The Association of Mini—Mental State Examination (MMSE) with Clinical Dementia Rating (CDR)

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Research Article
Published December 4, 2020

Abstract

Objective: The purpose of our study is to i) determine if the Mini—Mental State Exam (MMSE) is a significant predictor of Clinical Dementia Rating (CDR) among elderly adults and ii.) to explore if measures of cognitive decline can improve the predictive power of a proposed statistical model.
Participants: N=150 patients aged 60—96 from the United States enrolled in the second iteration of the Open Access Series of Imaging Studies (OASIS—2).
Methods: Logistic Generalized Linear Mixed Models (GLMM) with random intercepts were used to examine the association of MMSE and CDR while considering covariates of age, MMSE, normalized whole brain volume (nWBV), and estimated total intracranial volume (eTIV).
Results: MMSE was a statistically significant predictor of dementia (95% CI: 0.282—0.503; p—value <0.0001). For a given subject, the estimated odds of dementia via CDR scale will decrease by 62.3% for each unit increment in MMSE score after adjusting for age. There was strong evidence that the addition of nWBV improved the predictive power of the model (95% CI: 0.177—0.583; p—value = 0.0002), but not the addition of eTIV (95% CI: 0.582—1.434; p—value=0.6938).
Conclusion: The significant association between MMSE and CDR is in agreement with previous research, indicating that the MMSE may provide a cost and time—effective clinical tool to predict the risk of dementia. Additionally, measures of brain volume, but not intracranial volume, appear to provide a valuable and additive predictive power related to dementia.

Introduction

Dementia is a growing healthcare concern as the life expectancy of the general population increases [1]. According to the World Health Organization, there currently 50 million people living with dementia worldwide [2]. The global cost of Alzheimer's Disease, the most common form of dementia, was $604 billion in 2010 [3]. A major factor contributing to the increasing morbidity of dementia is the improper diagnosis of the condition. Dementia is frequently diagnosed using the Clinical Dementia Rating (CDR), a physician—based interview geared to assess the severity of common dementias. However, the CDR measure is time consuming (60—90 minutes) to administer and requires expert training [4]. Alternative screening methods for common forms of dementia could reduce healthcare costs and expedite appropriate diagnosis. The (Mini—Mental State Exam) MMSE is one commonly utilized method to screen for cognitive impairment in the elderly [5]. The MMSE is an attractive clinical measure because it can be easily and quickly (5—10 minutes) collected in a clinical setting by trained medical staff. However, literature up to date has not addressed if MMSE scores are a significant predictor of CDR. If MMSE is a significant predictor of CDR, it may be an advantageous method to estimate odds of dementia or used as a screening tool to determine if a CDR examination is necessary. Additionally, quantitative measures of neurophysiology obtained from imaging techniques such as magnetic resonance imaging (MRI) could enhance the prediction of dementia.

Methods

Data Source

The dataset used is from the Open Access Series of Imaging Studies (OASIS), specifically the OASIS—2: Longitudinal MRI Data in Non—demented and Demented Older Adults [6]. OASIS is a publicly available dataset including basic and clinical neuroscience data. All data for

OASIS—2 were collected during clinical visits. Data were collected from over 1000 participants over 30 years, across ongoing projects at the Washington University in St Louis Alzheimer's Disease Research Center. Specifically, the data constitutes various parameters from magnetic resonance imaging (MRI), positron emission tomography (PET), demographics and dementia diagnostics. Because this is a public data source, IRB approval was not needed.

Primary Variables of Interest

Patient dementia status was established by the Clinical Dementia Rating scale. CDR consists of a scale of 0, 0.5, 1, and 2 indicating the severity of dementia, with 0 being non—demented and 2 being moderate cognitive impairment. For the primary analysis, the CDR variable was dichotomized as non—demented (CDR=0) and demented (CDR > 0).

The primary variable of interest was MMSE, which is a commonly used test for detecting cognitive impairment [5]. MMSE score ranges from 0, indicating poor cognitive performance, to a score of 30, representing high cognitive performance.

Other relevant variables included age and the MRI derived measures of estimated total intracranial volume (eTIV) and normalized whole brain volume (nWBV). eTIV was computed by scaling the manually—measured intracranial volume of the atlas by an Atlas Scaling Factor (ASF), which standardizes for head size. nWBV was computed using the FAST program in the FSL software suite. The unit of nWBV is percent, which represents the percentage of total white and gray matter within the estimated total intracranial volume [6].

Statistical Analysis

Descriptive data analysis to demonstrate the baseline characteristics of participants was performed. The variables investigated for baseline distribution were gender, age, socioeconomic status, years of education, MMSE, nWBV, and eTIV, stratified by dichotomized Clinical Dementia Rating (CDR).

nWBV and eTIV were measured on differing scales, requiring values to be standardized via z—score formula to avoid convergence issues. Further, for the primary analysis, CDR was dichotomized as non—demented (healthy) (CDR=0) and demented (CDR > 0).

Since participants had repeated measurements due to multiple examination visits, conditional modeling approaches were implemented to account for the within—subject variability in outcome measures. Logistic generalized linear mixed models (GLMMs) with random intercept were first used to generate a reduced model, using MMSE and age as fixed effects with CDR as the outcome. A second GLMM was built by adding eTIV and nWBV into the model as fixed effects, to examine if brain MRI indicators of cognitive impairment can improve model fit. Given that random intercepts already account for cluster invariant factors, education level and socioeconomic status were not included as covariates in the GLMMs. Age was selected as a potential confounder since dementia risk increases as an individual gets older [7—9]. Since head sizes differ from person to person, and that prior studies have indicated possible links between head circumference, brain volume, and dementia risk, eTIV and nWBV were considered potential confounders and were adjusted for in our statistical models [10—12].

A likelihood ratio test (LRT) using a 50/50 mixture of χ_0^2 and χ_1^2 random variables was performed to see if the addition of random intercepts improves model fit. There was strong evidence to reject the null hypothesis that the variance of the random intercept term was zero. Therefore, including random intercept had a significantly better fit than only with fixed effect terms.

A sensitivity analysis was performed by fitting a multinomial GLMM model treating CDR as an *ordinal* outcome and including MMSE, age, nWBV and eTIV as fixed effects.

For model fitting, SAS 9.4 was used. The exploratory data analysis was performed in R 3.5.1. Statistical significance was determined at an α—level below 0.05 for p—values.

Results

Participants and Descriptive Data

Figure 1 illustrates the sample sizes at each examination visit throughout the course of the study along with the number of dementia cases. The sample is comprised of 150 participants aged 60—96. The mean follow—up time for the cohort was 2.91 (± 0.01) years. Sample size greatly attenuates as the number of visits becomes more frequent. Similarly, prevalent dementia also decreases quickly after the second visit. Much of the loss—to—follow—up was due to censoring and was not further elaborated by the primary authors. Six subjects were absent for the Visit 2 exam but returned for subsequent visits. Additionally, two missing Mini—Mental State Examination (MMSE) measurements were excluded from the main analysis.

Table 1 displays patient demographic information at the Visit 1 baseline examination. Supplemental analyses

visualizing the distribution of Clinical Dementia Rating (CDR) and MMSE is included in the *Appendix*. Approximately 59% of subjects were female and around half of the subjects were between 70—79 years during the first visit. Average age among the Visit 1 cohort was 75.45 (± 7.55) years, while the mean number of years of education was 14.53 (± 2.87). Participants were evenly distributed by socioeconomic (SES) status, with the exception of very few subjects in the lowest SES level. When stratified by dichotomized Clinical Dementia Rating (CDR), 65 participants were diagnosed with dementia at baseline. Mean age and age distributions were relatively similar between dementia and healthy patients. The majority of dementia patients fell between socioeconomic groups 2 and 4, whereas healthy participants were more likely to be in the higher two SES groups. In regards to education, healthy subjects had on average approximately a year and a half more of school than those with dementia. Additionally, normalized whole brain volume and estimated total intracranial volume were slightly lower in those with dementia compared to healthy participants at Visit 1.

Model Generation

Two generalized linear mixed models (GLMMs) with random intercepts were fit for the analyses. For the primary analysis, CDR was dichotomized as non—demented (healthy) (CDR=0) and demented (CDR > 0). The first model is a reduced model examining MMSE as a predictor of CDR after adjustment for age. The second model consists of MMSE predicting CDR after adjusting for age, estimated total intracranial volume (eTIV), and normalized whole brain volume (nWBV). Given that random intercepts account for baseline confounding, education level and socioeconomic status were not included as covariates in the GLMMs.

Model 1: Reduced Model

Table 2 displays the results for the first model, which evaluated the first hypothesis to determine the MMSE score and age indicated dementia. Model 1 used a generalized linear mixed model (GLMMs) to test the primary hypothesis, with a random intercept term for the subjects and fixed effect terms for age and MMSE. Model 1 confirmed the hypothesis that MMSE was a statistically significant predictor of dementia (95% CI: 0.282—0.503; p—value <0.0001). For a given subject, the estimated odds of having dementia using the CDR scale will decrease by 62.3% for each unit increment in MMSE score. Age was not a statistically significant predictor of dementia in the model (95% CI: 0.925—1.034; p—value = 0.4323) after adjusting for MMSE.

Model 2: Full Model

Table 2 also displays the results for Model 2, which evaluated the hypothesis that MRI derived brain measures are important predictors of dementia. Similar to Model 1, Model 2 used a GLMM to test the hypothesis, with a random intercept for subjects, and MMSE, standardized nWBV, standardized eTIV, age as fixed effects. There was strong evidence for the hypothesis that the addition of nWBV and eTIV improved the predictive power to the reduced model with χ^2 = 127.95 (df = 2) and p—value <0.0001. Standardized nWBV was a statistically significant predictor in the model (95% CI: 0.177—0.583; p—value = 0.0002). Standardized eTIV was not statistically significant within the model (95% CI: 0.582—1.434; p—value=0.6938).

Sensitivity Analyses

A multinomial model treating CDR as an ordinal variable was fit (compared to the primary analysis where it was treated as a binary variable). Conclusions did not change (eTIV is not a statistically significant predictor of severity of dementia, whereas the other variables are statistically significant predictors).

Discussion

The study findings confirmed the first hypothesis that MMSE is a statistically significant predictor of dementia as indicated by CDR. However, age was not a statistically significant predictor of CDR after adjusting for MMSE. The analyses also confirmed the second hypothesis that quantitative outcomes related to neurophysiology (nWBV) are important predictors of cognitive function and will improve the fit of the crude model. While nWBV was a significant predictor of CDR, eTIV was not, after standardizing for both. This finding suggests that a combination of behavioral and neurophysiologic measures (specifically measures based on brain tissue volume) may be needed to generate optimized predictive models for patients with dementia.

The finding of a significant association between MMSE and CDR is in agreement with previous research related to the association between MMSE and CDR. MMSE has been found to be a significant predictor and also to discriminate well between stages 0.5, 1, 2 and 3 for CDR but not between stage 0 and 0.5 [13]. We did not examine how MMSE discriminates between stages of CDR in this sample, which may be of interest to examine in future analyses. The finding on the significant association between nWBV and CDR is also coherent with trends in a

similar direction; nWBV has been found to interact with education to yield a significant association with cognitive decline as indicated by CDR<0.5, in a particular stratum of tau protein levels [14].

While the sample was representative of the general population with dementia and analyses yielded statistically significant results in keeping with previous findings, there were some limitations in both data collection methodology and the statistical analysis methodology. Authors of previous studies have expressed concerns with the possibility of MMSE administration may contribute to staging of the CDR scores, hence leading to bias in the association [13]. In the public dataset we utilized, it is unclear whether the investigators administering the MMSE in the OASIS sample were blinded with regards to the CDR of the participants, and hence not able to conclude how this may have affected the conclusion on their association. Given the retrospective nature of the data, differential loss to follow up was found to profoundly lower sample size for repeated examinations. Furthermore, SES and education level—although accounted for in the random intercepts of GLMM models—were not included as adjustable confounding variables, thus potentially introducing the risk of bias in our findings. Future investigations which gather data from a prospective study would be valuable in providing context on a temporal scale. To build upon the conclusions yielded from this analysis, future examination of the interaction between MMSE and nWBV would be valuable, as the interaction between behavioral measures and brain volume may add to our current understanding of the pathophysiology of dementia. Future analyses of this dataset may also stratify outcome by visit and see if the association between MMSE and CDR holds across visits. We did not assess for non—linearity in the relationship between MMSE and nWBV, which could be performed in future analyses by modeling different representations of MMSE and nWBV such as dichotomization or divided into quartiles.

The results of this study implicate that MMSE and nWBV measurements may be a useful screening tool for physicians to determine whether a CDR evaluation is necessary. Since the CDR test takes a considerable amount of time and training for physicians, implementing the use of MMSE that can be administered by a nurse could lead to significant improvements in efficiency. nWBV measurements from MRI can also be used in conjunction with the MMSE to screen potential demented patients for CDR evaluations. In the long term, these results would aid in the accurate screening and detection of dementia in a timely manner so that significant costs of treatment and care—taking can be mitigated.

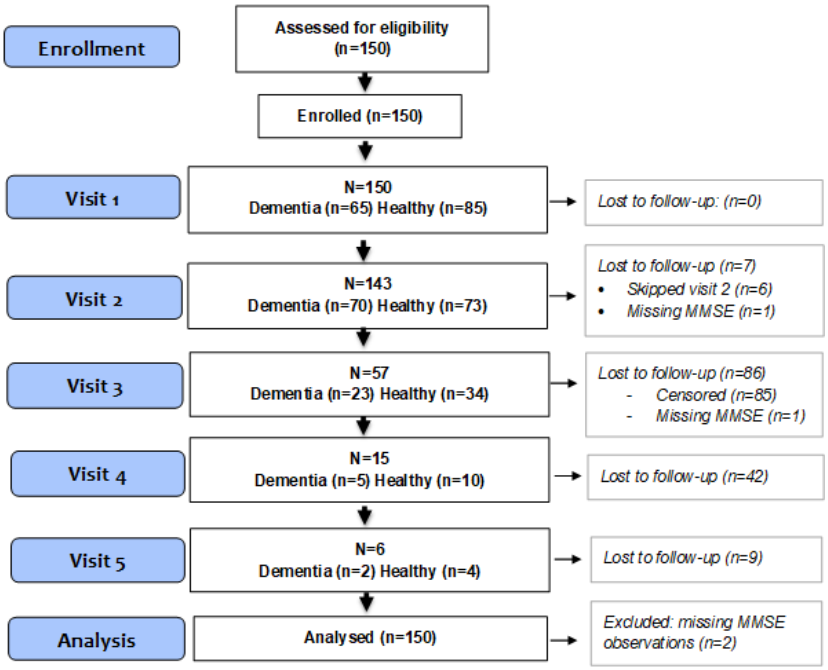
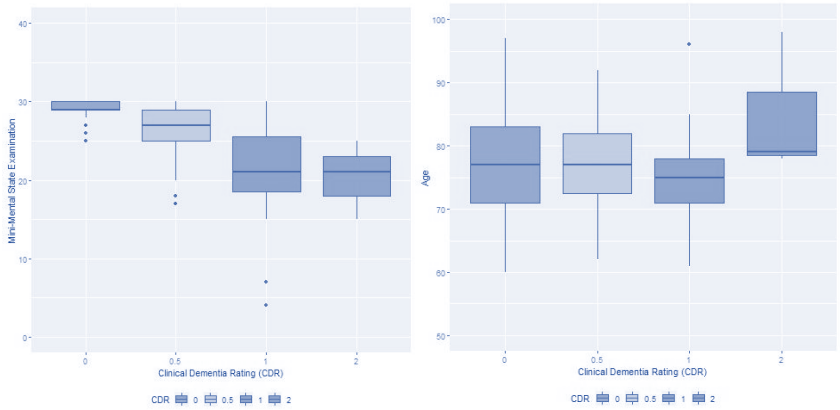
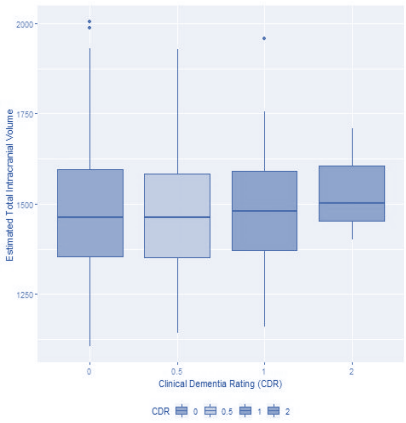


Figure 1. Study Flow Diagram. Note: The number of missing or excluded data is for observations. All participants were included in the final analysis.



2—A

2—B



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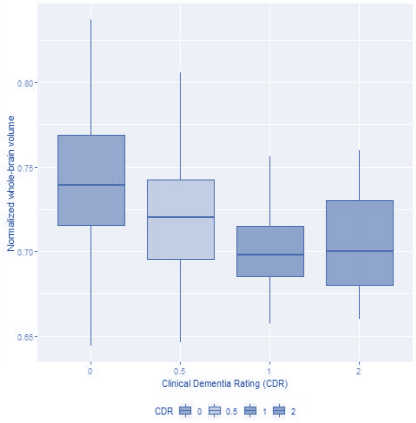

2—D

Figure 2: 2—A: Boxplot depicting distribution of MMSE by CDR; Figure 2—B: Boxplot depicting distribution of age by CDR; Figure 2—C: Boxplot depicting distribution of eTIV by CDR; Figure 2—D: Boxplot depicting distribution of nWBV by CDR

Note: CDR = Clinical Dementia Rating; MMSE = Mini—Mental State Examination; eTIV = estimated total intracranial volume ; nWBV = Normalized Whole Brain Volume

Table 1: Participant Characteristics at Visit 1

	Total	**Dementia (CDR > 0)**	**Healthy (CDR = 0)**
Sample Size, n (%)	150 (100%)	65 (43.33%)	85 (56.67%)
Sex			
Male	62 (41.33%)	36 (55.4%)	26 (30.6%)
Female	88 (58.67%)	29 (44.6%)	59 (69.4%)
Age (mean, ±SD)	75.45 (±7.55)	74.95 (±6.80)	75.82 (±8.09)
Age Distribution (n,%)			
60—69	34 (22.67%)	12 (18.46%)	22 (25.88%)
70—79	71 (47.3%)	36 (55.4%)	35(41.2%)
80—89	41 (27.3%)	15 (23.1%)	26 (30.6%)
90+	4 (2.7%)	2 (3.1%)	2 (2.35%)
Socioeconomic Status* (n,%)			
1 (Highest Status)	33 (23.24%)	11 (19.30%)	22 (25.88%)
2	42 (29.58%)	13 (22.81%)	29 (34.12%)
3	34 (23.94%)	15 (26.32%)	19 (22.35%)
4	30 (21.13%)	16 (28.07%)	14 (16.47%)
5 (Lowest Status)	3 (2.11%)	2 (3.51%)	1 (1.18%)
Years of Education (mean, ±SD)	14.53 (±2.87)	13.66 (±2.90)	15.20 (±2.69)
nWBV (%)‡ (mean, ±SD)	0.74 (±0.04)	0.72 (±0.03)	0.74(±0.04)
eTIV (cm^3)† (mean, ±SD)	1474.427 (±174.68)	1473.85(±173.08)	1474.87 (±176.93)

**There were 8 missing observations for socioeconomic status at Visit 1*
‡nWBV = Normalized Whole Brain Volume
†eTIV = Estimated Intracranial Whole Brain Volume

Table 2: Models
(Exponentiated values)

Model 1 — GLMM with random intercepts for predicting CDR			
	Odds	**95% CI**	**p—value**
MMSE	0.377	0.282, 0.503	<0.0001
Age	0.978	0.925, 1.034	0.4323
Model 2 — GLMM with random intercepts for predicting CDR			
MMSE	0.356	0.259, 0.491	<0.0001
Age	0.893	0.827, 0.964	0.0041
Std. nWBV	0.321	0.177, 0.583	0.0002
Std. eTIV	0.914	0.582, 1.434	0.6938

Note: Std. nWBV=standardized nWBV; Std. eTIV = standardized eTIV

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