Clinical and Genetic Predictors of Delayed Remission After Multiple Levels of Antidepressant Treatment: Toward Early Identification of Depressed Individuals for Advanced Care Options

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ABSTRACT

Objective: To identify clinical and genetic characteristics that can be used to recognize depressed patients who are likely to respond quickly versus those who will have a more delayed response following multiple treatment trials.

Methods: The data used were obtained from the National Institute of Mental Health–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which was conducted between July 2001 and September 2006. Of the 4,041 treatment-naive participants in the original study, 1,953 with DNA samples were included. Major depressive disorder (*DSM-IV* criteria) was defined as baseline score > 14 on the 17-item Hamilton Depression Rating Scale. Time to remission was defined from the entry point to when a score ≤ 5 on the Quick Inventory of Depressive Symptomatology, Clinician Rating was achieved, irrespective of the type or number of treatments received. A Kaplan-Meier estimator was used for data description, proportional hazard regression for model building, and logistic regression for measures of predictive accuracy.

Results: The overall rate of remission across all levels of treatment was 65.6%, and the overall median (interquartile range) of time to remission was 11.4 (6.0–17.9) weeks. The predictors of delayed remission included unemployment ($P = .004$), severe medical comorbidity ($P < .0001$), severe baseline depression ($P < .0001$), more than 4 dysthymic symptoms ($P = .005$), more than 9 posttraumatic stress symptoms ($P = .005$), and serotonin receptor 1A ($P = .006$) and cytochrome P450 2D6 ($P = .002$ for C/T and $P = .0004$ for T/T) genetic variants. The final model had good predictive measures of accuracy of area under the curve (70%) and sensitivity (88%).

Conclusions: The results offer clinical tools for clinicians to identify depressed individuals who are likely to have delayed remission with multiple antidepressant treatments and therefore might be candidates for advanced care options.

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Major depressive disorder (MDD) poses a great burden for individuals and society at large due to its high prevalence,[1] comorbidities,[2] and associated disability.[3] This burden is compounded by the poor predictability of antidepressant treatment response. Recognizing antidepressant nonresponse is made even more urgent now by the emergence of advanced care options such as device therapies and ketamine. Identifying persons who are likely to experience significantly delayed response to multiple standard treatment regimens would allow clinicians to move directly to advanced care options, an approach similar to what is currently being practiced in other difficult-to-treat medical conditions such as HIV[4] or cancer.[5]

Many studies have been conducted to identify predictors of depression remission or response in actual practice.[6] For example, Trivedi et al,[7] using National Institute of Mental Health (NIMH)–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data,[8] found individuals with lower remission rates to have more comorbid psychiatric and medical disorders as well as lower baseline functioning. Similarly, Villafuerte et al[9] reported better response to citalopram treatment in individuals homozygous for the G allele at rs1364043 in *HTR1A* and the C allele of rs6298 in *HTR1B*. A non-STAR*D study by Fournier et al[10] identified chronic depression, older age, and lower intelligence as prognostic variables of response to paroxetine treatment or to lithium or despiramine augmentation.

The aforementioned studies and several others[7,11–15] were limited to predicting response or remission to 1 level of antidepressant treatment. Predictive factors for failure to multiple levels of antidepressant treatments have not been examined. Thus, the goal of the current analysis was to determine if baseline sociodemographic, clinical, and genetic characteristics of depressed individuals could be used to predict suboptimal response or ultimate nonresponse to all levels of treatment in the STAR*D study. Unlike the previous studies that included the clinical and genetic factors in separate analyses, this analysis incorporated both in the same model and thus improved on the adjustment of confounding.

METHODS

Study Population

The study design of STAR*D has been described in detail elsewhere.[16] Briefly, it was a NIMH-sponsored, prospective, randomized, multistep study conducted to determine response to subsequent treatments for the participants who did not respond to initial citalopram treatment. The original data set can be assessed at the NIMH website.[8] The original study—conducted between July

Clinical Points

- Despite all available treatments, up to one-third of people treated for depression ultimately do not get better.
- These people at high risk for delayed remission are more likely to be middle aged and unemployed and have severe depression, severe comorbid medical and psychiatric conditions, and certain serotonin and cytochrome P450 2D6 variants.

2001 and September 2006—enrolled treatment-naive male and female outpatients, aged 18–75 years, with *DSM-IV* diagnosis of moderate-to-severe nonpsychotic MDD, ie, baseline score > 14 on the 17-item version of the Hamilton Depression Rating Scale.[17] The study was conducted at 18 primary care and 23 specialty care centers in the United States. Of the 4,041 participants in the original cohort, only the 1,953 who provided blood samples for DNA extraction and analysis were included in this study. The study was reviewed and approved by institutional review boards at all sites, and written informed consent was obtained at each treatment level.

There were 4 treatment levels in STAR*D, as summarized in Table 1; treatments included single medications, medication combinations, and cognitive-behavioral psychotherapy. All Level 1 participants received citalopram treatment up to 60 mg/d; those who did not achieve remission or who developed intolerable side effects were randomized in Level 2 using an equipoise-stratified randomized design,[18] which allowed participants to exercise some control over subsequent treatment selection.[19] Persons who did not remit or could not tolerate a level moved to the next higher level.

Clinical Measures

For this analysis, all the levels were treated as a single cohort. A remission event was defined as a score ≤ 5 on Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C).[20] Time to remission in weeks was calculated from the Level 1 entry point to whenever remission was achieved regardless of the type or number of treatments received. Data for individuals who did not remit throughout the study period or quit the study were censored. Sociodemographic and clinical characteristics were measured at baseline.

Genetic Markers

Blood samples for DNA extraction and analysis samples were collected from 1,953 participants. DNA was extracted using Gene-Pure chemistry (Qiagen). Samples were arrayed using a Tecan Genesis robot and then sex-verified with a set of 3 X-linked and 2 Y-linked markers.[21] The available single nucleotide polymorphisms (SNPs) in the database were selected to represent candidate genes based on the potential involvement in the mechanisms of action of antidepressant medications. The process involved, including specific variants tested, has been described elsewhere[21]; all of the available SNP markers in the database were included and were the serotonin receptors *HTR1A* (n = 2) and *HTR2A* (n = 13); the serotonin transporter *SLCA4* (n = 11); tryptophan hydroxylase-1 (*TPH1*) (n = 6); tryptophan hydroxylase-2 (*TPH2*) (n = 8); monoamine oxidase A (n = 1); the cytochrome P450 (CYP) enzymes *CYP2D6* (n = 8), *CYP2C19* (n = 3), *CYP3A4* (n = 1), and *CYP3A5* (n = 1); and P-glycoprotein *MDR1* (n = 3).

Analytic Methods

The times to depression remission were analyzed and plotted using a Kaplan-Meier estimator.[22,23] Proportional hazard regression[22] was used to fit 5 multivariable models in a unidirectional stepwise pattern that reflects a potential order of collecting and applying data to predict the risk of nonremission at baseline in an actual clinical setting. First, the covariates that were significant in the univariable analyses at the 20% level were included in building the first 3 models: Model 1 (sociodemographic variables only), Model 2 (clinical variables only), and Model 3 (genetic markers only). Then, the significant variables from Models 1 and 2 were merged to build Model 4. Finally genetic markers were added to Model 4 to build Model 5.

The following interaction terms were considered: age × gender, age × race, age × level of education, and race × gender. Each above model was checked for violation of model assumptions and overall goodness of fit. Predictive measures of accuracy were calculated using logistic regression method. Models 3, 4, and 5 were compared with χ^2 test of the difference in the models' log likelihood ratios with degrees of freedom as the difference in the number of variables in each model. The analyses were performed using SAS statistical software (SAS 9.3 version).

RESULTS

Descriptive Statistics

The baseline demographic characteristics of 1,953 STAR*D participants with nonpsychotic depression are summarized in Table 2. The majority were female (62%), white (81%), non-Hispanic (86%), married or cohabiting (43%), employed (63%), privately insured (51%), and in the middle adulthood group (51%). Over 87% had at least a high school level of education. The overall proportion of remission across the 5-year study period, irrespective of number or types of treatment received, was 65.6%, and the overall median (interquartile range) of time to remission was 11.4 (6.0–17.9) weeks. Remission was defined as a score of 5 or less on the QIDS-C, and time to remission, as number of weeks from Level 1 entry point to whenever remission was achieved.

Sociodemographic Variables and Time to Remission

Table 2 displays the relationships between the time to remission and sociodemographic variables. The number of middle-aged adults (41–64 years) who remitted was 5%–6% less than that of young (18–40 years) and older adults (65 years and above), and the median time to remission of the middle-aged adults who ultimately remitted was 14 weeks, ie,

Table 1. STAR*D Study Design and Participants With Major Depression by Treatment Level and Outcome Status[a]

Variable	Level 1	Level 2	Level 2a[b]	Level 3	Level 4
Treatment type	**Initial therapy:** citalopram	**Switch options:** sertraline, bupropion, venlafaxine **Switch or augmentation option:** cognitive therapy **Augmentation options:** bupropion, buspirone	**Switch options:** bupropion, venlafaxine	**Switch options:** mirtazapine, nortriptyline **Augmentation options:** lithium, thyroxine	**Switch options:** tranylcypromine, mirtazapine + venlafaxine
Remitters	857 (43.9)	429 (47.9)	6 (27.3)	77 (30.0)	32 (37.2)
No remitters	882 (45.2)	261 (29.1)	14 (66.6)	82 (31.9)	27 (31.4)
Dropouts	214 (11.0)	206 (23.0)	2 (9.1)	98 (38.1)	27 (31.4)
Total, N	1,953	896	22	257	86

[a]Values shown as n (%) unless otherwise noted.
[b]Participants with no satisfactory therapeutic response to cognitive therapy in Level 2.
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

2 weeks more than that of young adults and 5 weeks more than that of older adults ($P < .0001$). The older adults remitted at a mean of 9 weeks. There was no clear gender difference in the number of weeks to remission (men and women, 13.3 vs 12.6 weeks, respectively; $P = .1$). However, African Americans experienced longer time to remission than white individuals and other minorities. There was a dose-response association between the highest level of education and time to remission as about 80% of individuals with at least a master's-level education remitted and the median time to remission was 12 weeks (95% CI, 8.9–12.9), compared to a 50% remission rate for those with less than high school education, for whom time to remission was 16 weeks (95% CI, 12.6–20.9) ($P < .0001$). There was no significant difference between never-married individuals and married or cohabiting partners (12.7 vs 12.6 weeks respectively), but widowed, divorced, or separated individuals had a longer time to remission of 14 weeks (95% CI, 13.0–15.9). Currently employed or retired individuals had a shorter time to remission than unemployed individuals (12.0 vs 15.6 weeks; $P < .0001$). Those with private insurance remitted faster than those with Medicaid/Medicare (11.9 vs 16.1 weeks; $P < .0001$). There was no statistical difference between the latter and the uninsured.

Clinical Variables and Time to Remission

The results of bivariate analysis of key clinical characteristics are displayed in Table 3 and Supplementary eFigure 1. There was a significant dose-response relationship between baseline depression severity and time-to-remission curves ($P < .0001$). While more than 80% of mildly depressed individuals (QIDS-C score 6–10) remitted with median time to remission of 2 months, only 50% of very severely depressed individuals (QIDS-C score > 20) remitted with median time of 5 months. Similarly, Supplementary eFigure 1F shows a dose-response relationship between remission rate and baseline medical comorbidity, which was defined as follows: None/Mild: absent or past medical problems; Moderate: current medical conditions requiring first-line treatment; Severe: current medical conditions uncontrolled or involving multiple organs; Extremely Severe: current medical conditions uncontrolled, involving multiple organs, and requiring immediate treatment. Eighty percent of individuals without medical comorbidity remitted with median time of slightly more than 2 months in contrast to 50% of the extremely severely ill patients who remitted with a median time of 5 months ($P < .0001$).

Prior psychotropic exposure was also a strong predictor of delayed remission ($P < .0001$). Eighteen percent reported taking psychotropics, including serotonin reuptake inhibitors and tricyclic antidepressants, for clinical conditions other than major depressive disorder. The duration of the current major depressive episode was significant ($P = .0007$): 61% of chronically depressed individuals (onset > 2 years) remitted and at a median of 14 weeks, whereas 70% of those diagnosed in less than 6 months remitted and at a shorter duration of 12 weeks. The results of the association between the time to remission and comorbid psychiatric syndromes, measured with Psychiatric Diagnostic Screening Questionnaire (PDSQ),[24] are provided in Supplementary eTable 1. Statistically significant conditions include dysthymia ($P < .0001$), posttraumatic stress disorder (PTSD; $P < .0001$), generalized anxiety disorder ($P < .0001$), obsessive-compulsive disorder ($P < .0001$), panic disorder ($P < .0001$), agoraphobia ($P < .0001$), social phobia ($P < .0001$), eating disorder ($P = .0008$), somatization ($P < .0001$), substance abuse/dependence ($P = .02$), and any personality disorder ($P = .007$). Supplementary eFigure 2A shows a remarkable dose-response relationship between a number of comorbid psychiatric symptoms and increased time to remission. Alcoholism and family history of suicide, depression, or bipolar disorder were not significantly related to depression remission.

Genes and Time to Remission

The results of the bivariate analyses of time to remission of depression and several single nucleotide polymorphisms are presented in Supplementary eTable 2. The signals of the genetic markers are relatively weak compared to sociodemographic and clinical characteristics: serotonin 5HTR1A receptor (rs1364043) ($P = .037$), monoamine oxidase A (rs1465108) ($P = .045$), CYP2D6 (C2850T) ($P = .089$), CYP2C19 (2C19*3) ($P = .06$), CYP3A4 (rs2740574) ($P = .017$), CYP3A5 (rs776746) ($P = .016$), and serotonin transporter SLC6A4 ($P = .036$).

Table 2. Estimated Median Time to Remission With 95% Confidence Interval Estimates of Relevant Demographic and Social Characteristics in Data from STAR*D (N = 1,953)

Variable	Subgroup Size,[a] n (%)	Subgroup Remitters, n (%)	Weeks to Remission, Median (95% CI)	Unadjusted Hazard Ratio (95% CI), *P* Value[b]
Age, y				
≥65	100 (5.1)	68 (68.0)	9.3 (6.9–12.3)	Reference
41–64	1,002 (51.3)	631 (63.0)	14.1 (13.3–15.0)	0.63 (0.5–0.8), .0003
18–40	851 (43.6)	595 (69.9)	12.0 (11.1–12.6)	0.86 (0.7–1.1), .2
Sex				
Male	748 (38.3)	488 (65.2)	13.3 (12.7–14.3)	Reference
Female	1,205 (61.7)	806 (66.9)	12.6 (12.0–13.1)	1.10 (1.0–1.2), .1
Race[c]				
White	1,584 (81.2)	1,094 (69.1)	12.7 (12.1–13.1)	Reference
Black	321 (16.4)	164 (51.1)	14.7 (13.0–18.3)	0.73 (0.6–0.9), .0003
Other	47 (2.4)	36 (76.6)	12.3 (9.0–14.9)	1.2 (0.9–1.7), .3
Education level				
Master's/doctoral	162 (8.3)	126 (77.8)	11.7 (8.9–12.9)	Reference
College	637 (32.6)	462 (72.5)	12.0 (11.1–12.7)	0.89 (0.7–1.1), .3
High school	916 (46.9)	580 (63.3)	13.9 (13.0–14.7)	0.72 (0.6–0.9), .0005
Less than high school	238 (12.2)	126 (52.9)	15.7 (12.6–20.9)	0.64 (0.5–0.8), .0007
Marital status				
Never married	545 (27.9)	370 (67.9)	12.7 (12.0–13.9)	Reference
Married/cohabiting	838 (42.9)	587 (70.0)	12.6 (12.0–13.0)	0.97 (0.8–1.1), .6
Separated/divorced/widowed	570 (29.2)	337 (59.1)	14.4 (13.0–15.9)	0.79 (0.7–0.9), .002
Employment status				
Employed/retired	1,238 (63.4)	888 (71.7)	12.0 (11.1–12.4)	Reference
Unemployed	715 (36.6)	406 (56.8)	15.6 (14.1–18.0)	0.67 (0.6–0.7), < .0001
Insurance type				
None	670 (34.5)	404 (60.3)	14.9 (13.6–16.7)	Reference
Medicaid/Medicare only	275 (14.2)	149 (54.2)	16.1 (14.1–21.9)	0.94 (0.8–1.1), .5
Private	998 (51.4)	735 (73.6)	11.9 (10.4–12.1)	1.45 (1.3–1.6), < .0001
Homeless				
No	1,939 (99.3)	1,291 (66.6)	12.9 (12.4–13.4)	. . .
Yes	14 (0.7)	3 (21.4)	. . .[d]	. . .
Living with spouse				
No	528 (38.1)	333 (63.1)	13.0 (12.0–14.0)	Reference
Yes	858 (61.9)	596 (69.5)	12.7 (12.0–13.3)	1.06 (0.9–1.2), .4
No. of persons living in the household				
0	606 (31.1)	396 (65.3)	13.6 (12.4–14.7)	Reference
1	556 (28.5)	380 (52.9)	12.7 (11.9–14.0)	1.08 (0.9–1.2), .3
2 or more	790 (40.5)	517 (65.4)	12.9 (12.1–13.6)	1.06 (0.9–1.2), .4
Volunteering				
No	1,610 (82.5)	1,041 (64.7)	13.0 (12.7–13.9)	Reference
Yes	341 (17.5)	251 (73.6)	12.2 (10.9–13.7)	1.16 (1.0–1.3), .04
Being on medical or psychiatric leave				
No	1,798 (92.2)	1,210 (67.3)	12.6 (12.1–13.0)	Reference
Yes	152 (7.8)	83 (54.6)	20.9 (14.9–24.1)	0.63 (0.5–0.8), < .0001

[a]There were missing responses in race (n = 1), insurance type (n = 10), living with spouse (n = 567), number of persons living in the household (n = 1), volunteering (n = 2), and being on medical or psychiatric leave (n = 3).
[b]Hazard ratio/*P* value: comparing time to remission of subgroups to the reference subgroup.
[c]A total of 86% of participants were non-Hispanic.
[d]Could not be calculated due to small group size.
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.
Symbol: . . . = not applicable.

Predictive Models

The results of the 5 models with their accuracy measures are compared in Supplementary eTable 3 and eFigure 1. The sociodemographic-only and clinical variables–only models performed well with areas under the curve (AUC) of 63% and 67%, sensitivities of 97% and 90%, and specificities of 8% and 22%, respectively (Figure 1). The genetic variables–only model had a lower accuracy of AUC of 56%. Compared with the individual models, the combined Model 4, containing sociodemographic and clinical variables, had better model fitness and accuracy measures—AUC = 68.7%, sensitivity = 90%, and specificity = 20%. Similarly, Model 5, containing Model 4 and 2 genetic markers, had better model fitness than Model 4 ($\chi^2_2 = 12.4$, $P = .002$) and slightly higher accuracy measures—AUC = 70%, sensitivity = 88%, and specificity = 24%. Among the interaction terms tested, only age × education level yielded borderline significance ($\chi^2_6 = 10.99$, $P = .089$), suggesting that the positive effect of higher education level on time to remission was limited to the individuals aged 65 years and above.

Table 4 shows the relative risk (RR) of the predictors and time to remission. For interpretation, the further the RR was below 1.00, the lower the likelihood of achieving remission, and vice versa for RR > 1. In the sociodemographic category,

Table 3. Estimated Median Time to Remission With 95% Confidence Interval Estimates of Relevant Clinical Characteristics in Data from STAR*D (N = 1,953)

Variable	Subgroup Size, n (%)	Subgroup Remitters, n (%)	Median Time to Remission in Weeks (95% Confidence Interval)	Unadjusted Hazard Ratio[a] (95% CI), *P* Value[a]
Depression severity				
Mild (QIDS-C score 6–10)	72 (3.7)	60 (83.3)	6.9 (4.3–9.9)	Reference
Moderate (QIDS-C score 11–15)	750 (38.4)	559 (74.5)	10.4 (9.4–11.9)	0.62 (0.5–0.8), .0005
Severe (QIDS-C score 16–20)	889 (45.5)	557 (62.7)	14.1 (13.1–15.0)	0.41 (0.3–0.5), < .0001
Very severe (QIDS-C score > 20)	241 (12.4)	118 (49.0)	19.9 (15.0–24.0)	0.28 (0.2–0.4), < .0001
Medical comorbidity				
None/mild	382 (19.6)	304 (79.6)	9.7 (9.0–12.0)	Reference
Moderate	474 (24.3)	348 (73.4)	12.0 (11.3–13.0)	0.80 (0.6–0.9), .004
Severe	738 (37.8)	459 (62.2)	13.0 (12.6–14.1)	0.64 (0.6–0.7), < .0001
Extremely severe	359 (18.4)	183 (51.0)	19.8 (16.0–23.4)	046 (0.4–0.6), < .0001
Prior psychotropic exposure				
No	1,374 (70.4)	945 (68.8)	12.3 (12.0–12.9)	Reference
Yes	578 (29.6)	349 (60.4)	15.7 (14.0–18.0)	0.70 (0.6–0.8), < .0001
Age at first MDE, y				
< 18	725 (37.1)	463 (63.9)	13.6 (12.7–14.7)	Reference
18–40	871 (44.6)	603 (69.2)	12.7 (12.1–13.9)	1.14 (1.1–1.3), .03
41–59	309 (15.8)	199 (64.4)	12.7 (11.6–14.0)	1.05 (0.9–1.2), .58
≥ 60	48 (2.5)	29 (60.4)	9.7 (6.1–14.0)	1.45 (1.0–2.1), .05
No. of past MDEs				
0	432 (25.7)	297 (68.8)	12.0 (10.0–12.6)	Reference
1–2	612 (36.3)	413 (67.5)	12.7 (12.0–13.9)	0.92 (0.8–1.1), .26
3 or more	640 (38.0)	440 (68.8)	13.0 (12.3–14.1)	0.90 (0.8–1.0), .17
Onset of current MDE, mo				
< 6	775 (39.7)	543 (70.1)	12.1 (11.6–13.0)	Reference
6–24	666 (34.1)	437 (65.6)	13.1 (12.6–14.3)	0.86 (0.8–1.0), .02
> 24	512 (26.2)	314 (61.3)	13.8 (12.9–15.3)	0.79 (0.7–0.9), .0007
Premenstrual worsening of depression				
No	262 (37.8)	174 (66.4)	12.1 (10.0–13.6)	Reference
Yes	431 (62.2)	306 (71.0)	12.0 (11.3–12.9)	1.08 (0.9–1.3), .4

[a]Hazard ratio/*P* value: comparing time to remission of subgroups to the reference subgroup.
Abbreviations: MDE = major depressive episode; QIDS = Quick Inventory of Depressive Symptomatology, Clinician Rating; STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

the middle-aged adults (41–65 years) had a higher risk of nonremission ($P = .03$) than the younger adults (18–40 years), but no significant difference was seen between the younger and older adults. Concerning education, there was no difference in remission rates in individuals with college degree and those with higher degrees; however, high school graduates had lower remission rate than master's or doctoral degree holders. Unemployed individuals had 24% less likelihood of achieving remission ($P = .004$) than employed or retired individuals. Compared with the mildly depressed group, the very severely and severely depressed groups were, respectively, 56% and 49% less likely to achieve remission ($P = .001$ and .002, respectively). The effect of medical comorbidity was similar to that of depression severity: extremely severely and severely ill individuals were, respectively, 48% and 32% less likely to achieve remission ($P < .0001$ and .002, respectively). For psychiatric comorbidities, the presence of 9 or more PTSD symptoms or 4 or more dysthymic symptoms significantly reduced the likelihood of remission by 30% ($P = .005$) and 27% ($P = .005$), respectively. Finally, the participants with *HTR1A* genotype C/C had 62% better remission rate than A/A counterparts ($P = .006$); likewise, in those with *CYP2D6*, C/T or T/T had better remission than C/C by 33% and 59%, respectively ($P = .002$ for C/T and $P = .0004$ for T/T).

Figure 1. Receiver Operating Characteristics of the Models

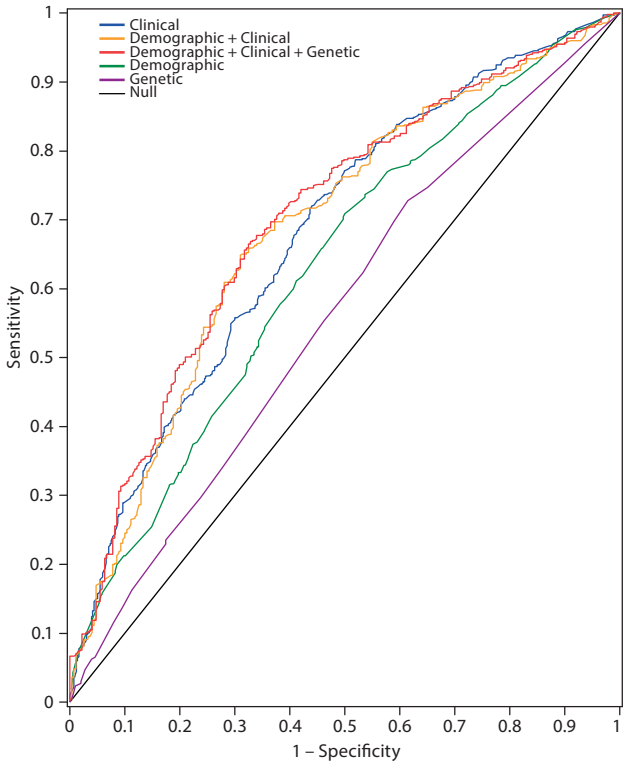

Table 4. Final Model Showing the Relative Risks of the Predictors of Long-Term Antidepressant Treatment Response

Predictor	Relative Risk (95% CI)	*P* Value
Sociodemographic		
Age, y		
18–40	1.00	
41–65	0.81 (0.67–0.98)	.032
≥65	1.35 (0.87–2.08)	.178
Education level		
Master's/doctoral	1.00	
College	0.97 (0.72–1.30)	.813
High school	0.72 (0.53–0.97)	.0319
Less than high school	1.01 (0.70–1.45)	.9787
Employment		
Employed/retired	1.00	
Unemployed	0.76 (0.62–0.92)	.004
Clinical		
Depression severity		
Mild	1.00	
Moderate	0.71 (0.27–0.72)	.117
Severe	0.51 (0.33–0.78)	.002
Very severe	0.44 (0.27–0.72)	.001
Medical comorbidity		
None/mild	1.00	
Moderate	0.84 (0.66–1.07)	.155
Severe	0.68 (0.53–0.87)	.002
Extremely severe	0.52 (0.38–0.72)	<.0001
No. of PTSD symptoms		
0	1.00	
1–9	0.92 (0.76–1.12)	.419
>9	0.70 (0.54–0.90)	.005
No. of dysthymic symptoms		
0–1	1.00	
2–4	0.86 (0.67–1.10)	.213
>4	0.73 (0.59–0.91)	.005
Genetic		
HTR1A rs1364043		
A/A	1.00	
C/A	1.02 (0.85–1.23)	.803
C/C	1.62 (1.12–2.28)	.006
CYP2D6 C2850T		
C/C	1.00	
C/T	1.33 (1.11–1.60)	.002
T/T	1.59 (1.23–2.06)	.0004

Abbreviation: PTSD = posttraumatic stress disorder.

DISCUSSION

This secondary analysis of the STAR*D study considered a broad list of potential predictors of antidepressant response across multiple treatment trials. Overall, we identified 3 sociodemographic, 4 clinical, and 2 genetic factors associated with delayed remission after multiple levels of antidepressant treatment in the STAR*D cohort (Table 4). The results demonstrate good predictive capacity with high sensitivity in identifying high-risk individuals for delayed remission.

Age, Education, and Employment

Of the sociodemographic characteristics examined, only age, education level, and employment were predictors of remission to multiple levels of antidepressant treatment. However, the effect of age was not linear. Middle-aged adults, who constitute about half of the sample, appear to have a lower remission rate than the younger or older groups. This U-shaped relationship between age and treatment remission might explain the hitherto inconsistent evidence of the relationship of age to depression.[25] Based on the age × education interaction analysis, the predictive effect of education level was pronounced in the older adults only.

The employment effect remained statistically significant and independent of other socioeconomic factors. This finding suggests that assisting unemployed depressed persons to find work or referring for job training programs[26,27] may be a useful intervention to enhance the effectiveness of the antidepressant treatments. A recently published article[28] demonstrates that early improvement in work productivity is strongly associated with higher remission rates. After adjustment, race is notably not a predictor of delayed remission to multiple levels of antidepressant treatment, although it should be noted Friedman et al[29] had suggested that African American individuals were more likely to have worsening of depression with treatment.

Depression Severity, Psychiatric, and Medical Comorbidities

The previously known relationship between baseline depression severity and poor antidepressant outcome[30] was also reflected in the current analysis. Baseline depression severity was defined by baseline Quick Inventory of Depressive Symptomatology–Self-Report scores as mild,[6–10] moderate,[11–15] severe,[16–20] and very severe.[21–23,25–28] Severely and very severely depressed individuals had lower likelihood of remission. Although several comorbid depressive-, anxiety-, personality-, and substance-related conditions were initially associated with the long-term antidepressant outcome (Supplementary eTable 1), only high number of PTSD (>9) and dysthymic (>4) symptoms remained after multiple adjustments. As discussed previously,[31] these findings suggest that previous physical or emotional trauma and chronic depressive symptoms may require a different treatment approach. In addition to psychiatric comorbidity, individuals with severe uncontrolled or multiple-organ medical conditions have low likelihood of benefiting from antidepressant treatment. The presence and severity of comorbid medical illnesses should be considered in the initial evaluation; those with severe medical comorbidities may require more aggressive treatment, including early augmentation or combination of medications. It is yet unclear whether adequate treatment of comorbid medical conditions would improve outcome.

Serotonin-1A Receptor and CYP2D6

This study has demonstrated the key contribution of 2 variants of the serotonin-1A (*HTR1A*) and CYP2D6 genes to prediction of remission to multiple antidepressant treatments. *HTR1A* is located both presynaptically and postsynaptically and acts on autoreceptors to prevent the serotonin release via negative feedback. Villafuerte et al[9] and Yu et al[32] have previously reported the influence of *HTR1A* gene (among others) on initial antidepressant response. We have further demonstrated that the effect of *HTR1A* gene,

in particular, is not limited to just the initial antidepressant treatment. There are multiple influences of genetic variants of *CYP2D6*,[33] ranging from poor to ultrarapid metabolism. The particular variant found in this study to be associated with slower response to treatment was C2850T, which contributes to several genotypes, including *2, *2XN, *17, and *29, that confer normal, higher, or lower metabolism. Several drugs used in the STAR*D algorithm (venlafaxine, nortriptyline, mirtazapine) are CYP2D6 substrates, and their blood levels may have been affected. Thus obtaining genetic testing would be very helpful, particularly in individuals with other risk factors for delayed remission.

CONCLUSION

Nine important factors can be used to identify depressed individuals who are less likely to respond to multiple rounds of antidepressant treatments and might be candidates for advanced care options. These factors are middle age, lower education, unemployed status, severe depression, greater levels of medical comorbidity, comorbid PTSD or dysthymia, and specific *HTR1A* C/C (5q12.3) and *CYP2D6* 2850 C/T and T/T genotypes (22q13.2).

We would encourage caution in the interpretation of these results as this was a secondary analysis limited to available data only. We cannot conclude that we have considered all of the possible predictors of remission. Also, different statistical methods were used to develop the models (proportional hazard regression) and to estimate the predictive measures (logistic regression) because there is as yet no standardized method of obtaining predictive measures from time-to-event analysis. The low specificity indicates that the model is weak in minimizing false labeling of depressed individuals as at high risk for delayed remission. Future studies may consider improving on our models by adding inflammatory or imaging biomarkers.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Clinical and Genetic Predictors of Delayed Remission After Multiple Levels of Antidepressant Treatment: Toward Early Identification of Depressed Individuals for Advanced Care Options

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List of Supplementary Material for the article

1. **eTable 1** Estimated median time to remission with 95% confidence interval estimates of important comorbid psychiatric symptoms in STAR*D data (n = 1953)
2. **eTable 2** Estimated median time to remission with 95% confidence interval estimates of SNPs with *p*-value < 0.2 in the limied STAR*D data (n = 1953)
3. **eTable 3** Models comparisons
4. **eFigure 1** Kaplan-Meier plots of time to remission in weeks and key baseline characteristics
5. **eFigure 2** Predictors and Time to remission

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Estimated median time to remission with 95% confidence interval estimates of important comorbid psychiatric symptoms in STAR*D data (n = 1953)

Variable	Category (events, n)	% Nonremitters	Median time to complete remission in weeks (95% CIE)	Hazard Ratio	Log-Rank test p-value
Dysthymic symptoms	0 - 1 (250, 350)	28.6	10.0 (9.1, 12.1)	Reference	<0.0001
	2 - 4 (370, 493)	24.9	11.7 (9.8 - 12.7)	0.98	
	> 4 (659, 1077)	38.8	14.6 (13.9, 15.7)	0.65	
PTSD symptoms	0 (395, 540)	26.9	10.3 (9.3, 12.0)	Reference	<0.0001
	1 - 9 (620, 897)	30.9	12.5 (12.0, 13.0)	0.84	
	> 9 (259, 476)	45.6	18.3 (15.9, 21.0)	0.53	
Eating disorder symptoms	0 (516, 772)	33.2	12.4 (11.7, 13.1)	Reference	0.0008
	1 - 3 (359, 506)	29.1	12.7 (11.7, 13.7)	0.98	
	> 3 (406, 647)	37.2	14.0 (12.9, 15.1)	0.79	
OCD symptoms	0 (675, 941)	28.3	12.0 (10.4, 12.6)	Reference	<0.0001
	1 - 3 (489, 755)	35.2	13.3 (12.6, 14.4)	0.80	
	> 3 (116, 230)	49.6	20.1 (15.3, 24.0)	0.54	
Panic disorder symptoms	0 (494, 681)	27.5	11.9 (10.0, 12.4)	Reference	<0.0001
	1 - 3 (435, 630)	31	12.8 (12.3, 13.9)	0.86	
	> 3 (351, 613)	42.7	15.1 (13.9, 18.0)	0.64	
Psychotic symptoms	0 (967, 1372)	29.5	12.1 (11.9, 12.7)	Reference	<0.0001
	1 (189, 305)	38	13.9 (12.6, 15.0)	0.81	
	> 1 (126, 251)	49.8	20.9 (17.0, 24.1)	0.54	
Agoraphobia symptoms	0 (647, 879)	26.4	11.6 (10.0, 12.1)	Reference	<0.0001
	1 - 3 (325, 493)	34.1	12.9 (11.7, 14.1)	0.81	
	> 3 (304, 545)	44.2	18.0 (15.4, 20.9)	0.56	
Social phobia symptoms	0 - 3 (579, 811)	28.6	11.7 (10.0, 12.1)	Reference	<0.0001
	4 - 9 (373, 567)	34.2	12.9 (12.1, 14.0)	0.81	
	> 9 (325, 541)	39.9	15.7 (14.0, 17.9)	0.65	
GAD symptoms	0 - 3 (280, 377)	25.7	11.6 (9.4, 12.7)	Reference	<0.0001
	4 - 6 (297, 409)	27.4	11.7 (10.0, 12.4)	0.96	
	> 6 (702, 1134)	38.1	14.4 (13.6, 15.0)	0.66	
Somatization symptoms	0 (388, 499)	22.2	9.7 (9.1, 11.4)	Reference	<0.0001
	1 - 3 (596, 904)	34.1	13.3 (12.6,14.1)	0.71	
	> 3 (287, 507)	43.4	17.9 (14.7, 20.9)	0.52	
Alcohol use disorder symproms	0 (985, 1481)	33.5	12.9 (12.3, 13.7)	Reference	0.917
	1 or more (295, 446)	33.9	12.9 (12.3, 14.1)	1.01	
Any substance use disorder symptoms	0 (1180, 1748)	32.5	12.7 (12.1, 13.0)	Reference	0.0151
	1 or more (100, 175)	42.9	16.6 (14.0, 21.3)	0.78	
Any personality disorder	No (880, 1328)	33.7	12.9 (12.1, 13.4)	Reference	0.007
	Yes (11, 31)	64.5	24.0 (13.9, --)	0.45	

Supplementary eTable 2. Estimated median time to remission with 95% confidence interval estimates of SNPs with *p*-value < 0.2 in the limied STAR*D data (n = 1953)

	SNPs*	Category (events, n)	% Nonremitters	Median time to complete remission in weeks (95% CIE)	Hazard Ratio	Log-Rank test p-value
HTR1A	rs1364043	A/A (684, 1070)	36.1	13.3 (12.6, 14.1)	0.71	0.0367
		C/A (408, 595)	31.4	13.0 (12.4, 14.1)	0.76	
		C/C (61, 80)	23.7	12.0 (9.1, 13.0)	Reference	
HTR2A	rs731245	C/C (294, 439)	33.0	13.1 (12.4, 14.1)	0.90	0.164
		C/T (502, 790)	36.5	13.0 (12.4, 14.0)	0.88	
		T/T (332, 471)	29.5	12.3 (11.3, 13.9)	Reference	
	rs2770296	A/A (632, 983)	35.7	13.6 (12.9, 14.7)	0.81	0.126
		G/A (421, 637)	33.9	12.9 (12.0, 14.0)	0.83	
		G/G (102, 130)	21.5	11.3 (8.9, 12.1)	Reference	
	rs927544	C/C (94, 126)	25.4	11.8 (8.9, 12.9)	1.20	0.17
		C/T (405, 584)	30.7	12.7 (12.0, 14.0)	1.08	
		T/T (624, 974)	35.9	13.0 (12.4, 13.9)	Reference	
	rs1923882	A/A (89, 126)	29.4	12.4 (10.3, 14.9)	1.05	0.154
		G/A (396, 611)	35.4	14.0 (13.0, 14.9)	0.90	
		G/G (686, 1018)	32.6	12.6 (12.0, 13.0)	Reference	
TPH2	rs2129575	G/G (651, 969)	32.8	12.9 (12.1, 13.9)	0.93	0.103
		G/T (407, 630)	35.4	13.9 (12.7, 15.0)	0.83	
		T/T (91, 131)	30.5	12.6 (9.7, 14.9)	Reference	
	rs2171363	A/A (258, 422)	38.9	13.0 (12.3, 14.7)	0.87	0.141
		A/G (560, 854)	34.4	13.1 (12.4, 14.3)	0.89	
		G/G (341, 483)	29.4	12.7 (11.9, 14.0)	Reference	
	rs17110747	A/A (35, 48)	27.1	13.0 (11.1, 14.9)	1.25	0.202
		A/G (275, 393)	30.0	12.6 (1.3, 13.9)	1.10	
		G/G (932, 1428)	34.7	13.0 (12.6, 13.9)	Reference	
MOA-A	rs1465108	A/A (207, 342)	39.5	14.1 (12.7, 16.1)	0.90	0.045
		G/A (291, 420)	30.7	12.4 (11.9, 13.0)	1.12	
		G/G (561, 842)	33.4	13.0 (12.3, 14.0)	Reference	
CYP2D6	_2D6_C2850T	C/C (544, 839)	35.2	13.9 (13.0, 14.9)	0.91	0.089
		C/T (531, 780)	31.9	12.3 (11.6, 12.9)	1.04	
		T/T (195, 300)	35.0	12.7 (12.0, 14.7)	Reference	
CYP2C19	_2C19_star3	A/A (1267, 1909)	33.6	13.0 (12.4, 13.6)	2.46	0.062
		A/C (4, 12)	66.7	40.4 (9.3.-)	Reference	
CYP3A4	_3A4_rs2740574	A/A (1041, 1525)	31.7	12.7 (12.1, 13.4)	1.36	0.017
		A/G (147, 241)	39.0	13.0 (11.7, 14.9)	1.22	
		G/G (83, 155)	46.5	14.1 (12.7, 20.9)	Reference	
CYP3A5	_3A5_rs776746	A/A (98, 175)	44.0	14.0 (13.0, 17.0)	0.75	0.016
		A/G (248, 388)	36.1	13.3 (12.4, 15.7)	0.91	
		G/G (925, 1357)	31.8	12.6 (12.0, 13.1)	Reference	
MDR1	_MDR1_rs2032582	G/G (505, 805)	37.3	13.9 (12.7, 14.7)	0.86	0.107
		G/T (516, 753)	31.5	12.7 (12.0, 13.9)	0.96	
		T/T (246, 359)	31.5	12.6 (11.1, 13.1)	Reference	
	_MDR1_C3435T	C/C (371, 582)	36.3	13.1 (12.3, 14.3)	0.88	0.184

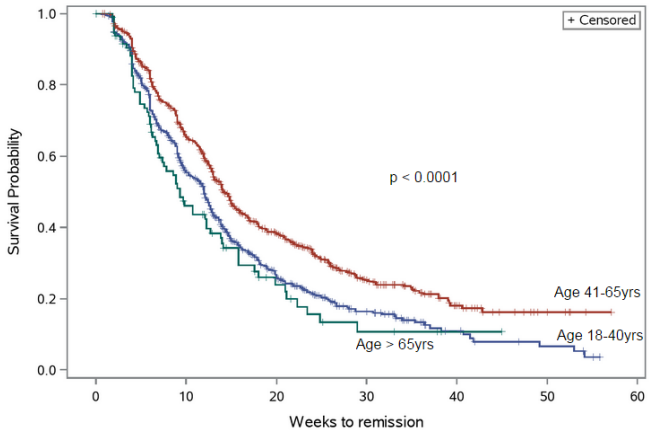
		T/C (596, 905)	34.1	12.9 (12.3, 14.0)	0.89	
		T/T (307, 434)	29.3	12.4 (11.0, 13.6)	Reference	
PK-deletion variants	_2D6_1863ins	-/+ (1, 1)	--	--	--	--
		+/+ (1266, 1915)	--	--	--	--
SLC6A4	rs16965628	C/C (978, 1434)	31.8	12.6 (12.0, 13.0)	1.06	0.052
		G/C (166, 281)	40.9	14.7 (12.9, 16.6)	0.87	
		G/G (24, 37)	35.1	14.8 (9.3, 20.4)	Reference	
	rs2066713	C/C (397, 620)	36.0	14.0 (12.7, 15.0)	0.80	0.036
		C/T (489, 720)	32.1	12.6 (12.0, 13.1)	0.90	
		T/T (166, 235)	29.4	11.4 (9.6, 13.9)	Reference	
	rs140700	A/A (6, 10)	40.0	13.9 (3.0, 17.6)	1.05	0.016
		A/G (157, 218)	28.0	12.0 (9.4, 12.9)	1.28	
		G/G (796, 1263)	37.0	13.9 (12.9, 14.3)	Reference	

Supplementary eTable 3. Models comparisons

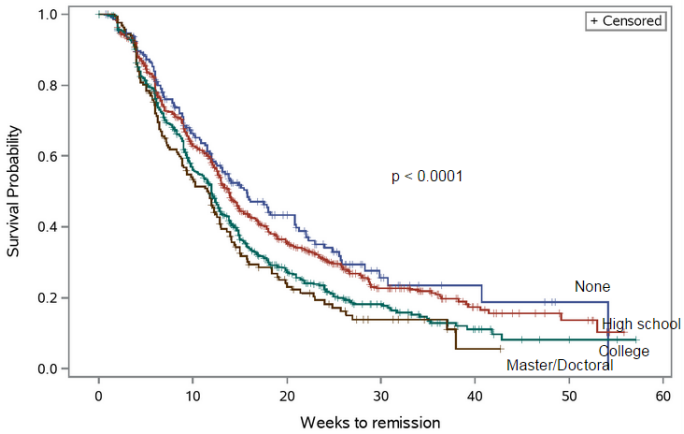
	Model 1. Sociodemographics only	Model 2. Clinical variables only	Model 3. Genetic variables only	Model 4. Demographic + clinical	Model 5. Demographic + clinical + genetic
Age	0.021			0.028	0.01
Gender	0.0063			ns	ns
Education level	0.0002			0.017	0.008
Employment	0.015			0.004	0.005
Insurance type	0.055			ns	ns
Medical comorbidity		<0.0001		0.0012	0.0005
Depression severity		<0.0001		<0.0001	<0.0001
Prior psychotropic exposure		ns		ns	ns
PTSD		0.055		0.02	0.02
GAD		ns		ns	ns
Dysthimia		0.005		0.01	0.02
Somatization symptoms		0.03		ns	ns
Agoraphobia		0.01		ns	ns
Any personality disorder		0.04		ns	ns
HTR1A rs1364043			0.048		0.02
CYP2D6_C2850T			0.0013		0.0003
MOA-A rs1465108			0.026		ns
AUC, %	62.9	68.1	56.2	68.7	70.1
Sensitivity, %	97.3	89.3	100.0	89.8	87.6
Specificity, %	7.8	24.3	0.0	20.2	23.5

Supplementary eFigure 1 (A – H). Kaplan-Meier plots of time to remission in weeks and key baseline characteristics

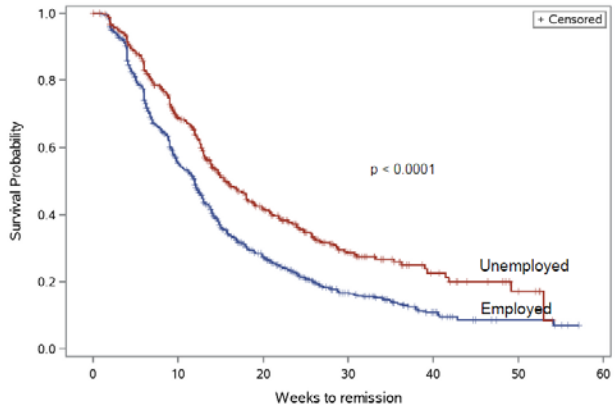
A. Age group



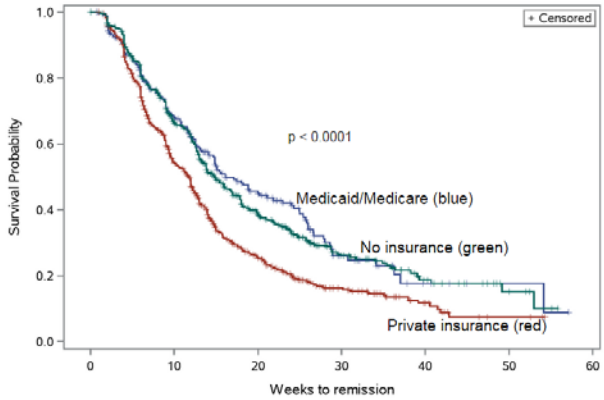
B. Highest level of education



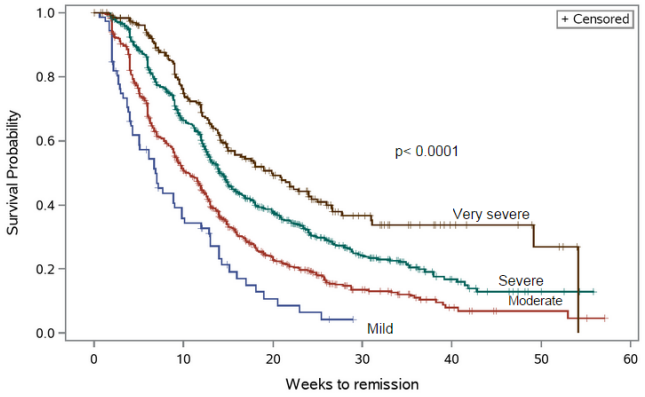
C. Employment status



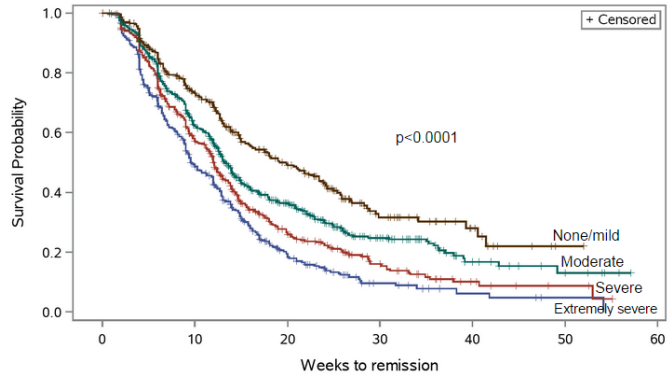
D. Insurance status



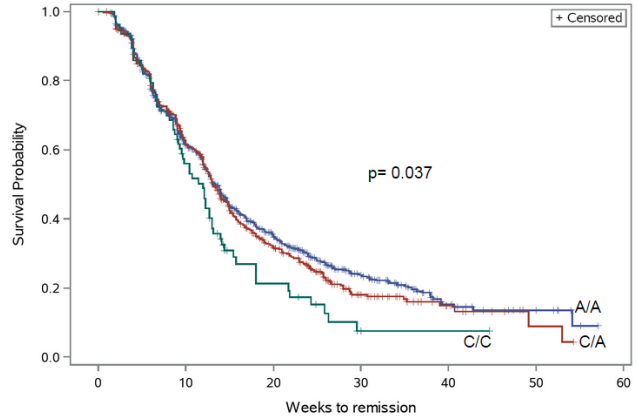
E. Depression severity



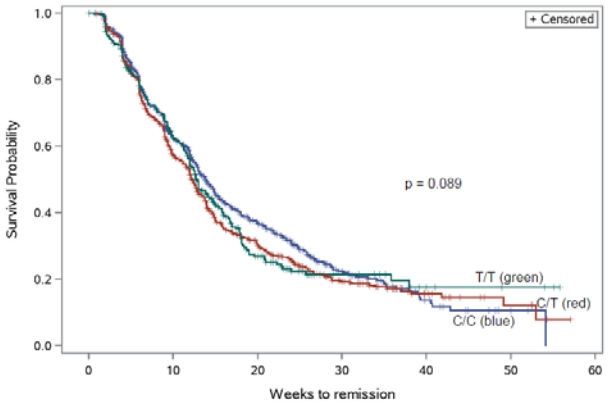
F. Medical comorbidity



G. HTR1A rs1364043



H. CYP2D6_C2850T



Supplementary eFigure 2. Predictors and Time to remission.

2a. Showing the dose-response relationship between number of comorbid psychiatric symptoms and increased time to remission.

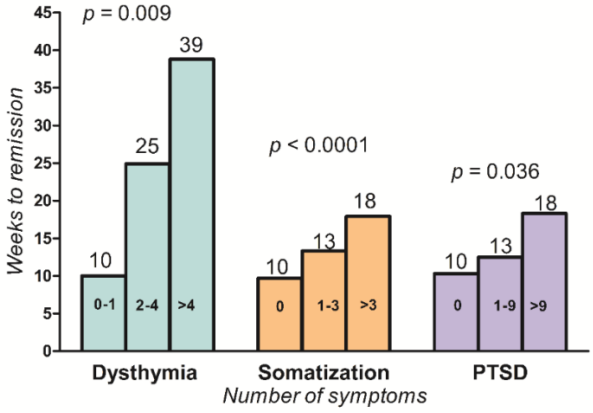


Figure 2b. Showing the association serotonin 5HT1A receptor marker and and increased risk of non-remission.