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CDR State Transition Probabilities in Alzheimer's Disease with and without Cholinesterase Inhibitor Intervention in an Observational Cohort

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Abstract

Cholinesterase inhibitors and memantine are medications used in the treatment of Alzheimer's disease (AD). These agents have been shown to reduce the rate AD progression in randomized trials. The objective of this study is to evaluate the association between treatment with cholinesterase inhibitors or memantine and the probability of transitioning to a more severe Clinical Dementia Rating (CDR) state. Analysis was limited to possible or probable AD patients from NACC-UDS with three or more observations, baseline CDR score of 0.5 or 1, and without reported use AD drugs at enrollment. Use of an AD drug at any observation after baseline was classified as treatment. Odds of CDR stage were calculated by multinomial logistic regression controlling for baseline age, baseline MMSE score, education, marital status, race, gender, place of residence, and time since last measure. The resulting coefficients from logistic regression were used to calculate transitional probabilities. A total of 1,114 patients were included. No differences were observed in the probability of transitioning to more severe CDR states based on treatment, but treated patients had lower odds of death, OR 0.49 (95% CI 0.31 to 0.79) compared to untreated. Ultimately, this study failed to detect a difference in the probability of progressing to a more severe AD state as a result of treatment in an observational cohort of AD patients, but is limited by non-randomized treatment selection and small dataset. The NACC-UDS dataset is ongoing and this analysis may be improved if repeated when more data is available.

Keywords

Alzheimer's disease; disease progression; drug therapy; economic; models; probability

INTRODUCTION

Cholinesterase inhibitors and memantine are medications used in the treatment of Alzheimer's disease (AD). These agents have been shown to reduce the rate AD progression by Clinical Dementia Rating (CDR) compared to untreated controls in randomized trials [1–3]. Extrapolating the observed benefits of cholinesterase inhibitors to population based

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outcomes has a number of limitations, including the short duration of follow-up in clinical trials and lack of observational population-based AD studies.

The clinical course of AD has been modeled by Neumann et al. [2]. The investigators used the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) to produce transition probabilities, the probability of progressing to more severe AD states over time. Disease progression was modeled as mild-moderate-severe by CDR score. These results have been used in many cost-effectiveness models for AD treatment [5–7]. The CERAD population comprised data collected from 1986 to 1995. Since the study's publication, treatment of AD has changed with the introduction of cholinesterase inhibitors. Based on data from clinical trials, these agents are expected to delay progression. A more contemporary analysis of AD progression based on CDR was undertaken by Spackman and colleagues [9]. The results of this study provide CDR transition probabilities based on a cohort of AD patients in the National Alzheimer Coordinating Center's Uniform Data Set (NACC-UDS). AD patients in the NACC-UDS database may be more reflective of current clinical management of AD than AD patients in CERAD. Results of this study show that AD patients in NACC-UDS have a lower probability of transitioning to more severe CDR states and a lower probability of institutionalization than previously found in CERAD. This study, however, does not differentiate transition probabilities of AD patients treated with cholinesterase inhibitors versus those not treated with cholinesterase inhibitors.

Transition probabilities for MMSE with differentiation by treatment status were calculated as a follow-up to Spackman et al. [8]. Exploratory analysis showed that, use of an AD drug during the previous year was associated with greater probability of transitioning to a more severe state. These findings are hypothesized to be due to confounding by treatment indication. More severe AD patients may be more likely to be prescribed AD drugs and also may be more likely to progress to more severe states.

The primary objective of this study is to evaluate the association between treatment with cholinesterase inhibitors or memantine (AD drugs) and the probability of transitioning to a more severe CDR state and to institutionalization after controlling for disease severity. This project attempts to identify a group of AD patients in the NACC-UDS database who may represent new initiation on AD treatment. Comparing to untreated controls of similar baseline severity, transitional probabilities for AD progression can be calculated for treated and untreated AD patients. An observational cohort of AD patients who are newly initiated on treatment will be represented by mild AD patients in the NACC-UDS database who do not report use of AD drugs at baseline enrollment, then report use of an AD drug at any time during subsequent data collection. These patients will be compared to patients of similar baseline severity who never report use of AD drugs.

METHODS

Population

The National Alzheimer Coordinating Center's Uniform Data Set (NACC-UDS) is funded by the National Institute of Aging for the purpose of gathering information about AD for use in research. The 29 participating AD Centers are responsible for study participant recruitment and data collection. Comprehensive patient-specific data has been annually collected beginning September 2005 on standardized data collection forms. The NACC-UDS is a large, longitudinal dataset, with over 16,000 participants over the age of 65 and 5,512 participants with a diagnosis of possible or probable AD as of summer 2009. The dataset also includes suspected non-AD dementias, mild cognitive impairment, and non-demented controls. The NACC-UDS is not considered a population based sample due to non-random enrollment of patients by participating AD Centers. The proportion of married

and living with spouse, as well as education exceeding twelve years may be greater in the dataset than in the overall population of AD patients.

Data

Each study patient was uniquely identified by NACC Identification number (NACC-ID). Duplicate observations with the same visit date were eliminated from analysis. CDR scores in the dataset range from mild (0.5 to 1), to moderate (2), to severe (3). Only patients with a baseline CDR score of 0.5 or 1 were included in the analysis. Detailed date of birth and date of death was not available. Therefore, all patients are assigned a birth and death date of July 1st. Age at each observation was calculated by the difference between visit date and assigned birth date divided by 365.25.

Patients were considered to have taken an AD drug if they reported rivastigmine, donepezil, galantamine, or memantine. The analysis was restricted to patients who did not report use of any AD drug upon enrollment in NACC-UDS. Use of an AD drug at any observation after baseline was classified as treatment. Once treated, patients will be considered treated for the entire analysis, even if drug use is no longer reported on data collection points beyond Year 2 because we are unable to determine precisely when treatment has ended or detect short term gaps in treatment. Only a small percentage of study participants have more than three visits in the analysis by Spackman [9], therefore this data only is reflective of short treatment duration.

Variables included in the analysis include age at baseline, Mini Mental State Exam (MMSE) score at baseline, education, marital status, race, gender, place of residence, and time since last measure. The MMSE is a common instrument for measuring cognitive decline in AD, ranging from zero to thirty, thirty being the highest possible level of cognition. The analysis was adjusted for baseline MMSE score to control for residual confounding by indication. Other measures of disease severity such as the Functional Activities Questionnaire (FAQ) and Neuropsychiatric Index (NPI) are collected in the NACC-UDS, but are not included in this analysis. While patients are limited to those with mild AD as measured by CDR scores, the CDR instrument may not be sufficiently sensitive to detect AD severity differences that may lead to prescribing AD therapy. We adjusted for baseline MMSE as well as CDR to control for a second measure of baseline AD severity that may have influenced treatment decisions, although both MMSE and CDR may lack sensitivity for changes in mild AD. Education level was self-reported as years of education achieved, with 12 representing high school, 16 for Bachelor's degree, 18 for Master's degree, and 20 for Doctoral degree. Patients were classified as married if married or living as married. Race is self-reported as White, Black or African American, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Asian, or Other. Binomial variables were created for marital status, white race, Hispanic, gender, institutionalization. Possible AD and probable AD were considered as a diagnosis of AD. Patients were classified as institutionalized if in an assisted living or adult family home, skilled nursing facility, or adult family home. We controlled for time since last measure, as not all patients had observations separated by exactly one year.

Only patients with possible or probable AD were considered to have a diagnosis of AD and were included in the analysis. Patients were further limited to only those with three or more observations. To evaluate the impact of this limitation, sensitivity analysis was performed to include patients with two or more observations.

Statistical analysis

Descriptive statistics were used to analyze CDR score and differences in patient demographics by treatment status. The association between current and previous CDR stage

by treatment status after baseline was calculated by multinomial logistic regression clustered by NACC-ID, controlling for baseline age, baseline MMSE score, education, marital status, race, gender, and time since last measure. The association between CDR stage and institutionalization in treated versus non-treated groups was also calculated by multinomial logistic model controlling for the above demographic characteristics.

The resulting coefficients from logistic regression were used to calculate transitional probabilities using the average baseline age, baseline MMSE score, education, marital status, race, and gender for all included patients.

RESULTS

The characteristics of the AD population used in the analysis are presented in Table 1. There were a total of 2,557 observation points. A total of 1,114 patients were included in the analysis: 816 remained untreated for all data collection points and 298 reported treatment at least once after baseline. Of those who were treated, 127 (43%) reported with memantine, 205 (69%) with donepezil, 42 (14%) with galantamine, and 38 (13%) with rivastigmine. Treated and untreated groups were similar in the mean time between data collection points, years of education, total number of data collection points, and gender. Compared to untreated patients, treated patients had shorter time between visits, had lower mean baseline age, lower baseline MMSE, and a higher proportion of patients diagnosed with probable AD rather than possible AD. Treated patients were more likely to live in single family residence and living with spouse, partner, relative, or friend, and treated patients were also more likely to be married compared to untreated patients.

Several independent variables were associated with being in a more severe CDR state. Results of logistic regression analysis are presented in Table 2. A previously moderate CDR state was associated with increased odds of a being in moderate CDR state, severe CDR state, and death. Hispanic ethnicity and higher baseline MMSE score were associated with lower odds of being in moderate CDR stage compared to mild. Patients with greater time since last visit, OR 4.9 (95% CI 1.8 to 13.37), and lower baseline MMSE score, OR 0.71 (95% CI 0.66 to 0.78), were more likely to be in severe CDR compared to mild. Patients with lower baseline MMSE score, OR 0.85 (95% CI 0.81 to 0.90) were more likely to die rather than be in mild state. Use of an AD drug was associated with lower odds of death, OR 0.56 (95% CI 0.34 to 0.92).

Annual transitional probabilities are presented in Table 3. Both treated and untreated patients previously in mild state are likely to stay in mild. If previously in mild state, treated patients were slightly more likely to stay in mild state than untreated patients (94.6% versus 95.8%), but this result did not reach statistical significance. Figure 1 shows the predicted percent of patients in each disease state by year. Overall, the difference in predicted AD progression is not substantially different between treated and untreated patients.

Transitional probabilities for institutionalization could not be calculated due to insufficient transitions to institutionalization in the included dataset.

Sensitivity analysis

Transitional probabilities surrounding severe disease state was limited by the number of patients who met the inclusion criteria of three or more observations. To increase the sample size additional analysis was undertaken to include patients with two or more observations. Results of the sensitivity analysis are presented in as an appendix to this document. Transitional probabilities were similar to those in the original analysis. Treated and untreated patients had nearly identical probability of transitioning out of mild disease state,

shown in Fig. 1A. This potentially reflects an inability to detect a treatment effect with only two observations. Patients may be started on AD drugs at any point during the second year of observation, as little as two weeks prior to reporting AD drug use. Thus, a substantial number of patients considered treated may not have had sufficient time to observe a treatment effect at the second observation point.

Because treated patients may have been exposed to as short as two weeks of drug therapy before being considered treated, transitions from baseline to the second observation may not be a reliable way to detect treatment benefit. Additional analysis was conducted to include only transitions from second data collection point onward. Results of this analysis are presented in Table 2A and Fig. 2A and were not significantly different than the original analysis.

A bias toward healthy AD patients receiving treatment while unhealthy AD patients forgo or are not offered treatment may exist. In addition, Treated and untreated patients may differ on characteristics unobservable in the dataset. Also, the effects of treatment may not persist after discontinuation. Additional analysis was undertaken to address both of these issues by restricting the data to only patients who had ever reported use of an AD drug. Odds of more severe CDR state and death by use of an AD drug were calculated by multinomial logistic regression as previously described, but with use of an AD drug only during the past two weeks as the exposure of interest, rather than AD drug use at any point. In this analysis, use of an AD drug during the past two weeks was associated with reduced odds of being in severe state compared to mild, OR 0.31 (95% CI 0.1 to 0.99). In this analysis, odds of death did not differ between treated and untreated patients (OR 0.91 95% CI 0.37 to 2.21).

A bias toward healthy AD patients receiving treatment while unhealthy AD patients forgo, or are not offered treatment, was assessed by restriction of the data to only patients who remained alive. Results of this analysis were similar to the original analysis.

DISCUSSION

This study reflects on the effectiveness of AD treatment in an observational cohort of AD patients. However, it is limited by both observational study design and small sample size. There were insufficient data to inform transitions around severe CDR states and odds of institutionalization. This may reflect a loss to follow-up as patients are moved into an institutional setting. If so, the database may underestimate transitions to severe CDR states if severe CDR state is associated with institutionalization. Despite controlling for baseline CDR and MMSE score, systematic differences remain between treated and untreated AD patients. While restricted to initially mild cases, treated patients were more likely to be more severe, younger, married, living with family or friend, and non-institutionalized. This may reflect a socioeconomic influence on prescribing, or that AD patients with better supportive care are more likely to be prescribed AD treatment. These patients may have different rates of progression or death due to overall superior care compared to untreated AD patients.

Treatment was not significantly associated with differences in AD progression, but was associated with reduced odds of death. This may reflect either a treatment effect of reduced AD related mortality, or it may reflect treatment selection bias. A “healthy AD patient effect” bias may exist if AD patients who have limited life expectancy as a consequence of non-AD related diseases are less likely to be prescribed drugs for AD. These patients are considered untreated in the analysis and have higher odds of dying than more healthy AD patients who may have received treatment. This bias was not confirmed in sensitivity analysis, which resulted in similar odds as the original analysis.

Restriction of the data to only treated patients, then modeling the effect of treatment in the past two weeks resulted in an apparent positive treatment effect of AD drugs. Use of AD drugs within two weeks prior to health state assessment was associated with reduced odds of being in a more severe state compared to mild. This might suggest a transient treatment effect among patients who recently have taken AD drugs, although this protective effect is lost when the drug is discontinued. It could also be that once patients begin to progress they are no longer prescribed treatment since CI is only indicated in mild or moderate AD. Again it is difficult to separate a treatment effect from possible confounding by indication.

Mild AD patients included in this analysis were more likely to remain in mild state than the results of the original model by Spackman (2010) using the NACC-UDS dataset (94.6% compared to 77.6%). Compared to the NACC-UDS cohort used in the original model, the patients used in the analysis were slightly younger, and had higher MMSE scores. There were fewer transitions to more severe states among this cohort. Those who did transition to moderate or severe had higher probability of death than was seen in the original model, particularly those patients who remained untreated. The higher probability of death observed among untreated patients compared to treated patients may be the result of selecting for untreated patients who may remain untreated due to unrelated severe illness or limited life expectancy unrelated to AD.

This study failed to detect a statistically significant difference in the probability of progressing to a more severe AD state as a result of treatment in an observational cohort of AD patients, but is limited by non-randomized treatment selection and small dataset. The NACC-UDS dataset is ongoing and this analysis may be improved if repeated when more data is available.

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Appendix A Tables and Figures for Sensitivity Analysis

Table 1A

Odds of independent variables, CDR state, and death compared to mild including patients with two or more observations

CDR stage	OR (95% CI) compared to mild
Moderate	
Previously moderate	37.35 (16.01, 87.17)
Previously severe	Unable to evaluate
Time since last visit	1.15 (0.72, 1.82)
Baseline age	1 (0.99, 1.02)
Baseline MMSE	0.74 (0.72, 0.77)
White race	1.28 (0.89, 1.85)
Hispanic	0.45 (0.25, 0.8)
Female gender	1.14 (0.83, 1.58)
Years of education	1.03 (0.99, 1.07)

CDR stage	OR (95% CI) compared to mild
Married	0.99 (0.71, 1.37)
Ever taken AD drug	1.64 (1.21, 2.23)
Constant	31.77 (6.33, 159.32)
Severe	
Previously moderate	127.52 (44.77, 363.24)
Previously severe	Unable to evaluate
Time since last visit	3.74 (1.83, 7.62)
Baseline age	0.96 (0.94, 0.99)
Baseline MMSE	0.7 (0.66, 0.74)
White race	0.54 (0.26, 1.14)
Hispanic	0.3 (0.07, 1.36)
Female gender	1.49 (0.74, 2.98)
Years of education	1.1 (0.98, 1.22)
Married	0.52 (0.24, 1.11)
Ever taken AD drug	1.82 (0.94, 3.54)
Constant	53.46 (1.63, 1749.79)
Death	
Previously moderate	69.04 (30.28, 157.43)
Previously severe	Unable to evaluate
Time since last visit	0.02 (0.01, 0.11)
Baseline MMSE	0.87 (0.82, 0.91)
White race	2.43 (1.31, 4.51)
Hispanic	0.41 (0.15, 1.09)
Baseline age	1.07 (1.04, 1.09)
Female gender	0.98 (0.69, 1.39)
Years of education	0.97 (0.92, 1.03)
Married	1.37 (0.95, 1.99)
Ever taken AD drug	0.67 (0.44, 1.03)
Constant	0.24 (0.01, 4.28)

Table 2A

Odds of independent variables, CDR state, and death compared to mild including only transitions after second data collection point

CDR stage	OR (95% CI) compared to mild	CDR stage	OR (95% CI) compared to mild
Moderate		Severe	
Previously moderate	34.22 (11.41, 102.64)	Hispanic	0.08 (0.01, 0.66)
Previously severe	Unable to evaluate	Female gender	1.57 (0.67, 3.66)
Time since last visit	0.96 (0.51, 1.82)	Years of education	1.06 (0.89, 1.25)
Baseline age	1.02 (1, 1.04)	Married	0.68 (0.28, 1.67)
Baseline MMSE	0.73 (0.69, 0.78)	Ever taken AD drug	1.75 (0.68, 4.54)

CDR stage	OR (95% CI) compared to mild	CDR stage	OR (95% CI) compared to mild
White race	1.1 (0.6, 2.02)	Constant	139.18 (1.79, 10830.36)
Hispanic	0.32 (0.1, 1.04)	Death	
Female gender	1.64 (1.01, 2.66)	Previously moderate	39.75 (14.36, 110.03)
Years of education	1.05 (0.99, 1.12)	Previously severe	Unable to evaluate
Married	0.95 (0.57, 1.58)	Time since last visit	0.05 (0.01, 0.21)
Ever taken AD drug	1.14 (0.7, 1.85)	Baseline age	1.07 (1.03, 1.1)
Constant	16.49 (1.37, 198)	Baseline MMSE	0.84 (0.79, 0.9)
Severe		White race	1.74 (0.92, 3.3)
Previously moderate	107.17 (28.32, 405.57)	Hispanic	0.34 (0.11, 1.07)
Previously severe	Unable to evaluate	Female gender	0.93 (0.62, 1.4)
Time since last visit	6.85 (2.24, 20.91)	Years of education	1 (0.93, 1.06)
Baseline age	0.96 (0.93, 0.98)	Married	1.35 (0.87, 2.07)
Baseline MMSE	0.69 (0.63, 0.76)	Ever taken AD drug	0.49 (0.3, 0.81)
White race	0.59 (0.19, 1.82)	Constant	0.78 (0.03, 21.54)

Fig. 1A.
Percent of Patients in AD Disease State by Treatment Status Including Patients with Two or More Observations

Fig. 2A.

Percent of Patients in AD Disease State by Treatment Status Excluding Baseline to First Data Collection Point Transitions

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Fig. 1.

Table 1

Characteristics of population analyzed

	Overall (n=1114)	Untreated (n = 816)	Treated (n = 298)	
Time between measures mean (sd)	1.09 (0.29)	1.09 (0.30)	1.07 (0.26)	$p = 0.02$
Base age mean (sd)	76.37 (10.43)	76.65 (10.84)	75.59 (9.19)	$p = 0.13$
Years of education mean (sd)	14.56 (3.64)	14.50 (3.73)	14.72 (3.37)	$p = 0.09$
Base MMSE mean (sd)	26.00 (3.73)	26.44 (3.40)	24.80 (4.27)	$p < 0.01$
MMSE score mean (all obs) (sd)	26.95 (14.0)	28.18 (14.39)	23.90 (23.89)	$p < 0.01$
Baseline probable AD	0.34 (0.47)	0.26 (0.44)	0.55 (0.50)	$p < 0.01$
Observations per patient				
Three	67.1%	67.9%	65.6%	
Four	32.3%	31.6%	33.5%	
Five	0.7%	0.5%	0.9%	
Gender				
Male	51.1%	50.9%	51.7%	
Female	48.9%	49.1%	48.3%	
Residence at baseline				
Single family	85.2%	83.5%	89.9%	
Retirement community	9.1%	10.1%	6.4%	
AL/boarding/AFH	3.3%	3.9%	1.7%	
SNF/NH	0.6%	0.9%	0.0%	
Other	1.4%	1.5%	1.3%	
Unknown	0.4%	0.3%	0.7%	
Living situation at baseline				
Lives alone	27.1%	29.5%	20.5%	
Lives with spouse or partner	60.3%	58.0%	66.8%	
Lives with relative or friend	9.6%	8.8%	11.7%	
Lives with group	1.3%	1.4%	1.0%	
Other	1.5%	2.1%	0.0%	
Unknown	0.2%	0.3%	0.0%	
Marital status				
Married	60.8%	58.7%	66.4%	
Widowed	23.3%	24.6%	19.5%	
Divorced	9.7%	10.2%	8.4%	
Separated	1.1%	1.2%	0.7%	
Never married	3.3%	3.3%	3.4%	
Living as married	1.6%	1.6%	1.7%	
Other	0.3%	0.4%	0.0%	
Unknown	0.0%	0.0%	0.0%	
Race				
White	82.2%	81.7%	83.6%	
Black or African American	12.0%	12.4%	11.1%	

	Overall (n=1114)	Untreated (n = 816)	Treated (n = 298)
American Indian or Alaska Native	0.4%	0.3%	0.7%
Native Hawaiian or other Pacific Islander	0.1%	0.1%	1.0%
Asian	2.2%	2.6%	0.0%
Other	3.1%	2.9%	3.7%
Unknown	0.0%	0.0%	0.0%
Hispanic	9.3%	10.0%	7.4%

AL: assisted living facility, AFH: adult family home, SNF: skilled nursing facility, NH: nursing home

Table 2

Odds of independent variables, CDR state, and Death compared to mild

CDR stage	OR (95% CI) compared to mild
Moderate	
Previously moderate	41.87(17.32, 101.18)
Previously severe	Unable to evaluate
Time since last visit	1.34 (0.74, 2.42)
Baseline age	1.02 (1, 1.03)
Baseline MMSE	0.74 (0.71, 0.78)
White race	0.97 (0.64, 1.47)
Hispanic	0.57 (0.3, 1.08)
Female gender	1.23 (0.83, 1.81)
Years of education	1.03 (0.98, 1.08)
Married	0.93 (0.63, 1.39)
Ever taken AD drug	1.48 (1.04, 2.1)
Constant	13.75 (2.06, 91.84)
Severe	
Previously moderate	189.78 (62.27, 578.35)
Previously severe	Unable to evaluate
Time since last visit	4.9(1.58, 15.23)
Baseline age	0.98 (0.95, 1.01)
Baseline MMSE	0.71 (0.66, 0.77)
White race	0.43 (0.18, 1.07)
Hispanic	0.18 (0.02, 1.95)
Female gender	1.49 (0.69, 3.21)
Years of education	1.06 (0.92, 1.23)
Married	0.76 (0.35, 1.64)
Ever taken AD drug	1.49 (0.69, 3.2)
Constant	18.61 (0.41, 843.72)
Death	
Previously moderate	67.53 (28.21, 161.61)
Previously severe	Unable to evaluate
Time since last visit	0.02 (0, 0.1)
Baseline age	1.06 (1.04, 1.09)
Baseline MMSE	0.85 (0.81, 0.9)
White race	1.62 (0.92, 2.86)
Hispanic	0.6 (0.23, 1.55)
Female gender	0.93 (0.63, 1.37)
Years of education	1 (0.95, 1.07)
Married	1.57 (1.06, 2.33)
Ever taken AD drug	0.56 (0.35, 0.88)
Constant	0.55 (0.03, 11.12)

Table 3

Annual CDR transitional probability by treatment status

t	t+1			
	Mild	Moderate	Severe	Dead
Overall				
Mild (95% CI)	0.946 (0.936, 0.956)	0.017 (−0.013, 0.048)	0.001 (0, 0.003)	0.026 (0.018, 0.034)
Moderate (95% CI)	0.282 (0.102, 0.463)	0.27 (0.141, 0.399)	0.066(0.015, 0.118)	0.434 (0.273, 0.594)
Severe (95% CI)	Unable to evaluate	0.032 (−0.038, 0.101)	0.07 (−0.055, 0.196)	0.898 (0.733, 1.064)
Dead (95% CI)	0	0	0	1
Treated after baseline				
Mild (95% CI)	0.946 (0.931, 0.96)	0.032 (−0.023, 0.087)	0.002 (0, 0.004)	0.017 (0.009, 0.025)
Moderate (95% CI)	0.322 (0.104, 0.54)	0.373 (0.215, 0.532)	0.092 (0.007, 0.177)	0.295 (0.148, 0.441)
Severe (95% CI)	Unable to evaluate	0.058 (−0.066, 0.182)	0.13 (−0.079, 0.339)	0.812 (0.537, 1.086)
Dead (95% CI)	0	0	0	1
Untreated after baseline				
Mild (95% CI)	0.944 (0.933, 0.956)	0.014 (−0.011, 0.038)	0.001 (0, 0.002)	0.031 (0.021, 0.04)
Moderate (95% CI)	0.264 (0.091, 0.436)	0.234 (0.111, 0.356)	0.057 (0.011, 0.103)	0.487 (0.316, 0.659)
Severe (95% CI)	Unable to evaluate	0.025 (−0.031, 0.081)	0.055 (−0.049, 0.16)	0.92 (0.783, 1.057)
Dead (95% CI)	0	0	0	1