Silicosis Diagnostic Rule

Description of diagnostic rule and impact of misclassification error

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Setup

Packages used

```
if (!require("pacman", quietly = TRUE)) {
  install.packages("pacman")
}

pacman::p_load(
  tidyverse,  # Used for basic data handling and visualization.
  gt,         # Used to print html tables.
  report      # Used to cite packages used in this session.
)
```

Session and package dependencies

```
R version 4.4.1 (2024-06-14 ucrt)
Platform: x86_64-w64-mingw32/x64
Running under: Windows 11 x64 (build 22631)

Matrix products: default


locale:
[1] LC_COLLATE=Spanish_Mexico.utf8  LC_CTYPE=Spanish_Mexico.utf8
[3] LC_MONETARY=Spanish_Mexico.utf8 LC_NUMERIC=C
[5] LC_TIME=Spanish_Mexico.utf8

time zone: Europe/Berlin
tzcode source: internal

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] report_0.5.8    gt_0.10.1       lubridate_1.9.3 forcats_1.0.0
 [5] stringr_1.5.1   dplyr_1.1.4     purrr_1.0.2     readr_2.1.5
 [9] tidyr_1.3.1     tibble_3.2.1    ggplot2_3.5.1   tidyverse_2.0.0
[13] pacman_0.5.1
```

Description

A diagnostic prediction model to **rule out** pneumoconiosis in construction workers was developed and published in 2007.[1] The study population consisted of Dutch natural stone and construction workers age 30 years and older.

Outcome

The diagnosis of pneumoconiosis was defined as a chest x ray (CXR) indicative for pneumoconiosis (ILO profusion category 1/1), for which the ILO international classification of radiographs of pneumoconioses 2000 version was used. The most up-to-date version of this guideline is the 2022 revised edition.[2] The ILO score is assigned upon examination of small opacities on CXR, in comparison to standardized CXR images, and is composed of a major category, which is followed by a subcategory. For instance, a score of 1/0 means that 1 was assigned as the major category, while 0 was strongly considered as the alternative. Conversely, a score of 0/1 means that the radiologist assigned 0 as the major category, but strongly considered 1 as suitable. A score 1/1 means that the CXR is consistent with the standard CXR graded as 1 in the ILO classification report.

As mentioned earlier, an ILO score 1/1 was considered as the reference standard for pneumoconiosis to develop the diagnostic prediction rule.[1] This contrasts with standard recommendations at the time mentioning that an ILO category 1/0 or higher should be considered consistent with the presence of pneumoconiosis.[3] This decision was made under the rationale that a 1/0 cutoff could lead to greater misclassification. For the outcome consignation, three different radiologists provided a score and the median score was used. Out of the 1291 workers included for analysis, a total of 37 (2.9%) had a score 1/1, whereas 131 (10.1%) were graded 1/0.

Predictors

Lung function measured with a pneumotacometer on the same day of CXR obtention and worker questionnaire variables were assessed as potential predictors of pneumoconiosis. Seven candidate predictors were identified in univariable analysis:

- Age
- Smoking status
- Job title
- Time working in the construction industry
- Feeling unhealthy
- Cumulative exposure to silica index
- Standardized residual FEV1

Continuous variables were dichotomized and modeled separately, as continuous and binary. Since there were no differences in the AUC of a prediction model with continuous vs binary predictors, the latter were kept to simplify the diagnostic rule usage.

The final model included five predictors:

Predictor	Value	Score	Beta
Age	40 years	1.0	0.72
Smoking habit	Current smoker	1.0	0.70
Job title	High exposure job title	1.5	1.14
Work duration in construction industry	15 years	1.5	1.00
Self-related health	Feeling unhealthy	1.25	0.84
Standardized residual FEV1	-1.0	1.25	0.91

Area under the curve of the prediction rule

The uncorrected AUC of the model was 0.81 (95%CI: 0.75 to 0.86). The corrected AUC was 0.76. A cutoff point of 3.75 is suggested as optimal, with the following classification measures:

	CXR +	CXR -	
Rule +	33	534	567
Rule -	4	720	724
	37	1254	1291

- Sensitivity: 89.2%,
- Specificity: 57.4%,
- Negative Predictive Value: 99.4%,
- Positive Predictive Value: 85.2%

Model Validation

In the original Suarthana study,[1] the prediction model was only internally validated. A formal external validation procedure was not performed as currently recommended in TRIPOD+AI guidelines.[4]

To scope for studies reporting the use of the diagnostic prediction rule and any posterior external validation studies, the citations of the diagnostic rule development model were retreived from Google Scholar on 10/09/2024 and screened. Google Scholar was chosen due to its wide coverage of literature sources. A total of **59** records citing the paper were found. In comparison, other databases retreived less results: PubMed-MEDLINE (n = 11), Web of Science (n = 22), Scopus (n = 32), semantic scholar (n = 34), and dimensions (n = 26). All documents were reviewed, including those in other languages for which automatic translations were obtained to screen for any calclulations of the probability of silicosis based on the prediction rule. Out of **59** records citing the paper, **5 records**[5–9] reported having used the diagnostic prediction rule to classify workers' risk of pneumoconiosis and are described in the next subheadings:

Nicol, et al.[5]

In a case series of 6 young stonemasons from the UK who were diagnosed with silicosis after performing a high-resolution computed tomography (HRCT) (three of them with progressive massive fibrosis), the diagnostic rule was applied and all 6 cases had a probability of having silicosis of 0%.[5] All these 6 cases would have not been referred for further chest x-ray investigation based solely on the diagnostic prediction rule score.

Meijer, et al.[6]

A subset of 180 participants enrolled in the study used for the development of the diagnostic prediction rule were invited for further examination with chest HRCT, of which a total of **n=79** participants ultimately participated in the study and underwent HRCT.[6] Participants invited were intended to be representative of the different risk score categories of the diagnostic prediction rule. A final diagnosis of silicosis was not made based on HRCT and consensus by radiologists, so the study only reports HRCT findings for different ILO thresholds (0/0, 1/0, and 1/1), agreement between individual HRCT features between radiologists, and studied the association between the cumulative exposure index to silica and HRCT findings, controlling for smoking.

In participants with a normal CXR (ILO 0/0), only 34.9% had a normal HRCT. In these patients, findings suggestive of silicosis such as well-defined round opacities (8%) and parietal pleural abnormalities (24%) were frequent on HRCT. Emphysema was also frequent (41%), as well as irregular and/or linear opacities (22%).

Misclassification error of chest X-Ray

CXR based on Meijer, et al.[6]

A subset of 180 participants enrolled in the study used for the development of the diagnostic prediction rule were invited for further examination with chest high resolution computed tomography (HRCT), of which a total of **n=79** participants underwent HRCT.[6] However, a final diagnosis of silicosis was not made based on HRCT and consensus by radiologists, and the study limited to report HRCT findings with their frequencies among different ILO thresholds.

CXR based on ILO 1/0 cut-off from Hoy, et al.[10]

A recent study has estimated misclassification error of CXR using ILO categories against HRCT as the reference standard.[10] Using the standardized cut-off of 1/0, CXR diagnostic performance against HRCT was as follows:

	HRCT +	HRCT -	
CXR +	25	2	27
CXR -	15	68	83
	40	70	110

```
Sensitivity (%): 62.5

Specificity (%): 97.1

False Positive Rate (%): 2.9

False Negative Rate (%): 37.5

Positive Predictive Value; (%): 92.6

Negative Predictive Value; (%): 81.9

Likelihood Ratio (+): 21.87

Likelihood Ratio (-): 0.39

Accuracy (%): 84.5

Diagnostic Odds Ratio: 56.67
```

CXR based on ILO 1/1 cut-off from Hoy, et al.[10]

Using the summary data reported by Hoy, et al.[10] for different ILO scores, a 2x2 table can be recreated for the 1/1 ILO threshold:

	HRCT +	HRCT -	
CXR +	23	2	27
CXR -	17	68	83
	40	70	110

```
Sensitivity (%): 57.5

Specificity (%): 97.1

False Positive Rate (%): 2.9

False Negative Rate (%): 42.5

Positive Predictive Value; (%): 92

Negative Predictive Value; (%): 80

Likelihood Ratio (+): 20.12

Likelihood Ratio (-): 0.44

Accuracy (%): 82.7

Diagnostic Odds Ratio: 46
```

Accounting for misclassification error

Corrected ROC curve analysis of prediction models can be done by taking into account misclassification error for binary outcomes, provided that disease prevalence and misclassification rates are known.[11] Zawistowski, et al. simulate the value of the true outcome and then introduce different misclassification rates to understand the impact of misclassification on the prediction models' AUC.

In the case of the diagnostic prediction rule, we do not know the value of the true outcome, which would have been determined with HRCT. Instead, the diagnostic prediction rule used CXR as the reference test, which means that only the value of the misclassified outcome is know. Zawistowski's[11] procedure can be adapted to obtain the reverse-misclassified outcome instead, by using the information from Hoy, et al.[10], which would allow to estimate what the diagnostic rule AUC would have been had HRCT been used instead of CXR. The original functions, as well as the adapted reverse-misclassification function are found in the following script which is sourced into this document:

```
source("scripts/Zawistowski_misclassification_functions.R")
```

Instead of parameters `gamma0` (false-positive rate) and `gamma1` (true-positive rate), the `misclassify_reverse` function uses parameters `rev_g0` (probability of HRCT+ given CXR+) and `rev_g1` (probability of HRCT- given CXR-). From Bayes' theorem:

Probability of HRCT+ given CXR+ (`rev_g0`)

$$P(\text{HRCT+} \mid \text{CXR+}) = \frac{\text{Sensitivity} \times P(\text{HRCT+})}{P(\text{CXR+})}$$

```
P(HRCT+ | CXR+) = 0.85185
```

Probability of HRCT- given CXR- (`rev_g1`)

$$P(\text{HRCT-} \mid \text{CXR-}) = \frac{\text{Specificity} \times P(\text{HRCT-})}{P(\text{CXR-})}$$

```
P(HRCT- | CXR-) = 0.81928
```

Note that these simulations assume that outcome misclassification is non-differential.

```r
source("scripts/Diagnostic_rule_AUC_misclassification.R")
```

Results

Outcome	Mean	Median	Q1.25.	Q3.75.	Min	Max
CXR	0.740	0.741	0.715	0.766	0.592	0.865
CXR-corrected	0.784	0.786	0.762	0.810	0.637	0.893
HRCT	0.532	0.535	0.518	0.550	0.425	0.602

```
Absolute difference in AUC: -0.044
```

References

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