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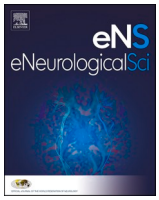

Letter to the Editor

Evaluation of the gold cost criteria as a diagnostic criteria of amyotrophic lateral sclerosis

Dear Editor

The Gold Coast criteria (GCC) are new diagnostic criteria for amyotrophic lateral sclerosis (ALS), which were recently proposed by an international panel convened as a joint initiative by the International Federation of Clinical Neurophysiology, the ALS Association, the World Federation of Neurology, and the Motor Neuron Disease (MND) Association at Gold Coast, Australia, in September 2019 [1].

The GCC consist of three main components: 1. Progressive motor impairment documented through history or repeated clinical assessments after a period of normal motor function. 2. The presence of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction in at least one body region, or LMN dysfunction in at least two body regions. 3. Exclusion of mimicking diseases through appropriate investigations [2].

The utility of needle EMG and nerve conduction studies was affirmed in the diagnosis of ALS [3,4]. However, there is a concern that emerged about the sensitivity of revised El Escorial (rEE) and Awaji criteria during the early stages of ALS, also findings in diagnostic delays which cause reducing recruitment into trials [5–7]. Also, EEC and Awaji criteria are characterized by high complexity leading to high inter-rater variation [7].

We aimed to establish robust evidence using the recent literature about GCC. We searched PubMed, Web of Science, Scopus and Embase to include all the trials about GCC and to provide a narrative discussion about its diagnostic accuracy and limitations. We used a combination of keywords related to GCC and ALS: (“Gold Cost Criteria”; “GCC”; “Gold Cost”) AND (“Amyotrophic Lateral Sclerosis”; “ALS”; “motor neuron”; “Gehrig Disease”; “Guam Disease”).

We included four trials [2,8–10] conducted in 1937 ALS and 411 Non-ALS patients. [Supplement, Fig. 1] Baseline characteristics of the included studies are detailed in [Supplement, Table 1]. To ensure the quality of studies, we performed an assessment of quality using QUADAS-2 tool. [Supplement, Fig. 2]. The study conducted by Stikvoort Garcia et al. [10] lacked clarity due to a bias observed in the reference standard test. Insufficient information was provided regarding whether the interpretation of reference standard results was done without knowledge of the index test results.

Our analysis, conducted with Meta Disc V 2.0 [11], encompassed three studies [2,8,9]. One study was excluded due to insufficient data [10,11]. The sensitivity ranges from 88 % to 97 %, with a high pooled sensitivity of 0.93 (95 % CI 0.88, 0.96, $I^2 = 0.934$) with a high pooled specificity of 0.84 (95 % CI 0.22, 0.99, $I^2 = 0.955$) [Fig. 1]. The pooled positive likelihood ratio (PLR) was 5.928 (95 % CI 0.506, 69.45), which indicates a moderate increase in the likelihood of a positive test result in individuals with ALS compared to those without. However, the wide confidence interval highlights the need for caution and the potential variability in this estimate. The pooled negative likelihood ratio (NLR) was 0.081 (95 % CI 0.038, 0.17), indicating a relatively low likelihood of obtaining a negative test result in individuals with ALS compared to those without. The narrow confidence interval suggests a more precise estimate, indicating reasonably good diagnostic performance for ruling out the condition with a negative test result. The diagnostic odds ratio was 73.568 (95 % CI 3.713, 1457.687) which is considered a robust diagnostic performance. However, the wide confidence interval indicates some uncertainty, and further studies or larger sample sizes may be needed to narrow down the range and provide a more precise estimate of the diagnostic accuracy.

Shen et al. [2] encourage the application of GCC in clinical practice as a diagnostic criterion of ALS, which report greater sensitivity (96.6 %, 95 % CI = 95.3 %–97.5 %) than other diagnostic criteria like rEEC (85.1 %, 95 %CI = 82.9 %–87.1 %) and Awaji (85.3 %, 95 %CI = 83.2 %–87.3 %) [2], however, the study included highly suspected ALS patients, resulting in only 1.9 % without ALS diagnosis. The high sensitivity (96.7 %) and low specificity (17.4 %) yield unacceptable false positive ALS diagnoses for a severe disease. The study’s skewed patient distribution limits its applicability to less selected cohorts. Pugdahl et al. [8] conducted a trial to evaluate the diagnostic accuracy of GCC in five European centers, which showed that sensitivity for the GCC was 88.2 %, which was higher than for previous criteria, and they explained the higher sensitivity by the fact that the GC criteria consider progressive muscular atrophy (PMA) as a form of ALS with high specificity preserved.

Interestingly, in 2021, Hannaford et al. [9] showed that specificity was comparable across the 3 criteria (88.5 % for GCC, 96.2 % for rEEC, and 95.5 % for Awaji criteria) which was higher than the specificity found in Shen et al. study [2] even that the inclusion criteria was the same in both studies which arise a debate [2,8]. However, the GCC criteria differ from the older criteria by including patients with progressive muscular atrophy (PMA) but excluding those with isolated upper motor neuron (UMN) signs like primary lateral sclerosis (PLS). In Hannaford et al. study [9], an incorrect reference standard including PLS led to 17 false negatives, 16 of whom actually met the rEE and Awaji criteria for ALS. Additionally, 29 and 27 PMA patients were wrongly classified as ALS according to the AW and rEE criteria, respectively. This misclassification occurred because both criteria require UMN signs. A correct reference standard would have increased GCC criteria sensitivity and decreased sensitivity for AW and rEE criteria, favoring the GC criteria.

In another study conducted in 2021, Vucic et al. [5] advocate for GCC due to its simplicity, reliability, validity, and clinical usefulness. Similarly, Jongh et al. [12] reported a minor delay in diagnostic time with GCC compared to rEE criteria, with rEE criteria at 10.0 (6.2–16.7) months and GCC at 10.4 (6.3–18.0) months. Despite this small difference, which is likely not significant due to the wide confidence intervals,

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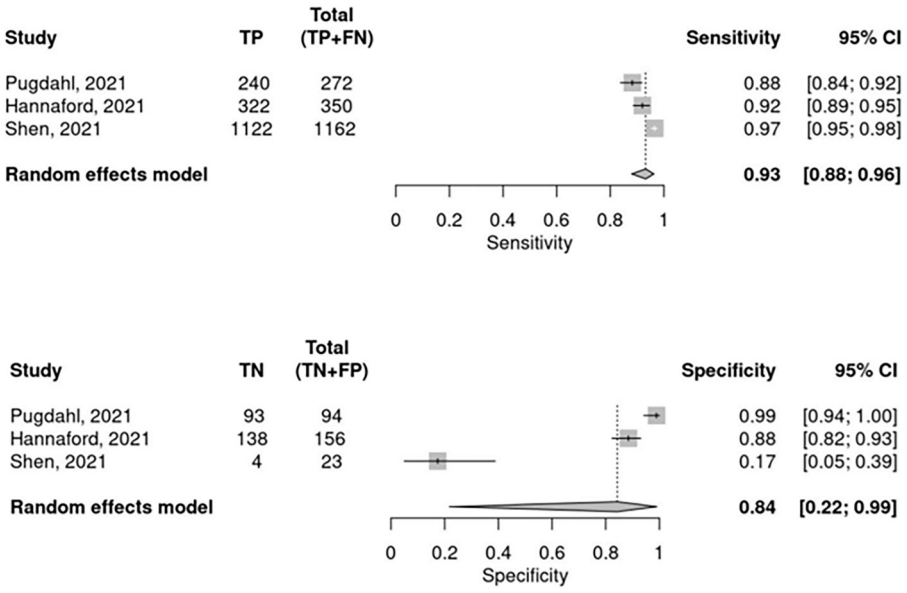

Fig. 1. Forrest plots show the sensitivity and specificity of GCC.

the findings support the use of GCC. This minor delay is understandable, as GCC includes additional patients with only LMN affection, who progress slightly slower.

The challenge lies in establishing robust evidence supporting the utilization of GCC and determining the generalizability of GCC diagnostic criteria. Across all different ALS presentation types such as bulbar onset, spinal onset, and limb onset, there is an observable enhancement in sensitivity and specificity values when compared to the older diagnostic criteria. In Pugdahl study [8], it was noted that spinal onset exhibited a sensitivity of 91.2 %, surpassing the values of Awaji and EEC, along with an impressive specificity of 98.6 %. Diverse sensitivity values were documented for bulbar onset in studies conducted by Pugdahl (83.5 %), Hannaford (90.9 %), and Shen (96.6 %) [2,8,9]. Meanwhile, the study by Shen et al. [2]highlighted notable specificity values for limb onset (17.4 %). However, this finding raises considerable suspicion as Hannaford et al. [9] reported a significantly higher specificity of 88.5 % for limb onset [7]. A previous meta-analysis reported that diagnostic accuracy of Awaji criteria was higher in bulbar- than in limb-onset patients [13]. Also, it shows that the diagnostic performance of the Awaji criteria was higher than the rEE criteria with pooled sensitivity: 81.1 % vs 62.2 % [13]. In our review, it is important to acknowledge additional factors contributing to the variability, apart from the reasons already discussed. These factors include significant variations that exist within the study populations [2]. A crucial aspect of the GCC criteria, which involves excluding other disease processes, lacks a precise definition. The interpretation of this requirement may differ among laboratories, leading to variability in the diagnostic process. Also, while the GCC criteria are comparatively less complex than the rEE and Awaji criteria, there is still potential for variability in their application, as demonstrated in previous research on the rEE and Awaji criteria [7].

In conclusion, it is suggested that the GCC criteria should be used in clinical practice, although the available evidence may not be entirely sufficient. Moreover, it is advisable to conduct prospective multicenter studies that specifically address variability to further support these recommendations.

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Declaration of competing interest

The authors declare no competing financial interests.

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