Reconceptualization of the Erlangen Score for the Assessment of Dementia Risk: The ERlangen Score

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Abstract.
Background: The established Erlangen Score (ES) for the interpretation of cerebrospinal fluid (CSF) biomarkers in the diagnostics of Alzheimer's disease (AD) uses markers of amyloidopathy and tauopathy, equally weighted to form an easy-interpretable ordinal scale. However, these biomarkers are not equally predictive for AD.
Objective: The higher weighting of the $A\beta_{42}/A\beta_{40}$ ratio, as a reconceptualized ERlangen Score (ERS), was tested for advantages in diagnostic performance.
Methods: Non-demented subjects ($N = 154$) with a mean follow up of 5 years were assigned to a group ranging from 0 to 4 in ES or ERS. Psychometric trajectories and dementia risk were assessed.
Results: The distribution of subjects between ES and ERS among the groups differed considerably, as grouping allocated 32 subjects to ES group 2, but only 2 to ERS group 2. The discriminative accuracy between the ES (AUC 73.2%, 95% CI [64.2, 82.2]) and ERS (AUC 72.0%, 95% CI [63.1, 81.0]) for dementia risk showed no significant difference. Without consideration of the $A\beta_{42}/A\beta_{40}$ ratio in ES grouping, the optimal cut-off of the ES shifted to ≥ 2.
Conclusions: The ERS showed advantages over the ES in test interpretation with comparable overall test performance, as fewer cases were allocated to the intermediate risk group. The established cut-off of ≥ 2 can be maintained for the ERS, whereas it must be adjusted for the ES when determining the $A\beta_{42}/A\beta_{40}$ ratio.

Keywords: Alzheimer's disease, dementia risk, Erlangen Score, longitudinal study, neuropsychological trajectories

INTRODUCTION

A biological definition of Alzheimer's disease (AD) with surrogate markers for amyloid plaques and neurofibrillary tangles has been proposed to detect and treat early-stage AD [1–7]. These surrogate markers, such as decreased amyloid-β (Aβ) 42, decreased ratio of $A\beta_{42}$ to $A\beta_{40}$ ($A\beta_{42}/A\beta_{40}$), or elevated tau with phosphorylated threonine at position 181 (pTau) in cerebrospinal fluid (CSF) are changed years before the onset of cognitive deficits [8,9]. Therefore, a biological definition could allow therapy at the stages of subjective (SCI) or mild cognitive impairment (MCI) [10].

A disadvantage of a biological definition with different variables is the resulting number of possible combinations in which the parameters are not

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congruently changed. Especially in the case of the widespread AT(N) classification with its nominal scale [11], this results in combinations whose clinical significance and relation to AD are difficult to interpret. The Erlangen Score (ES) [12–14], which was established before the AT(N) classification, has the advantage of an ordinal scale, so that higher scores in non-demented individuals are associated with a higher risk of AD and dementia onset, respectively. The Erlangen Score is a sum score of two categories, amyloidopathy (lowered $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$) and tauopathy (increased total tau (tTau) or pTau), with three characteristics: normal (0), borderline pathological (1), and definitive pathological (2). The resulting scale from ES 0 to 4 provides the clinician with an easily interpretable and well-established prediction of the patient's risk of progression to dementia [12–17]. However, for the test interpretation, the scores 2 and 3 of the ES are combined into a category indicating intermediate risk for the presence of AD, which complicates the decision-making compared with a binary outcome. Furthermore, since the introduction of the ES, it has become increasingly apparent that the variables are not equally indicative of the risk of AD. Individuals with increased pTau and tTau without amyloidopathy have a significantly lower risk of developing dementia than individuals with positive surrogate markers for amyloidopathy [18, 19]. This biomarker constellation has been described as suspected non-Alzheimer pathology (SNAP), since the association to AD is unclear. In cohorts of cognitively healthy individuals or with MCI, the proportion of SNAP is nearly a quarter [20]. Consequently, the presence of amyloidopathy appears to be central to the presence of AD, but $A\beta_{42}$, in contrast to the $A\beta_{42}/A\beta_{40}$ ratio as a surrogate marker for amyloidopathy is also decreased in other neurodegenerative diseases, like Lewy body dementia, frontotemporal dementia or idiopathic intracranial hypertension [21–23]. Furthermore, the $A\beta_{42}/A\beta_{40}$ ratio seemed to be changed sooner than the $A\beta_{42}$ level in AD [24]. Unfortunately, the $A\beta_{42}/A\beta_{40}$ ratio was not routinely determined in several large cohorts, such as Alzheimer's Disease Neuroimaging Initiative (ADNI), and is not yet part of all diagnostic standards and recommendations.

The requirement for a revision of the Erlangen score should accordingly take into account (I) that an unambiguous statement regarding the risk of dementia can be made for as many individuals as possible, (II) that individuals with SNAP have a lower risk of dementia, and (III) that the $A\beta_{42}/A\beta_{40}$ ratio is superior to the $A\beta_{42}$ level in terms of sensitivity and specificity. Furthermore, the possibility of determining the risk of dementia in cohorts in which the $A\beta_{42}/A\beta_{40}$ ratio has not been determined should be retained (IV). Therefore, we propose to consider the $A\beta_{42}/A\beta_{40}$ ratio in a second step to the established Erlangen Score and to increase or decrease it by one point accordingly, provided that the value 0 is not undercut and the value 4 is not exceeded. This study compares the psychometric trajectories and dementia risk of the established score with those of the revised version to determine whether the concept version performs better.

MATERIALS AND METHODS

Study population

Individuals were enrolled at the memory department of the clinic for psychiatry and psychotherapy of the Friedrich-Alexander-University Erlangen-Nuremberg from April 2010 to April 2022. Participants were required to have a complete CSF examination available for $A\beta_{42}$, the $A\beta_{42}/A\beta_{40}$ ratio, pTau181, and tTau, a structural brain scan and a neuropsychological assessment within 6 months. Only participants with SCI or MCI and at least one follow-up visit more than 12 months from baseline were included. The inclusion criteria were described in detail by Oberstein et al. [25]. The follow-up period was 12 to 145 months. The study protocol Nr. 3987 was approved by the clinical ethics committee of the University of Erlangen-Nuremberg. The patients/participants provided their written informed consent to participate in this study.

Neuropsychological assessment

All participants of the Erlangen cohort were assessed using the German version of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery plus (CERAD-NB+) [26]. The rate of missing tests varied between 10.2% for Mini-Mental Status Examination (MMSE) and 33.6% for phonemic fluency. A total of 643 examinations was available from 152 subjects.

CSF ELISA

The concentrations of $A\beta_{40}$ and $A\beta_{42}$ in CSF were determined with commercially available ELISAs from IBL International (Hamburg, Germany) and

Fujirebio Europe (formerly Innogenetics, Ghent, Belgium), respectively. The Aβ ELISAs used only detect Aβ starting at Asp1, i.e., $A\beta_{1-42}$ and $A\beta_{1-40}$, respectively. The abbreviations $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio used in this manuscript therefore refer to the respective Aβ 1-x peptide variants until further notice. Total tau and pTau181 in CSF were measured with ELISAs from Fujirebio Europe. The calculation and values of the cut-offs and borderline zones are given elsewhere [12, 25].

Erlangen score

The Erlangen Score was formed using the criteria described by Lewzuk et al. [7, 12]. Values for amyloidopathy (decreased $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio) and tauopathy (increased pTau181 or tTau) are classified as normal (0), borderline (1), or definitely pathological (2). Classification is based on the cut-off values of the respective laboratory, with borderline values defined as a result within 10% of the threshold value (i.e., 10% decrease in $A\beta_{42}$ and/or $A\beta_{42/40}$ or 10% increase in tTau and/or pTau181). If $A\beta_{42}$ and the $A\beta_{42}/A\beta_{40}$ ratio are assigned different values, only the higher value is used for the amyloidopathy assessment. The same applies to pTau181 and tTau in the tauopathy score. The values for amyloidopathy and tauopathy are added to give a total score, which accordingly ranges from 0 to 4. An ES of 0 indicates "no neurochemical evidence for AD", an ES of 1 means "neurochemically unlikely AD". ES 2 and ES 3 are interpreted as "neurochemically possible AD", an ES 4 as "neurochemically probable AD". For the revision of the Erlangen score, the $A\beta_{42}/A\beta_{40}$ ratio was not taken into account in the first step and the value was formed as before, i.e., using only the $A\beta_{42}$ level, neglecting the $A\beta_{42}/A\beta_{40}$ ratio. In the second step, the $A\beta_{42}/A\beta_{40}$ ratio was evaluated as normal (–1) or pathological (1) and added to the result, provided that the value did not fall below 0 and did not exceed 4. In these cases, the values 0 and 4, respectively, were retained.

Statistics

Linear mixed-effect models (LMEM) were calculated for both the ES and the ERS for group 1 to 4 with group 0 as reference to assess whether the change in individual CERAD-NB+subtest scores differed between the groups. For the mixed-effects modelling, observations were at the bottom level (level one) while they were nested within the level two variable patient. Fixed effects were the ES and ERS groups, respectively, time from baseline in years, and the interaction term between time from baseline and ES and ERS groups, respectively. The models were specified with a random intercept, i.e., subject identification number, and slope, i.e., time from baseline in years. The CERAD-NB+sub scores (MMSE, Word List Memory, Word List Delayed Recall, Constructional Praxis Recall, Phonematic verbal fluency) were used as dependent variables.

To assess the effect of the different Erlangen scores on the risk of progression to dementia, Cox proportional hazard analyses were performed, corrected for MMSE and age at baseline, sex, and years of education. Survival was defined as the interval between enrolment and progression to dementia, which was defined as an MMSE below 25 and the impairment of daily life activities. The proportional hazards assumption was assessed using Schoenfeld residuals.

To assess the predictive validity of ES or ERS scores, receiver operating characteristic (ROC) curves including area under the curve (AUC) analysis were determined with conversion to dementia as a positive condition. The nonparametric method of DeLong et al. was used to compare the AUC in a paired samples scenario [26]. The Youden's index was used in conjunction with the ROC analysis to determine an optimal threshold value of the ES or ERS in terms of a dichotomous classification between low and high dementia risk.

Missing data were replaced by multiple imputation, as implemented in SPSS. Otherwise, missing data were handled using the maximum likelihood estimation of Cox proportional hazard models and LMEM.

Statistics was performed using SPSS (version 28.0; SPSS, Chicago, IL, USA). We used the TRIPOD checklist when writing our report [27].

RESULTS

152 non-demented subjects from the Erlangen memory clinic were included in this study. A flowchart of the study participants is shown in Supplementary Figure 1.

Participants´ baseline characteristics

The study's population comprised 58 females (38.2 %) and 94 males (61.8 %) with a mean age at baseline of 66.0 ± 9.7 years. The median MMSE at baseline was 28 with an interquartile range (IQR) of 3. The

Table 1
Study population characteristics

	0 ES	0 ERS	1 ES	1 ERS	2 ES	2 ERS	3 ES	3 ERS	4 ES	4 ERS	ES	ERS
n (female)	55 (22)	65 (26)	9 (4)	29 (6)	32 (7)	2 (1)	10 (2)	37 (17)	46 (23)	19 (8)	$\chi^2(4)=7.956$, $p=0.093$	$\chi^2(4)=5.039$, $p=0.0283$
	M / SD	M / SD	M / SD	M / SD	M / SD	M / SD	M / SD	M / SD	M / SD	M / SD		
Age [y]	61 / 8	61 / 8	61 / 9	66 / 9	67 / 9	73 / 11	64 / 8	71 / 8	72 / 8	71 / 10	$F_{(147,4)}=11.714$, $p<0.001$	$F_{(147,4)}=11.714$, $p<0.001$
Education [y]	14 / 3	14 / 3	14 / 3	15 / 3	15 / 3	14 / 2	16 / 3	14 / 4	13 / 3	14 / 4	$F_{(147,4)}=2.749$, $p=0.031$	$F_{(147,4)}=0.626$, $p=0.645$
	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR	Md / IQR		
MMSE	28 / 2	28 / 2	28 / 2	28 / 3	27.5 / 3	27	28 / 1.75	28 / 2	27 / 2.25	27 / 2.25	$H=34.901$, $df=4$, $p=0.032$	$H=10.206$, $df=4$, $p=0.037$

frequencies and baseline demographics for each ES and ERS group respectively are shown in Table 1. Compared with the ES, the ERS had substantially fewer individuals classified as category 2 (Table 1 and Fig. 1). The change in algorithm from ES to ERS also resulted in more subjects being assigned to group 3 than to group 4, which was mainly due to the different evaluation of subjects with a pathological change in the $A\beta_{42}/A\beta_{40}$ ratio but normal $A\beta_{42}$ levels ($n = 35$). Age and MMSE at baseline differed significantly between the groups in both the ES and the ERS (Table 1). The years of education differed only between the ES groups (Table 1).

In pairwise comparisons for the ES groups, group 3 was significantly older than group 0, $p < 0.001$, $M_{Diff} = 11.101$, 95% CI [6.24, 15.96], and group 1, $p < 0.001$, $M_{Diff} = 11.171$, 95% CI [2.31, 20.03]. In pairwise comparisons for the ERS groups, both group 3 and group 4 were significantly older compared to group 0, $p < 0.001$, $M_{Diff} = 10.058$, 95% CI [3.56, 16.56] and $p < 0.001$, $M_{Diff} = 9.314$, 95% CI [4.18, 14.45]. In both the ES and the ERS, group 4 performed significantly worse in MMSE in comparison to group 0, $z = 3.449$, $p = 0.006$ and $z = 2.891$, $p = 0.038$. All other Bonferroni-adjusted post-hoc analyses revealed no significant differences between the groups of the ES and the ERS scores, respectively.

Psychometric trajectories of the different ES and ERS groups

For both the ES and the ERS, the cross-sectional and longitudinal associations of each group with selected items of the CERAD-NB+, i.e., MMSE, Word List Memory, Word List Delayed Recall, Constructional Praxis Recall, and Phonematic Verbal Fluency Test were examined using LMEM with group 0 as the reference group (Fig. 2).

The trajectories of MMSE and Word List Memory in both ES and ERS group 4 were significantly worse than in the respective biomarker-negative control group. Moreover, when considering the ES group 4, the trajectories of Phonematic Verbal Fluency Test were significantly worse, and for the ERS group 4, additionally those of the Word List Delayed Recall. The longitudinal trajectories of MMSE also indicated significantly poorer outcome in both ES and ERS for group 3 compared to the control group. In addition, the ERS group 3 showed significantly worse trajectories in Constructional Praxis Delayed Recall and Phonematic Verbal Fluency Test. The different allocation of individuals to ERS compared to ES also
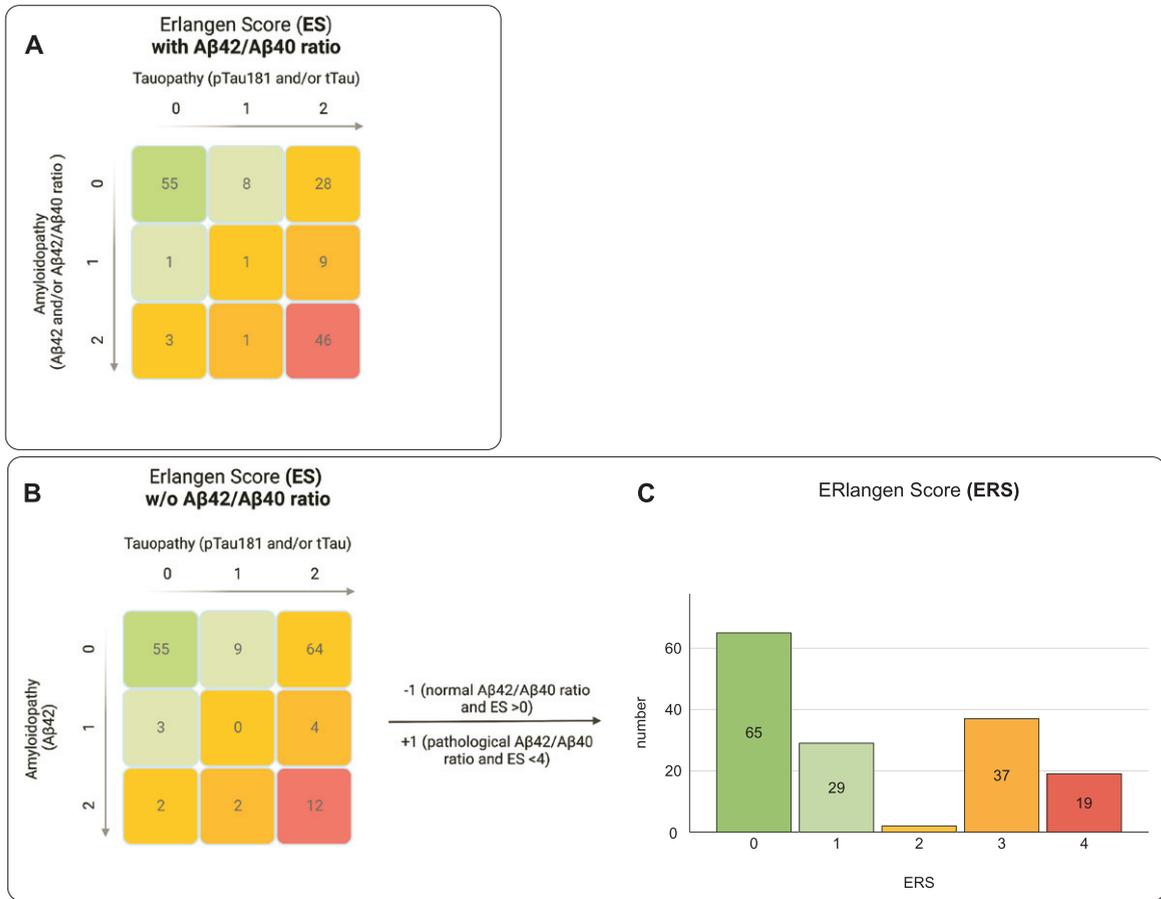
Fig. 1. Comparison of the grouping of the study population using the established Erlangen Score (ES) and the reconceptualized ERlangen Score (ERS). The ES was calculated with (A) and without (B) consideration of the $A\beta_{42}/A\beta_{40}$ ratio. The ERS was calculated in two steps. In step 1, the score is calculated as in the ES, but without considering the $A\beta_{42}/A\beta_{40}$ ratio, i.e., as in Fig. 1B. In the second step, in case of a pathological or normal $A\beta_{42}/A\beta_{40}$ ratio, +1 or –1 is added, provided the value is not below 0 or exceeds 4. By changing the weighting of the $A\beta_{42}/A\beta_{40}$ ratio in the ERS, substantially fewer participants were assigned to the intermediary risk group (yellow group) compared to the ES. The score of the ES can be derived by summing values for amyloidopathy and tauopathy (0 = normal, 1 = borderline pathological, 2 = definitive pathological). Colors indicate assumed dementia risk: low (green), mild (light green), intermediate (yellow), increased (orange) or probable (red).

resulted in all trajectories of the examined psychometric tests being more negative in group 4, i.e., the group with all altered biomarkers, than in group 3, which consisted mainly of patients with a pathological $A\beta_{42}/A\beta_{40}$ ratio and pTau or tTau but normal $A\beta_{42}$, but without reaching statistical significance. There were only two individuals in the ERS group 2, both of whom had worsened trajectories of MMSE, $M_{Diff} = -1.066, 95\%$ CI [–1.556, –0.557], Word List Memory, $M_{Diff} = -0.913$, 95% CI [–2.790, –0.243], and Constructional Praxis Recall, $M_{Diff} = -0.696$, 95% CI [–1.370, –0.022]. The results for ES group 2, which included 32 subjects, indicated no significant difference between the CERAD-NB + subtest at baseline and their trajectories compared with group 0. A complete list of all LMEM results for the CERAD-

NB+subtests is shown in Supplementary Table 1. In addition, an LMEM analysis was also performed for the ES without considering the $A\beta_{42}/A\beta_{40}$ ratio (Supplementary Table 2).

Dementia risk of the different ES and ERS groups

The risk of dementia in groups 0 to 4 was examined in a preliminary analysis using Kaplan Meyer curves and compared between each group of both ES and ERS scores by univariate and multivariate Cox regression models with the covariates age, sex, education, and MMSE at baseline (Fig. 3).

Subjects with ES scores 3, $p < 0.001$, adjusted hazard ratio (HR) 14.93, 95% CI [3.6, 61.5], and 4, $p = 0.002$, HR 5.3, 95% CI [1.9, 15.2], had a
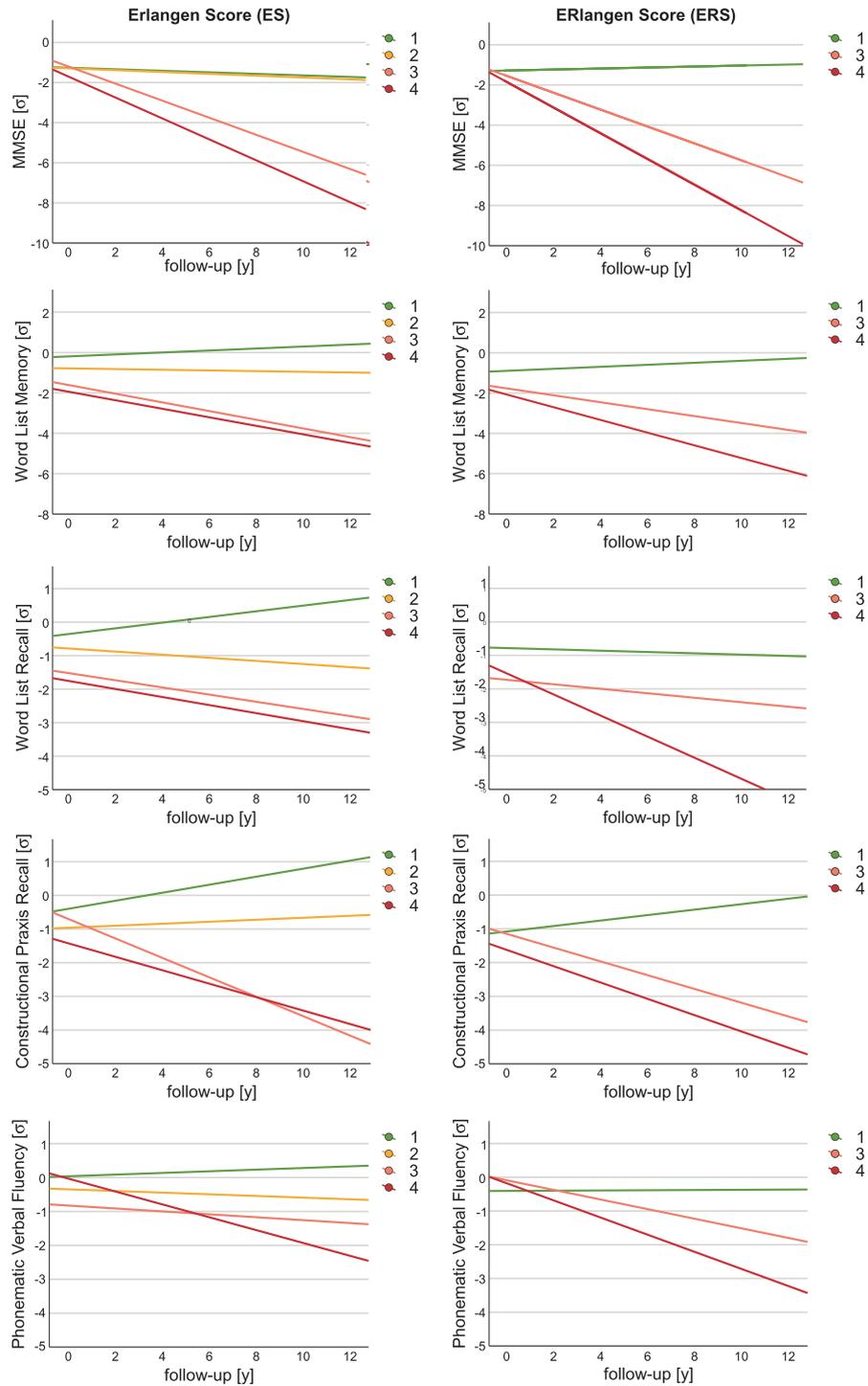
Fig. 2. Cognitive trajectories by Erlangen Score (ES) and ERlangen Score (ERS). For all CERAD-NB+subtests shown, the z-score was used for the linear mixed-effects model analyses of the ES (left) and the ERS (right). The cognitive trajectories are not shown for ERS group 2 because it included only two individuals. Exact *p*-values and 95% confidence interval are given in Supplementary Table 1. MMSE, z-score of the Mini-Mental State Examination; σ, standard deviation.

significantly higher risk of dementia than the control group with ES score 0. Similarly, the risk of dementia was also found to be significantly increased in groups 3 and 4 of the ERS compared with group 0, $p < 0.001$, HR 5.3, 95% CI [2.0, 14.0], and $p = 0.008$, HR 5.1, 95% CI [1.5, 16.9], respectively. Forty-one individuals (27.0%) progressed to dementia during the follow-up period, including the two individuals in ERS group 2. Of the 32 subjects with ES 2, three progressed to dementia during the follow-up period. Once the $A\beta_{42}/A\beta_{40}$ ratio was not considered in the calculation of the ES, group 2 showed a significant increase in the risk of dementia compared to the control group, HR 2.93, 95% CI [1.14, 7.53] (Supplementary Figure 2).

Discriminative ability of the ES and the ERS for dementia risk

The ROC curves for both the ES and the ERS were analysed to assess their predictive ability for dementia risk. The area under the curve (AUC) was 73.2%, 95% CI [64.2, 82.2], for the ES and 72.0%, 95% CI [63.1, 81.0], for the ERS score, respectively. The predicted risk of dementia determined by ROC analyses showed no significant difference between the ES and the ERS, $z = 0.811$, $p = 0.417$. The optimal cut-off value for a dichotomous difference between low and high dementia risk determined with the Youden index was 3 for the ES and 2 for the ERS. At the respective optimal cut-off values, the ES had a sensitivity of 71% and a specificity of 76%, and the ERS had a sensitivity of 73% and a specificity of 75%. If the existing cut-off value for "neurochemically possible AD" is used, i.e., cut-off at 2, the ES showed a slightly better sensitivity of 81% but a reduced specificity of 50.5%.

DISCUSSION

In this study, the reconceptualized ERlangen Score (ERS) showed advantages over the Erlangen Score (ES) in test interpretation with comparable overall test performance, as more cases in the ERS were assigned a definite dementia risk and fewer cases remained in the intermediate risk group, e.g., a score of 2 or the middle scale point. Thus, the separate weighting of the $A\beta_{42}/A\beta_{40}$ ratio improved group assignment in terms of interpretation of findings, whereas there was no significant difference between the ES and the ERS with respect to the prognosis of dementia risk and psychometric trajectories when

findings were assessed using the ordinal scale with 5 items.

In this cohort, individuals with an ES of 2 did not show an increased risk of dementia compared with the control group, so that the previous interpretation of the ES in terms of an intermediate risk of dementia did not apply to them [13, 14]. However, if only the CSF-$A\beta_{42}$ level and not the $A\beta_{42}/A\beta_{40}$ ratio was used for the evaluation of amyloidopathy, the established interpretation of the ES proved its validity, since group 2 showed a dementia risk and psychometric trajectories that were between the groups 0/1 and 3/4. The different results for ES group 2 as a function of $A\beta_{42}/A\beta_{40}$ ratio are likely due to the higher sensitivity of the $A\beta_{42}/A\beta_{40}$ ratio for detecting amyloidopathy at early stages of AD compared with $A\beta_{42}$ levels, leading to misclassification of individuals with pathological $A\beta_{42}/A\beta_{40}$ ratios and normal $A\beta_{42}$ levels [7, 28, 29]. Confirming the validity of the ES score without considering the $A\beta_{42}/A\beta_{40}$ ratio is of importance since only the $A\beta_{42}$ level and not the $A\beta_{42}/A\beta_{40}$ ratio was regularly determined in various study cohorts in the past [6, 30, 31]. The ERS continues to take $A\beta_{42}$ levels into account because the $A\beta_{42}/A\beta_{40}$ ratio has not been determined in several large cohorts and the ERS should be used as universally as possible. Given the higher sensitivity of the ratio and the indications that a lower $A\beta_{42}$ level without a pathological $A\beta_{42}/A\beta_{40}$ ratio was not associated with an increased risk of AD, we recommend that all parameters of the ERS, including the $A\beta_{42}/A\beta_{40}$ ratio, should always be determined with a view to possible therapy [21, 32]. In ES and ERS, pTau and tTau are interchangeable as their levels in CSF are highly correlated. Especially in the case of high tTau levels, the classification must be checked for the presence of other diseases, especially rapidly progressing neurodegenerative diseases, in order to avoid misclassification [7, 33]. The advantages of the ES compared to other nominal classifications, e.g., the ATN classification, remain in the ERS as well, since thanks to the ordinal scale no categories are formed in which the interpretation of findings is impaired due to incongruent changes in biomarkers. Additionally, ES in the absence of $A\beta_{42}/A\beta_{40}$ ratio and ERS share the same set of computational procedures, and the estimation of dementia risk can be performed with both scores using identical cut-offs. The accuracy of the ES (73.2%) and ERS (72.0%) is comparable to other established scores such as the Incidence of Dementia Risk Score, the Dementia Risk Score,

A number entering interval/(withdrawing) [months]

ES	0	24	48	72	96	120	144
0	55 (9)	45 (10)	35 (4)	29 (12)	15 (7)	6 (5)	1 (1)
1	9 (2)	7 (1)	6 (0)	5 (2)	3 (3)		
2	32 (4)	28 (8)	19 (5)	13 (4)	7 (5)	2 (2)	
3	10 (1)	8 (2)	4 (1)	3 (1)			
4	46 (5)	36 (9)	18 (4)	6 (4)			
	152 (21)	124 (30)	82 (14)	56 (23)	25 (15)	8 (7)	1 (1)

B number entering interval/(withdrawing) [months]

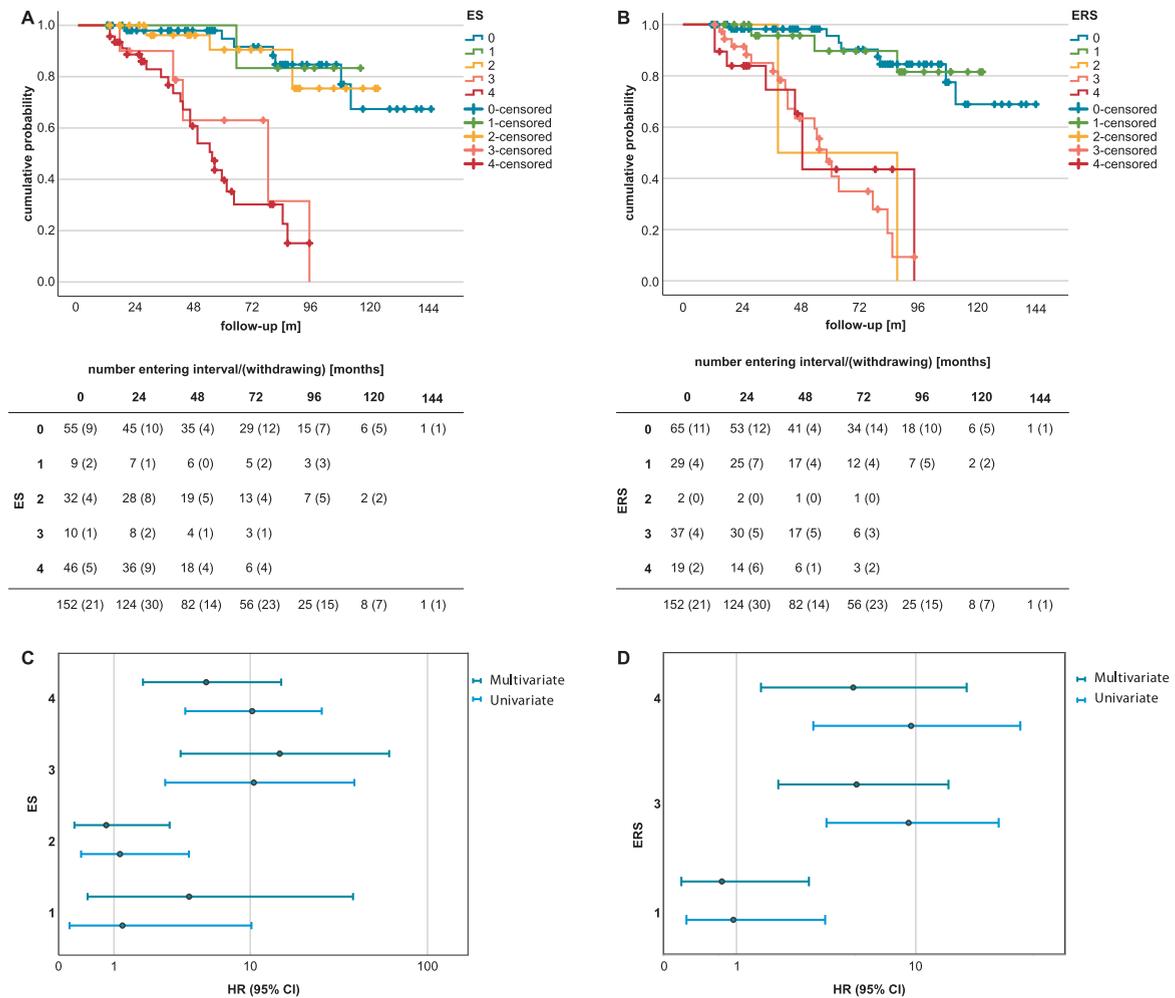| ERS	0	24	48	72	96	120	144
0	65 (11)	53 (12)	41 (4)	34 (14)	18 (10)	6 (5)	1 (1)
1	29 (4)	25 (7)	17 (4)	12 (4)	7 (5)	2 (2)	
2	2 (0)	2 (0)	1 (0)	1 (0)			
3	37 (4)	30 (5)	17 (5)	6 (3)			
4	19 (2)	14 (6)	6 (1)	3 (2)			
	152 (21)	124 (30)	82 (14)	56 (23)	25 (15)	8 (7)	1 (1)

Fig. 3. Comparison of dementia risk between the Erlangen Score (ES) and the reconceptualized ERlangen Score (ERS). Kaplan-Meier curves show the risk of dementia onset in nondemented individuals by ES (A) and ERS groups (B). Nondemented individuals with an ES of 1 or 2 showed no increased risk of dementia onset compared with controls. For both ES and ERS, dementia risk was increased in groups 3 and 4. This was confirmed when comparing hazard ratios for the occurrence of dementia between groups 1 to 4 versus the control group in a univariate and a multivariate Cox regression model with age, education and MMSE at baseline as covariates for the ES (C) and the ERS (D).

and the Australian National University Alzheimer's Disease Risk Index [34]. Future improvement of the test performance of the ERS might be achieved by incorporating additional biomarkers. In that case, the ordinal scale will allow those additional biomarkers to be considered without the groups becoming too small to study due to the various possible combinations of biomarker constellations.

Limitations

The limitations of this study include the study population, which was not a randomly chosen community sample but was generally well educated. The results thus may not be applied to the general population without reserve. Regarding the methods, it should be noted that the CERAD-NB+is standardized for the detection of AD [23]. Since many symptoms of AD can also be observed in other neurodegenerative diseases, it cannot be ruled out that early stages of other neurodegenerative diseases might not have been adequately detected. Another limitation is that no prediction regarding cognitive trajectories and dementia risk is made for ERS 2 because of the small group size.

Conclusion

The reconceptualization of the ES into the ERS is shown to be as valid as the ES with respect to

the ordinal scale and allows the established interpretation of the findings to be maintained even when the $A\beta_{42}/A\beta_{40}$ ratio is determined. By giving more weight to the $A\beta_{42}/A\beta_{40}$ ratio, it takes into account that pTau181-positive individuals without amyloidopathy have a lower risk of dementia compared with individuals with amyloidopathy.

CONFLICT OF INTEREST

PL received consultation and/or lecture honoraria from IBL International, Fujirebio Europe, AJ Roboscreen, Biogen, and Roche. PL is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and/or its supplementary material. Further datasets generated and/or analysed in the current study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230524.

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