous CPR or test, the SSLR for each risk group is the ratio of two risks or probabilities: for patients in that risk group, the probability of recurrence divided by the probability of no recurrence. This is similar conceptually to a RR for a treatment trial, defined as the ratio of the risk or probability of an outcome in the treatment group to the risk or probability of that outcome in the control group. Table 2 has five parts that illustrate how likelihood ratios can be treated as RRs for the calculation of SSLRs.

Part 1 shows how data are formatted for a meta-analysis of three hypothetical treatment trials with recurrence of prostate cancer as the primary outcome. Part 2 shows the usual approach to displaying results of a study with three or more risk groups, and how the SSLR for a single study is calculated. Part 3 reformats the same data to mimic the RRs of a treatment trial, illustrating how the RRs are identical to the LRs calculated in Part 2. Finally, Part 4 illustrates the general case for formatting the results of a study describing a CPR with three risk categories, and Part 5 illustrates the general form of the equation showing how the same approach can be extended to a test or CPR with any number of risk categories.

A Microsoft Excel spreadsheet that facilitates the preparation of multichotomous data for analysis (in this case 3 risk categories) is available for free download at https://doi.org/10.5281/zenodo.3936001. Column A should be filled in with the study name, Column B with the study year, Column C with the risk group labels, Column D with the number of patients in the risk group with the outcome of interest and Column F with the number of patients in the risk group without the outcome of interest. Columns E, G, H and I are calculated. The ‘Optional’ Columns J through L can be used to stratify the analysis on an important study variable such as the test’s cut-off, age group or reference standard used. Note that as an internal check, the sum of the number of participants in each row should equal the total number of participants in the study as a whole (Column H). Users should create the desired descriptive variable names appropriate for their data in Row 1. The data are now ready to be imported into Stata, SAS or R for analysis.

After importing the data into Stata 15.1 (StataCorp, College Station, Texas) we used the metan procedure (V.9) to perform a random effects meta-analysis of RRs using the following command (a random effects model was chosen as it is more conservative and accounts to some extent for between study as well as within study variance): metan RecurInRiskGroup RecurNotInRiskGroup NoRecurInRiskGroup NoRecurNotInRiskGroup, random by(RiskGroup) sortby(Year) cc(0.5) icols(AuthorYear) xlabel(0.05, 0.1, 0.2, 0.5, 2.0, 5.0, 10.0)

To create a forest plot for only the low risk stratum, the following command is used: metan RecurInRiskGroup RecurNotInRiskGroup NoRecurInRiskGroup NoRecurNotInRiskGroup if RiskGroup==“Low risk”, random sortby(Year) cc(0.5) icols(AuthorYear) xlabel(0.05, 0.1, 0.2, 0.5, 2.0, 5.0, 10.0)

For a script to perform these calculations in R, please see the online supplemental appendix.

Meta-analysis of the area under the ROC curve
In 2017, Debray and colleagues published a detailed guide to meta-analysis of prediction model performance. We have previously applied this guide to the meta-analysis of CPRs with more than two risk categories. Measures of discrimination (area under the curve (AUC)) and corresponding measures of uncertainty

### Table 1 Calculation of stratum specific likelihood ratios for a single study of the Cancer of the Prostate Risk Assessment (CAPRA) score to predict the likelihood that a patient has a biochemical recurrence of prostate cancer

| Generic risk group | Recurrence of prostate CA | No recurrence of prostate CA | Stratum specific likelihood ratio |
|--------------------|---------------------------|-----------------------------|---------------------------------|
| Low risk           | a                         | x                           | \[ LR_{low} = (a / D+) / (x / D-) \] |
| Moderate risk      | b                         | y                           | \[ LR_{moderate} = (b / D+) / (y / D-) \] |
| High risk          | c                         | z                           | \[ LR_{high} = (c / D+) / (z / D-) \] |

| CAPRA risk group   | Recurrence of prostate CA | No recurrence of prostate CA | Stratum specific likelihood ratio |
|--------------------|---------------------------|-----------------------------|---------------------------------|
| Low (0–2 pts)      | 69                        | 764                         | \[ LR_{low} = (69/210)/(764/1229)=0.53 \] |
| Moderate (3–5 pts) | 103                       | 432                         | \[ LR_{moderate} = (103/210)/(432/1229)=1.4 \] |
| High (6–10 pts)    | 38                        | 33                          | \[ LR_{high} = (38/210)/(33/1229)=6.7 \] |
|                    | 210                       | 1229                        |                                  |

CA, cancer; LR, likelihood ratio; pts, points.
Table 2  Developing a method for formatting data from tests or clinical decision rules with three or more outcomes to calculate stratum specific likelihood ratios

Part 1: Calculating risk ratios for a meta-analysis of treatment trials

| Study     | Recurrence | No recurrence | Recurrence | No recurrence | Risk ratio calculation |
|-----------|-------------|---------------|-------------|---------------|-----------------------|
| Study 1   | a₁          | b₁            | c₁          | d₁            | RR=(a₁/(a₁+b₁))/(c₁/(c₁+d₁)) |
| Study 2   | a₂          | b₂            | c₂          | d₂            | RR=(a₂/(a₂+b₂))/(c₂/(c₂+d₂)) |
| Study 3   | a₃          | b₃            | c₃          | d₃            | RR=(a₃/(a₃+b₃))/(c₃/(c₃+d₃)) |

Part 2: Usual presentation of a test with three or more risk groups to calculate likelihood ratios (as in table 1)

| CAPRA risk group | Recurrence | No recurrence | Likelihood ratio calculation |
|------------------|------------|---------------|------------------------------|
| Low              | 69         | 764           | LR_{Low}=(69/210) / (764/1229)=0.53 |
| Moderate         | 103        | 432           | LR_{Moderate}=(103/210) / (432/1229)=1.4 |
| High             | 38         | 33            | LR_{High}=(38/210) / (33/1229)=6.7 |

| CAPRA risk group | In risk group | Not in risk group | Likelihood ratio calculation |
|------------------|---------------|-------------------|------------------------------|
| Low              | 69            | 141*              | LR_{Low}=(69 / (69+141)) / (764/ (764+465))=0.53 |
| Moderate         | 103           | 107†              | LR_{Moderate}=(103 / (103+107)) / (432/ (432+797))=1.4 |
| High             | 38            | 172‡              | LR_{High}=(38 / (38+172)) / (33/ (33+1196))=6.7 |

Part 3: Alternate presentation of the same data to calculate likelihood ratios, treating them as risk ratios

| CAPRA risk group | Outcome or diagnosis present | Outcome or diagnosis absent | Likelihood ratio calculation |
|------------------|-------------------------------|-----------------------------|------------------------------|
| Low              | In risk group                 | Not in risk group           | LR_{i}=(D_{i+} / (D_{i+}+D_{i-})) / (D_{i-} / (D_{i-}+D_{i+})) |
| Moderate         | D_{1+}                        | D_{1+}+D_{3+}               | LR_{2i}=(D_{2+} / (D_{2+}+D_{2-}+D_{2+})) / (D_{2-} / (D_{2-}+D_{2+}+D_{2-})) |
| High             | D_{3+}                        | D_{3+}+D_{2+}               | LR_{3i}=(D_{3+} / (D_{3+}+D_{3-}+D_{3+})) / (D_{3-} / (D_{3-}+D_{3+}+D_{3-})) |

Part 4: Generic representation of how to present data for calculation of stratum specific likelihood ratios with n risk groups

| Risk group i     | D_{i+}                        | D_{i-}                       | $L_{R_{i}} = \frac{\sum_{j=1}^{n} D_{i+}}{\sum_{j=1}^{n} D_{i-}}$ |
|------------------|-------------------------------|------------------------------|--------------------------------------------------|

CAPRA = Cancer of the Prostate Risk Assessment

*Sum of number of patients in moderate and high risk groups with recurrence, that is, 103+38=141 for recurrence group.
†Sum of number of patients in low and high risk groups with recurrence, that is, 69+38=107 for recurrence group.
‡Sum of number of patients in low and moderate risk groups with recurrence, that is, 69+103=172 for recurrence group.
LR, likelihood ratio; RR, risk ratio.
(95% CIs or SEs) can be extracted from individual studies, where reported. In order to conduct meta-analysis, AUC values and reported 95% CIs are transformed to the logit scale and the variance of logit AUC calculated. Where measures of uncertainty are not reported, the variance of logit AUC can be estimated using equations proposed by Debray and colleagues.14 A random effects meta-analysis of logit AUC and variance values is then conducted with restricted maximum likelihood (REML) estimation, which can be completed, for example, using the metaan procedure in Stata 16 (StataCorp, College Station, Texas).14 20 The pooled logit AUC and 95% CIs are then back-transformed.14 The proportion of heterogeneity due to between study variation is estimated using the I² statistic. This method could be applied to the CAPRA score, which has a time to event outcome, using the updated framework and R code outlined in the 2019 paper by Debray et al.15

**Meta-analysis of calibration between observed and expected outcomes**

Calibration of a CPR refers to the level of agreement between predicted probabilities and observed frequencies of the outcome in a validation study. A summary estimate of calibration of a CPR can be calculated through meta-analysis of ‘observed: expected ratios’. Our experience, as also highlighted by Debray and colleagues,14 was that measures of calibration (O:E ratio, calibration slope or plot) are rarely reported in validation studies of CPRs. Most CPR validation studies will only present the observed number of outcomes in a risk group. If the number of outcomes that would have been ‘expected’ or ‘predicted’ based on the rule are not reported, they can be derived or estimated using different methods, depending on what information is available from both the derivation and validation studies.

Ideally, a derivation study of a rule with a binary outcome will present the regression coefficient or OR for each predictor in the model and the intercept.25 In this case, the proportion of participants expected to have the outcome can be calculated by incorporating the mean values of subject characteristics in the prediction model.14 In the absence of a full model, a derivation study of a rule may report predicted probabilities for each risk stratum, as is reported by Lim and colleagues for the CRB-65 rule.26 In this case, the expected number of outcomes in each validation study can be calculated by applying the corresponding predicted probability to the numbers of patients in each risk stratum.11 14 For example, if the derivation study reported 5% risk of the outcome in those in the low risk category, the expected number of outcomes in the low risk category in the validation study is 5% of those in the category.11

As recommended by Debray and colleagues,14 the O:E ratio can be calculated for each study on the log scale as follows: log (number of observed outcomes) – log (number of expected outcomes). If not reported, the variance of log (O:E) ratio can be estimated using equations proposed in their guide.14 A random effects meta-analysis of log O:E and variance values is conducted with REML estimation. We completed this using the metaan procedure in Stata 14, specifying the exponential option to back-transform results to the scale of interest (StataCorp, College Station, Texas).14 20 Between study heterogeneity is estimated using the I² statistic. As poor calibration can occur if the rule is applied in a population with a different baseline risk than the derivation population, meta-analyses of calibration performance can also pre-define subgroups based on factors that could influence this risk.14 For example, studies that apply the rule in a primary care setting could be meta-analysed separately to those that apply the rule to hospital inpatients. Again, this method could be applied to the CAPRA score, which has a time to event outcome, using the updated framework and R code described in detail by Debray and colleagues.15 Presentation of results of meta-analysis of AUC and calibration for the CAPRA score is outside of the scope of this paper, where we focus on novel methods of calculating summary estimates for SSLRs.

**RESULTS**

Table 3 presents data from 10 validation studies of the CAPRA score, formatted as shown in Parts 3 and 4 of table 2 discussed above. The LRs for low, moderate and high risk groups for prostate cancer recurrence for each study are shown in the final column. Formatted in this fashion, it becomes straightforward to use standard methods for calculating RRs in any statistical package.

The resulting forest plot (figure 1) shows summary estimates of the SSLRs for biochemical recurrence of prostate cancer of 0.40 (95% CI 0.32 to 0.49) for the low risk group, 1.24 (95% CI 0.99 to 1.55) for the moderate risk group and 4.47 (95% CI 3.21 to 6.23) for the high risk group. The I² values (84.7%, 96.1% and 90.6% for the low, moderate and high risk groups, respectively) and visual inspection reveal significant heterogeneity, which may reflect differences in the underlying patient populations.

Presentation of results as a forest plot has several strengths. First, it is a familiar format for meta-analysis, allowing a visual assessment of heterogeneity. A formal assessment of heterogeneity is typically provided; for example, in both R and Stata the I² statistic is calculated for each stratum and overall. Note that the LRs calculated for the Cooperberg study are identical to those calculated manually in table 2, an internal verification of the accuracy of our approach.25 A limitation is that the plot is labelled ‘Risk Ratio’, although this could easily be modified using a graphics programme (development of a native R package is underway).
Furthermore, summary estimates of SSLRs can be used to determine the risk of the outcome in a risk category if one knows the overall prevalence of that outcome in the population. In the 10 identified CAPRA validation studies, 17% of men experienced a biochemical recurrence at 5 years. By using the pretest probability of biochemical recurrence of 17% and the SSLRs of 0.40, 1.24 and 4.47, we can use Bayes’ formula to calculate the post-test probability of recurrence as 8% in the low risk group, 20% in the moderate risk group and 48% in the high risk group.

Table 3  Data for studies of the CAPRA score with the outcome of recurrence-free survival at 5 years, formatted for calculation of stratum specific likelihood ratios using Stata

| Author, year | Year | Risk group | Recur in risk group | Recur not in risk group | No recur in risk group | No recur not in risk group | LR |
|--------------|------|------------|---------------------|------------------------|-----------------------|--------------------------|----|
| Ishizaki, 2011 | 2011 | Low risk   | 21                  | 53                     | 64                    | 73                       | 0.61|
| Ishizaki, 2011 | 2011 | Moderate risk | 35                  | 39                     | 71                    | 66                       | 0.91|
| Ishizaki, 2011 | 2011 | High risk  | 18                  | 56                     | 2                     | 135                      | 16.7|
| Loeb, 2010    | 2010 | Low risk   | 35                  | 71                     | 669                   | 215                      | 0.44|
| Loeb, 2010    | 2010 | Moderate risk | 53                  | 53                     | 197                   | 687                      | 2.2 |
| Loeb, 2010    | 2010 | High risk  | 18                  | 88                     | 18                    | 866                      | 8.3 |
| Lughezzani, 2010 | 2010 | Low risk  | 82                  | 419                    | 826                   | 649                      | 0.29|
| Lughezzani, 2010 | 2010 | Moderate risk | 296                 | 205                    | 567                   | 908                      | 1.5 |
| Lughezzani, 2010 | 2010 | High risk  | 123                 | 378                    | 82                    | 1393                     | 4.4 |
| May, 2007     | 2007 | Low risk   | 28                  | 379                    | 399                   | 490                      | 0.15|
| May, 2007     | 2007 | Moderate risk | 218                 | 189                    | 409                   | 480                      | 1.2 |
| May, 2007     | 2007 | High risk  | 161                 | 246                    | 81                    | 808                      | 4.3 |
| Cooperberg, 2006 | 2006 | Low risk  | 69                  | 141                    | 764                   | 465                      | 0.53|
| Cooperberg, 2006 | 2006 | Moderate risk | 103                 | 107                    | 432                   | 797                      | 1.4 |
| Cooperberg, 2006 | 2006 | High risk  | 38                  | 172                    | 33                    | 1196                     | 6.7 |
| Zhao, 2007    | 2007 | Low risk   | 284                 | 580                    | 4449                  | 1424                     | 0.43|
| Zhao, 2007    | 2007 | Moderate risk | 445                 | 419                    | 1329                  | 4544                     | 2.3 |
| Zhao, 2007    | 2007 | High risk  | 135                 | 729                    | 95                    | 5778                     | 9.7 |
| Halverson, 2011 | 2011 | Low risk  | 9                   | 86                     | 167                   | 349                      | 0.29|
| Halverson, 2011 | 2011 | Moderate risk | 27                  | 68                     | 240                   | 276                      | 0.61|
| Halverson, 2011 | 2011 | High risk  | 59                  | 36                     | 109                   | 407                      | 2.9 |
| Budaus, 2012  | 2012 | Low risk   | 98                  | 436                    | 1182                  | 1221                     | 0.37|
| Budaus, 2012  | 2012 | Moderate risk | 280                 | 254                    | 990                   | 1413                     | 1.27|
| Budaus, 2012  | 2012 | High risk  | 156                 | 378                    | 231                   | 2172                     | 3.0 |
| Krishnan, 2014 | 2014 | Low risk  | 6                   | 40                     | 45                    | 254                      | 0.87|
| Krishnan, 2014 | 2014 | Moderate risk | 31                  | 15                     | 230                   | 69                       | 0.88|
| Krishnan, 2014 | 2014 | High risk  | 9                   | 37                     | 24                    | 275                      | 2.4 |
| Yoshida, 2012 | 2012 | Low risk   | 19                  | 99                     | 119                   | 266                      | 0.52|
| Yoshida, 2012 | 2012 | Moderate risk | 57                  | 61                     | 200                   | 185                      | 0.93|
| Yoshida, 2012 | 2012 | High risk  | 42                  | 76                     | 66                    | 319                      | 2.1 |

LR, likelihood ratio.

**DISCUSSION**

We have described a comprehensive approach to the meta-analysis of CPRs with more than two risk categories for an outcome. This approach builds on work by others who have developed approaches to calculating summary estimates of calibration (O:E ratio) and discrimination (area under the ROC curve) by adding a novel approach for the calculation of summary estimates of SSLRs. It does not require dichotomising data and avoids the inherent problems with meta-analysis of predictive values. While the focus of this article is on meta-analysis of CPRs with three or more risk categories for an outcome, our approach to the calculation of summary estimates of...
SSLR could also be applied to any multichotomous diagnostic test such as serum ferritin or d-dimer.\textsuperscript{23,24} Zwinderman and Bossuyt\textsuperscript{25} argue that meta-analysis of diagnostic LRs is not appropriate, since the positive and negative LRs are highly correlated for a dichotomous test, because they are calculated from sensitivity and specificity which are also highly correlated. Therefore, they suggest that bivariate meta-analysis of sensitivity and specificity should be performed instead of meta-analysis of LRs, with subsequent calculation of positive and negative LRs if desired. However, this is not relevant for SSLRs that are not calculated from sensitivity or specificity.

Future meta-analyses of multichotomous tests and CPRs should be encouraged to report summary estimates of discrimination, calibration and SSLRs (without dichotomising or collapsing categories) where the underlying data allow these calculations. Each of these metrics provides a different type of information. Discrimination, as measured by a summary estimate of the area under the ROC curve, provides an overall estimate of diagnostic accuracy, and is interpretable for an individual patient by telling us how likely the test or CPR is to correctly classify two randomly selected patients, one with and one without the outcome in question.

Calibration, the agreement between observed and predicted risk, speaks more to how accurately the rule classifies groups of patients with similar levels (for example, deciles) of risk. In some cases, a CPR that has relatively poor discrimination can have excellent calibration. An example is the Breast Cancer Risk Assessment Tool (BCRAT): a meta-analysis found that while the area under the ROC curve is only 0.64, it has very good calibration (O:E 1.08, 95% CI 0.97 to 1.20).\textsuperscript{26} Thus, the BCRAT is not helpful when determining the likelihood that an individual woman will be diagnosed with breast cancer in the next 5 years. However, one could state that for 1000 women with a similar BCRAT score, approximately 40 will develop breast cancer in the next 5 years (good calibration), but that we are unable to determine exactly which 40 in this group will develop cancer (poor discrimination).

Furthermore, summary estimates of SSLRs can also be used to determine the likelihood of an outcome in a risk category if one knows the overall prevalence of that outcome in the population. This information is potentially very helpful to clinicians and patients who are trying to interpret the results of a multichotomous test or CPR, and is more easily grasped and applied clinically than concepts such as area under the ROC curve or O:E ratios. And, since the SSLRs are characteristics of the test and are independent of disease prevalence, they can be applied to populations with different prevalences to calculate population-specific post-test probabilities for each risk category.
A limitation of LRs is that while in theory LRs are a feature of the test or risk score and should be consistent across populations (unlike predictive values), in reality it has been shown that there is a degree of variation in LRs between studies. By using a random effects model in our meta-analysis of SSLRs, we do account to some extent for variation. It is also possible to see this variation in the forest plot and see it reflected in the CI of the summary estimate. It is important to note that an important advantage of our approach is that it uses readily available methods in statistical packages to perform the calculations and create the forest plot.

In conclusion, we have developed a novel and easy to use approach to the calculation of summary estimates of SSLRs for any test with three or more outcome categories, and have presented a set of tools that can be applied using standard statistical software to the calculation of summary estimates of SSLRs, discrimination and calibration for multichotomous tests and CPRs.

Acknowledgements The authors would like to acknowledge the contribution of Borislav Dimitrov (deceased) to the development of the methodology for meta-analysis of calibration for multichotomous clinical prediction rules.

Contributors The project was conceptualised and led by Mark Ebell. Brian McKay wrote and tested the R code. Tom Fahey provided input on the conceptualisation, assisted with writing and reviewed the final manuscript. Mary Walsh and Fiona Boland collaborated on the meta-analysis of receiver operating characteristic curves and meta-analysis of observed:expected ratios, and Fiona Boland also helped create Table 2. All co-authors reviewed and approved the final manuscript.

Funding This work was supported in part by a 2019 Fulbright Teaching/Research Scholar award for Dr Ebell (grant number N/A), and funding from the Health Research Board of Ireland to support the HRB Primary Care Research Centre at the Royal College of Surgeons in Ireland, Research Centre Grant no. HRC/2014/1.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no data sets generated and/or analysed for this study. There was no original data collection for this study. R code and an excel spreadsheet for data preparation have been made available to the public under ‘Supplemental Files’. The data preparation spreadsheet (Excel) and the R code for stratum specific likelihood ratios can be found at the Zenodo archive. https://doi.org/10.5281/zenodo.3936001.

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ORCID iDs
Mark H Ebell http://orcid.org/0000-0003-3228-2877
Mary E Walsh http://orcid.org/0000-0001-8920-7419
Fiona Boland http://orcid.org/0000-0003-3228-0046
Tom Fahey http://orcid.org/0000-0002-5896-5783

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