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# Comment on “Does the 5-2-1 criteria identify patients with advanced Parkinson’s disease? Real-world screening accuracy and burden of 5-2-1-positive patients in 7 countries”

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## Abstract

The 5-2-1 criteria are intended to help general neurologists identify patients with advanced Parkinson’s disease who may benefit from treatment optimisation, such as with a device-aided therapy. Although the 5-2-1 criteria claim to address an unmet need, we urge readers to cautiously interpret the results of this validation study.

**Keywords** Advanced Parkinson’s disease, Device-aided therapy, 5-2-1 criteria, Validation, Positive predictive value

*Dear editor,*

We have read with great interest the article entitled, “Does the 5-2-1 criteria identify patients with advanced Parkinson’s disease? Real-world screening accuracy and burden of 5-2-1-positive patients in 7 countries” by Malaty et al. [1]. The authors correctly point out the lack of an objective and uniform method or tool for timely identification of patients with advanced Parkinson’s disease (PD) who are inadequately controlled on oral medication and who may benefit from treatment optimisation, such as the initiation of a device-aided therapy (DAT) [2]. The apparently user-friendly 5-2-1 criteria reviewed in the article have been proposed to meet this clinical need [2, 3]. Although these criteria are based on expert opinion (a Delphi study) and have not been developed

according to accepted scientific guidelines for multivariable models, they might still be fit for purpose [4, 5].

The authors present the results of a validation study of the 5-2-1 criteria in a cohort of 4714 patients from 7 different countries [1]. However, we are concerned about some aspects of the methodology and the non-reporting of less favourable test characteristics, as we will discuss below. We will also cover the response to our comments by Antonini et al. [3].

First, the composition of the study population might have resulted in overestimation of the 5-2-1 criteria’s performance measures. For accurate validation, a model should be evaluated in a setting that reflects its intended use [5]. The 5-2-1 criteria are intended for use by general neurologists who may typically lack expertise in identifying patients with advanced PD eligible for DAT referral. However, the population in this validation study, comprised of PD patients naive to DAT, had a higher prevalence of advanced PD (14.9%) compared to that observed in general neurological practice (6.7% in our own study) [6]. It is important to note that a high prevalence within a validation population will generally lead to overly optimistic estimates of both the positive predictive value

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(PPV) and sensitivity of the 5-2-1 criteria, particularly when compared with estimates derived from populations with lower prevalence, such as those seen in a general neurological practice [7, 8].

Second, in this validation study, the reference test (gold standard) was based on a single neurologist's assessment of each patient's disease severity [1]. This approach reflects the particular setting of the current study, i.e., the evaluating neurologists had substantial expertise in identifying patients with advanced PD. However, if we assume that the study population is representative of a general neurological practice, it is unlikely that all evaluating neurologists have such extensive experience in assessing advanced PD. This discrepancy could have led to outcome misclassification in the validation study (i.e. patients being misclassified by the 'gold standard' evaluating neurologist as having or not having advanced PD) [9]. A possible method to reduce such bias is to use a consensus of multiple experts as the gold standard [6, 10].

Third, the accuracy of the 5-2-1 criteria was misrepresented. The researchers define the correct classification rate (CCR) as the sum of true positives and true negatives divided by the total number of patients [1]. However, the percentages in the table on page 5 of the article by Malaty et al. do not correspond to the figures in the cross-tabulation shown [1]. In our Table 1, we have presented the tabular data from the article with our own calculations, which show a CCR of 75.7%, whereas the article reports 88.1%. Moreover, it is important to note that the CCR is a misleading evaluation metric in so-called imbalanced datasets [11]. For example, if the sensitivity of a test is as low as 0% in a setting with a prevalence of 14.9%, the CCR would still be 85.1% (table A1 in Appendix).

Finally, some less favourable test characteristics of the 5-2-1 criteria were not reported (Table 1) [1]. The authors chose to report the area under the curve (AUC) values, rather than also including the sensitivity (78.6%) and specificity (75.2%). As a summary metric, the AUC does not provide an immediate insight into the clinical implications of using the 5-2-1 criteria [12]. Similarly, the authors did not discuss the implications of the low PPV of 35.7%, which suggests that a significant proportion of 5-2-1-positive patients may not yet have advanced PD according to the reference test [1]. This low PPV implies that application of the 5-2-1 criteria could lead to many patients being classified as having advanced PD, potentially leading to premature referral for DAT and consequently an increased burden on the referral network.

Our outlined concerns about the validation study of the 5-2-1 criteria have been addressed by Antonini et al. [3] (published elsewhere in this journal). In their response, Antonini et al. also provide additional accuracy measures for both the unadjusted 5-2-1 screening criteria and the

adjusted regression model of these criteria. The authors seem to claim that the adjusted model reflects the true performance of the 5-2-1 criteria. However, below we argue that only the unadjusted analysis should be considered.

For the adjusted regression model of the 5-2-1 criteria, the apparent higher PPV comes at the cost of a much lower sensitivity of 41.9%. The authors erroneously state that a low false negative rate (FNR) was maintained. However, the FNR here refers to patients with advanced PD who are not identified by the 5-2-1 criteria and is calculated as  $100 - \text{sensitivity}$ . In the adjusted model, the FNR is 58.1%, which we consider to be very high. Contrary to the author's claim, the negative predictive value (NPV) is not a good indicator of the FNR, as the NPV depends on the prevalence [13]. While Antonini et al. argue that the 5-2-1 criteria would reduce under-referral, they neglect the implications of the low sensitivity of the adjusted model.

Because the adjusted model reported by Antonini et al. has different accuracy measures than the unadjusted analysis, we reconstructed the crosstabs (Table 2). The question then becomes, which crosstab reflects the true screening performance of the 5-2-1 criteria? The adjusted model with low sensitivity but high specificity and PPV, or the unadjusted 5-2-1 criteria with reasonable sensitivity but lower specificity and low PPV?

The adjusted model was constructed using multivariable logistic regression to adjust for potential confounders, such as country, age and gender [1]. Importantly, adjustment for confounding was unnecessary because confounding is only an issue in research on causal relationships, not in prediction research such as screening studies [9, 14]. In addition, the authors did not present the full regression model including the intercept and regression coefficients, making it impossible for the reader to apply the model to an individual patient of a particular gender, age and nationality [5]. Furthermore, it is unclear how the final regression model was derived, as not all modelling steps are documented [5, 12]. For example, the authors do not explain why a cut-off of 0.5 was chosen for the calculated probabilities of the adjusted model, whereas any other cut-off would result in a different ratio of sensitivity to specificity (see Appendix for more details).

We argue that the unadjusted analysis is the only correct method to assess the true performance of the 5-2-1 screening criteria. This method allows a direct assessment of the accuracy measures from the cross-tabulation data. Therefore, we maintain that the 5-2-1 criteria have acceptable sensitivity but relatively low specificity, resulting in a low PPV of 35.7%. This is consistent with our own analysis of the 5-2-1 criteria [6]. Possibly, the PPV could be increased by modification of the 5-2-1 screening

**Table 1** Data from Table 2 of the article by Malaty et al. (2022) [1] with our own calculations of the accuracy measures. It should be noted that we inverted the columns and rows of the cross table, so that "yes" and "positive" appear on the left and top of the cross table, respectively. In the cross table, the letters A, B, C and D are shown to indicate the calculation steps used to calculate the diagnostic measures

5-2-1 screening criteria	advanced PD			Σ	Malaty et al.			Our calculations of accuracy measures			
	pos	neg	Σ		yes	no	Σ	CCR (A+D)/(A+B+C+D)	SENS <sup>A/(A+C)</sup>	SPEC <sup>D/(C+D)</sup>	PPV <sup>A/(A+B)</sup>
≥ 2 h off-time/day	pos	552 <sup>A</sup>	994 <sup>B</sup>	1546							
	neg	150 <sup>C</sup>	3018 <sup>D</sup>	3168				88.1%	75.7%	75.2%	35.7%
	Σ	702	4012	4714							
	yes	494 <sup>A</sup>	713 <sup>B</sup>	1207				88.4%	80.5%	82.2%	40.9%
	pos	208 <sup>C</sup>	3299 <sup>D</sup>	3507							
	neg	702	4012	4714							
	Σ	yes	111 <sup>A</sup>	68 <sup>B</sup>	179				86.0%	86.0%	62.0%
	pos	591 <sup>C</sup>	3944 <sup>D</sup>	4535							
	neg	702	4012	4714							
	Σ	yes	289 <sup>A</sup>	511 <sup>B</sup>	800				87.1%	80.4%	41.2%
	pos	413 <sup>C</sup>	3501 <sup>D</sup>	3914							
	neg	702	4012	4714							
	Σ	yes	702	4012	4714						
	pos	289 <sup>A</sup>	511 <sup>B</sup>	800							
	neg	413 <sup>C</sup>	3501 <sup>D</sup>	3914							
	Σ	702	4012	4714							

Abbreviations: CCR=correct classification rate, SENS=sensitivity, SPEC=specificity, PPV=positive predictive value, pos=positive, neg=negative, Σ= row/column total.

**Table 2** Cross table based on the accuracy measures as provided in the response by Antonini et al. [3]. The calculation steps for creating the cross table of the adjusted model are described at the bottom of the table

	advanced PD			Σ	CCR	SENS	SPEC	PPV	NPV
	yes	no							
<b>adjusted regression model of 5-2-1 criteria</b>									
pos	294†	152§	446		88.1%	41.9%	96.2%	65.9%	90.4%
neg	408¥	3860*	4268						
Σ	702	4012	4714						
<b>unadjusted 5-2-1 screening criteria</b>									
pos	552	994	1546		75.7%	78.6%	75.2%	35.7%	95.3%
neg	150	3018	3168						
Σ	702	4012	4714						

Abbreviations: CCR=correct classification rate, SENS=sensitivity, SPEC=specificity, PPV=positive predictive value, NPV=negative predictive value, pos=positive, neg=negative, Σ=row/column total.

† the number of true positives was calculated as follows: sensitivity × total number of patients with advanced PD (41.9% × 702 = 294).

¥ the number of false negatives was calculated as follows: total number of patients with advanced PD – true positives (702 – 294 = 408).

\* the number of true negatives was calculated as follows: specificity × total number of patients without advanced PD (96.2% × 4012 = 3860).

§ the number of false positives was calculated as follows: total number of patients without advanced PD – true negatives (4012 – 3860 = 152).

criteria to require the presence of  $\geq 2$  criteria instead of  $\geq 1$ .

In conclusion, the 5-2-1 criteria represent a welcome initiative flagging an unmet need. However, the validation study has several shortcomings, and the adjusted models of the 5-2-1 criteria do not provide a realistic estimate of the screening accuracy. To demonstrate the added value of the 5-2-1 criteria for real-world practice, the tool should be validated in representative PD populations, preferably following the established guidelines of STARD and TRIPOD [5, 15].

#### Abbreviations

AUC	Area under the curve
DAT	Device-aided therapy
FNR	False negative rate
NPV	Negative predictive value
PD	Parkinson's disease
PPV	Positive predictive value

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12883-024-03692-2>.

Supplementary Material 1

#### Acknowledgements

Not applicable.

#### Author contributions

HRM drafted the manuscript. EB and TvL substantively revised it, after which HRM produced the final version of the manuscript. All authors read and approved the final manuscript.

#### Funding

HRM received funding from the Dutch Parkinson Patient's Association [grant number 2017-R04] and funding from the University Medical Center Groningen, Junior Scientific Masterclass [grant number GR-AGIKO 18–02]. Neither funding source was involved in the writing of this manuscript.

#### Data availability

No datasets were generated or analysed during the current study.

#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

Not applicable.

##### Competing interests

TvL reports having received consulting fees from AbbVie, Britannia Pharm., Eurocept, and Clexio, and research grants from the Michael J. Fox Foundation, the Dutch Brain Foundation, and the University Medical Center Groningen, all unrelated to this work. HRM and EB declare no competing interests.

##### Authors' information

HRM received the aforementioned grants for the research project "Development of a screening tool for timely referral for advanced therapy in Parkinson's disease". This ongoing project aims to develop and validate a clinical decision model using data from two large cohorts with prospectively collected data.

Received: 20 November 2023 / Accepted: 24 May 2024

Published online: 05 June 2024

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