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Predictive Modeling of Suicidal Ideation in Patients with Epilepsy

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Abstract

Objective: The prevalence of suicide in the United States has seen an increasing trend and is responsible for 1.6% of all mortality nationwide. While suicide has the potential to broadly impact the entire population, it has a substantially increased prevalence in persons with epilepsy (PWE) despite many of these individuals consistently seeing a health care provider. The goal of this work is to predict the development of suicidal ideation in PWE using machine learning methodology such that providers can be better prepared to address suicidality at visits where it is likely to be prominent.

Methods: The current study leverages data collected at an epilepsy clinic during patient visits to predict whether an individual will exhibit suicidal ideation (SI) at their next visit. The data used for prediction consisted of patient responses to questions about the severity of their epilepsy, issues with memory/concentration, somatic problems, markers for mental health, and demographic information. A machine learning approach was then applied to predict whether an individual would display suicidal ideation at their following visit using only data collected at the prior visit.

Results: The modeling approach allowed for the successful prediction of an individual's passive and active SI severity at the following visit (r=0.42, r=0.39) as well as the presence of SI regardless of severity (AUC=0.82, AUC=0.8). This shows that the model was successfully able to synthesize the unique combination of individual's responses to important questions during a

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Disclosures

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clinical visit and utilize that information indicate whether or not that individual will exhibit SI at their next visit.

Significance: The results of this modeling approach allow the healthcare team to be prepared, in advance to a clinical visit, for the potential endorsement of SI. By allowing the necessary support to be prepared ahead of time, it can be better integrated at the point-of-care, where patients are most likely to uptake potential referrals or treatment.

Keywords

Machine Learning; Epilepsy; Suicidal Ideation

Introduction:

The first national suicide prevention programs were implemented in the early 1990s, when suicide was recognized as a public health crisis.[1] Despite efforts to prevent suicide and suicidal ideation, rates have continued to increase since 1999. Over the past couple of decades, all but one US state saw a rise in rates of completed suicide and half saw an increase of over 30%.[2] In New Hampshire, where our clinic is located, the rate of suicide has risen more than 48%.[2] As a result of this sustained increase in incidence, suicide accounts for 1.6% of deaths within the US today (CDC).

While suicide is a global problem, certain populations are disproportionally affected. Persons with epilepsy (PWE) experience suicidal ideation (SI) with a lifetime prevalence of 23.3%,[3] a significant increase over the 9% seen in the general population.[4] As a natural follow-up to ideation, in PWE, the rate of completed suicide (CS) is 22% higher than that of the general population.[5] While PWE have higher rates of other known SI risk factors, such as psychiatric comorbidities and lower socioeconomic status,[6–8] this increase in ideation and completed suicide continues to be true even when controlling for these confounding factors.[9]

Unfortunately, the underlying causes that account for increased rates of SI in the epilepsy population are still not well understood. Traditional screening measures for psychiatric health can result in falsely elevated scores in PWE, so much so that epilepsy assessment measures, such as the NDDI-E, have been developed to accommodate these differences when screening for depression in this population.[10] Still, the epilepsy specific psychosocial and disease factors that contribute to longitudinal changes in SI for PWE are not well established. Given this gap in knowledge and the fact that suicidal thought and behavior do not exist in a vacuum, it is imperative that we understand how epilepsy itself impacts SI. This information could then be used to establish appropriate screenings and interventions to prevent progression to completed suicide.[11]

SI has been established as a strong risk factor for death by suicide. Longitudinal studies within the general population have shown it to be a significant predictor for CS.[12,13] In the year prior to suicide, 83% of patients will see a healthcare provider at least once, and most persons (55%) will receive healthcare services in the four weeks prior to death by suicide.[14] While public discussion has emphasized the importance of mental health treatment, the majority of people who die by suicide do not have a prior mental health diagnosis.[15] It

is therefore imperative that suicide prevention efforts are not confined to mental health settings. For PWE living with a chronic neurological disease, epilepsy providers are in a unique position to monitor changes in risk factors over time and can serve as a critical safeguard to prevent suicide.

These risk factors, however, can have complex and non-linear interactions related to suicidality that can make it difficult for a provider to monitor risk in addition to providing standard care for epilepsy. Our prior work exemplified the complicated nature of SI in this population concluding that seven separate constructs including comorbid psychiatric illness, unemployment, and worsening seizures were all associated with increased rates of SI in our patients. Adding to this complexity, different severity levels of each construct were associated with SI.[16] While this work was beneficial in understanding risk factors for suicide at the population level, it is difficult to translate this knowledge directly to patient care to identify individuals at risk for suicide.

The current study aims to leverage a machine learning approach to create an actionable tool for identifying SI in the clinical population. A machine learning approach is uniquely poised for this task because it is tuned to evaluate patients at the individual level. If a model can learn the complex relationship between risk factors and SI, it can be deployed in a clinical setting to help providers decide whether further action or mental health care would be justified. Ultimately, the goal of this work is to build a model that can predict suicidal ideation at a given clinical visit with high sensitivity and specificity. This information can be used in real time by a clinician to aid in care decisions and get those at high risk for suicide the help they need.

Methods

2.1 Sample & Data Acquisition.

The study cohort consisted of all patients seen in a New England outpatient epilepsy clinic between January 2013 and January 2019 with a documented epilepsy diagnosis (*International Classification of Disease* (ICD)-9: 345; ICD-10: G40*) who completed the tablet-administered Epilepsy Clinic Questionnaire. The Epilepsy Clinic Questionnaire is given to patients prior to each visit, and survey responses are automatically uploaded into the medical record at the time of the encounter. The questionnaire uses both single-selection categorical scales and interval scales to assess self-reported epilepsy symptoms, physical health, mood, cognition, and social factors. A full list of the 40 potential questions is shown in Supplementary Table 1. For all eligible patients and visits, individual demographic information and questionnaire responses were extracted from the electronic health record by a hospital data governance analyst. Patient-level data included date of birth, sex, race/ethnicity, and dates of service.

Suicidal ideation was measured in two ways, both as passive and active suicidal ideation. Agreement with the statement, “I would be better off dead” served as a marker for passive SI,[17] and self-reported ratings assessing “thoughts of ending one’s life” were classified as active ideation.[18] Both of these statements were rated by the responder on a 4-point Likert scale; (1=never, 2=rarely, 3=sometimes, 4=often). Each of these acted as an independent

outcome and thus were modeled separately. This allowed for model comparison regarding both accuracy and importance level for independent predictors.

The Committee for the Protection of Human Subjects at Dartmouth College and the Dartmouth-Hitchcock Institutional Review Board approved this study. The NDI reviewed and approved the protocol, and the Dartmouth-Hitchcock privacy office approved the method of data transmission. Informed consent and HIPAA authorization were waived per 45 CFR 46.116(d) and 45 CFR 165.512(i)(2)(ii), respectively.

2.2 Data Preprocessing

Preprocessing of the data was implemented within both R and Python programming languages (R version 3.6.2 and Python version 3.7). There were two categories of data collected throughout the course of this study. The first was patient level data and the second was encounter level data. Patient-level data remained static and included demographic items such as race, sex, and ethnicity. Encounter level data consisted of the 40 unique questions that were asked to participants at each visit to the clinic. The responses were in a variety of forms including structured ordinal responses (never, sometimes, often, always), numeric responses, and categorical responses (myself, a parent, a child, a caregiver [question: who is completing this questionnaire?]). For the purposes of a machine learning analytical approach (see below), structured ordinal responses were coded numerically, numeric responses were left as is, and categorical responses as well as static predictors (ethnicity, sex, race) were dummy coded.

Once the data was properly coded, it was formatted to combine both the patient level data and encounter level data in “long” format. In this way, each observation represented one encounter for a given subject. The independent variables included the patient level data as well as each question asked at a given encounter. The two outcomes of passive and active suicidal ideation as indexed by the questions “I’d be better off dead?” and “Thoughts about ending your life?” as well as the NDDI-E questionnaire score were removed from the data before modeling began as they contained information pertinent to the outcome. The final preprocessing step was to deal with missing values. If the outcome for a given encounter was missing, that encounter was dropped from modeling. All other missingness among the independent predictors was kept as part of the data and dealt with in the modeling step.

After all preprocessing, there were 13,769 unique encounters across all 3,067 subjects representing an average of 4.5 visits per person and 9 months between visits. Demographic characteristics for these patients can be found in supplementary table 2. Roughly 25% of subjects were passively suicidal during at least one encounter and 25% of subjects were actively suicidal during at least one encounter. Subjects had active suicidal ideation among 13.8% of all encounters and this outcome had 3.9% missingness. Subjects had passive suicidal ideation in 13.9% of all encounters and this outcome had 5.8% missingness.

2.3 Machine Learning Model Implementation

Model construction, training, and validation was also performed in Python using an *a priori* selected algorithm for this analysis: extreme gradient boosting implemented via a Python machine learning library.[19] There were two main reasons that this particular method was

chosen in this context. The first was due to its ability to capture non-linear relationships and interactions among the independent predictors and the second was its ability to find signal in missing data.[20]

All model training was done in a modified five-fold validation framework. At each iteration of this process, all observations corresponding to a randomized 80% of subjects comprised a training set to be validated by all data points that belonged to the remaining 20% of subjects. In this manner, a model would learn from five unique compositions of training data to make encounter-specific predictions on the unseen remainder. Due to the large sample size, we did not use stratification by outcome as we expected suicidal ideation to distribute evenly among the folds. Ultimately, this method yielded data point-specific predictions that were paired to each observed outcome in the data set. Importantly, under this framework, model performance could then be assessed based on the accuracy of these predictions across five unique instances of data that the model had never utilized during the training process. Critically, none of the model parameters or processing pipeline were tuned based on the results of the validation process. The combination of these important pipeline building steps ensured that there was no data leakage (i.e. a subject's observations being in both the training and validation set) as well as no overfitting (tuning the model parameters specifically to the data being tested).

After properly encoding the data and building out the framework for which to train and evaluate the models, the final step was to actually implement the machine learning algorithm. During the training process, the independent predictors consisted of subjects' demographics as well as the questions asked at that current encounter (time T). The outcome predicted was the outcome at the next encounter (time T+1). Essentially, the idea was to be able to determine whether or not a given individual would have some form of suicidal ideation at their next visit to the clinic based on the answers to the questionnaire during their current visit.

Once the final predictions on the held-out test set were made, these predictions were compared to the true values to capture model performance. In predicting the dimensional outcome (predicting suicidal ideation severity), a correlation was calculated between the true severity of SI and the predicted severity of SI. This value (r) was a representation of how well our predicted outcomes increased as the true severity increased across all observations. For the binary prediction (any SI vs. no SI), the model was evaluated through the quantification of the area under the receiver operating curve (AUROC). This value was calculated using the predicted probability at all observations that a person has SI. Essentially, to create the receiver operating curve (ROC), the sensitivity and specificity are determined using iteratively increasing cutoff probabilities for defining SI. In this way the AUROC captures an overall performance metric that balances true/false positives and negatives.

2.4 Model Interpretation and Prediction Behavior

A typical downfall of machine learning modeling, especially in relation to more traditional statistical approaches, is reflected in the popular metaphor of a "black box." Given empirical data as input, the model returns a prediction without indicating to the user the relative

contribution and effect the independent variables had in informing the model's prediction. Without a clear indication of the learning process, it is possible that the model is picking up on noise or data-specific bias rather than a "true" signal. This could lead to a model that lacks generalizability and would lose all predictive power when applied to data that lacks the bias or noise in the training data.

In recent years, a few novel methods have emerged to address this issue of interpretability. Among them is Shapley Additive Explanations (SHAP).[21] The SHAP approach constructs Shapley values from game theory (Shapley, 1953) to determine the marginal effect of one or more independent variables on model prediction output. The approach accomplishes this by iterating over input variables and perturbating their values to assess how specific changes in feature values effect the model's prediction. An added benefit of the SHAP methodology (and its associated visualizations) is that predictor influence can be appreciated in a holistic as well as a subject-specific manner. This affords a more complete analysis of outcome plausibility. Moreover, the explanatory nature of this methodology can be leveraged to discern novel patterns within and across variables to inform focus in future research efforts.

Results

3.1 Predicting Dimensional Outcomes (Predicting Severity of Suicidal Ideation)

The model predictions reflect, for a given subject at a given patient-clinician encounter, the severity of passive SI and active SI at the next encounter. The final model indicated an ability to predict true passive SI severity in the held-out, external validation group with a moderate correlation of $r = 0.43$ (Figure 1). For active SI as well, the association between the observed and predicted values was moderately correlated ($r = 0.39$) with predictions following an increasing trend in severity with higher observed values (Figure 2). All within fold accuracies are reported in supplementary table 3.

3.2 Model Feature Importance for Dimensional Outcomes

For the prediction of both passive and active SI, the most important features were associated with depression and quality of life. The top predictive feature was a rated response to a question concerning current level of depression, and in both models, increased depression severity indicated higher severity of suicidal ideation (Figure 3). Following the top predictive feature, the next three most important variables were also common across both models and interrogated aspects relating to quality of life, feeling that nothing they do is right, and ability to find pleasure. Interestingly, feeling guilty was more predictive of passive SI in relation to active SI. The relationship between age and the predicted outcome was also more evident in the prediction of passive SI with older age influencing model prediction towards increased ideation (Figure 3). Features relating to seizure recency and frequency were further down the rank ordered list of predictors (7^{th}-12^{th} most important). Despite being less informative overall than depressive symptoms, these items maintained predictive value providing additional signal to guide prediction. Seizure frequency was more important in the model's determination of active SI whereas seizure recency was more predictive of passive SI (figure 3).

3.3 Predicting Binary Outcomes (Predicting Presence of Suicidal Ideation)

Prediction of binary outcomes involved the utilization of an individual's questionnaire response data from a given encounter to predict whether or not there was the presence of active or passive SI at the next encounter regardless of severity. Through each of the prediction folds, the percentage of encounters in the held out set where passive suicidal ideation was indicated ranged from 13%–16% and for active ideation ranged from 11%–15%. The performance metric used to evaluate these models was area under the receiver operating curve (AUROC). For the binary classification task, the model was capable of predicting passive SI with an AUC=0.82 (Figure 4). For active SI, performance was comparable with an AUC=0.80 (Figure 5). All within fold accuracies are reported in supplementary figure 2. In consideration of the true positive and true negative trade-offs of the model's performance, the correct identification of 80% of subjects with SI (active or passive) is accompanied by the correct identification of 70% of subjects without SI (active or passive). A confusion matrix of true and false positive and negative predictions can be found in supplementary table 4.

3.4 Important Features in Binary Prediction

The features that were most informative to the dimensional prediction model were also informative to the binary prediction model with some minor variations (Figure 6). This, in addition to the fact that the most important features are known to be typically related to the outcome of interest, is evidence of the models' ability to discern patterns in the data that are reflective of true behavioral phenomenology, rather than irrelevant noise. Of additional note is that the distribution of SHAP scores for the most important features in the binary outcome models fell further into the negative range when compared with those in the dimensional outcome models. It is possible that this indicates when the complexity of differentiating between levels of severity is removed, (i.e. discerning between SI that is often vs always) the model is better at picking up on signal that indicates a lack of SI.

Discussion

The aim of this study was to build and assess a machine learning framework for identifying future suicidal ideation (SI) in PWE based on their responses to a questionnaire provided during a clinical visit. Given that suicide is a leading cause of death in PWE,[5] identifying SI prior to progression is the first step in mitigating completed suicide. This framework is based on an abundance of literature showing a strong association between SI and completed suicide.[12,13,22]

Self-reported depression had the highest predictive value for both passive and active suicidal ideation at the subject's next visit. We also found that as depression increases, so does the degree of SI. Additionally, traditional screening questions for assessing depression such as difficulty finding pleasure as well as the feeling that "nothing I do is right" were strongly predictive of worsening SI. Self-reporting of overall quality of life (QOL) rating was also found to be predictive of SI risk. Feeling that one would be better off dead was used as a marker for passive SI and thus was not included in the analysis. Subsequently, the overall NDDIE score was omitted as it relies heavily on the answer to this question. However, even

with the omission of the SI measures, where the model had no knowledge of whether or not the patient had previously reported SI, it was still able to accurately predict the degree of SI at the following visit. Taken together these findings suggest that psychological and mental health - specifically depressive symptoms and quality of life, are highly predictive of future SI in PWE.

This finding is in agreement with previous findings that suggest the greatest risk of suicide in epilepsy when comorbid psychiatric disease is present.[9] Depression is the most common psychiatric comorbidity in PWE.[11] Still, depression in the epilepsy clinic is frequently undetected, and it has been shown that even when routine screening is implemented, patients are not receiving adequate treatment.[23,24] Traditional treatment paradigms focus on seizure control alone; however, these data implore us to view depression not only as a comorbidity, but as a potential extension of the disease process itself.

While we found the strongest association between SI and psychological factors, markers of disease severity were also shown to be predictive of increasing SI risk. Both seizure frequency (number of seizures) and seizure recency (time from last seizure) were found to be independently predictive of SI at the following visit. This implies that worsening of disease state is also a risk factor for increased SI but, as independent risk factors, this also indicates that worsening disease may not look the same in all patients. Those with rare events may be in a state of acute risk transiently following seizure activity while those with frequent seizures may have a more sustained risk factor profile.

Practically speaking, the methodology for this study reflected the goal of testing the clinical validity of a machine learning-based predictive modeling approach. The validation framework provides insight into about the specificity and sensitivity for predicting the development of SI prior to a future visit to the epilepsy clinic. Importantly, this prediction excludes any information about SI at the current visit that would warrant more immediate action. Additionally, the model introspection via SHAP informs us that the model's decision-making process was based on independent variables that would be clinically expected to associate with SI. The repeated successes of the modeling approach in both the dimensional and binary predictive frameworks act as additional evidence that the model is stable and uncovering actual individual differences in characteristics leading to SI.

The availability of this information would allow clinicians to preemptively plan an intervention prior to a patient's next appointment. This could involve coordinating care with social workers, psychologists, or community health workers to ensure they are available during planned times. Potential resources, referrals and additional appointment scheduling could also be prepared in advance, allowing more time for direct patient care during an appointment. As practitioners, the foresight gained from this modeling approach allows us to work with health plans and hospital administrators to justify and arrange for additional visit time for patients flagged as being at risk for increasing SI. For patients who are flagged as high risk, it would allow for the arrangement of more frequent visits, follow-ups, nurse well checks, and even urgent clinical appointments if appropriate.

Limitations and Future Directions:

There are several limitations we hope to address in our future work. While patients with refractory epilepsy constitute only one-third of the epilepsy population, they make up the majority of patients at our center, potentially limiting the generalizability of our data to those with refractory disease. Related to data collection, we relied heavily on patient reports, which carry the inherent limitation of self-report bias. Furthermore, the data set did not include MRI, EEG or seizure semiology data due to sparsity in data collection and the fact that inclusion would increase model complexity and decrease interpretability. In addition, our center is located in an area where racial and ethnic minorities are underrepresented, further limiting the generalizability of our findings. In the future we hope to partner with other centers in order to better represent the epilepsy population as a whole. Despite these limitations, the goal of the work was to build a model that could accurately identify suicidal ideation in a clinical population. Given the positive results, our next steps include implementing this modeling approach as a steppingstone towards identifying potential completed suicides. Ultimately, we hope to be able to create a disease-specific screening tool to be embedded within which will allow us to alert the clinician ahead of time which patients are at high risk of impending suicide and require acute intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Persons with epilepsy are at a higher likelihood for suicide and suicidal ideation is a known risk factor.
- Machine Learning can be leveraged to accurately predict development of suicidal ideation at future healthcare visits.
- This would allow providers to, *in advance,* prepare the necessary items for further assessment and treatment.

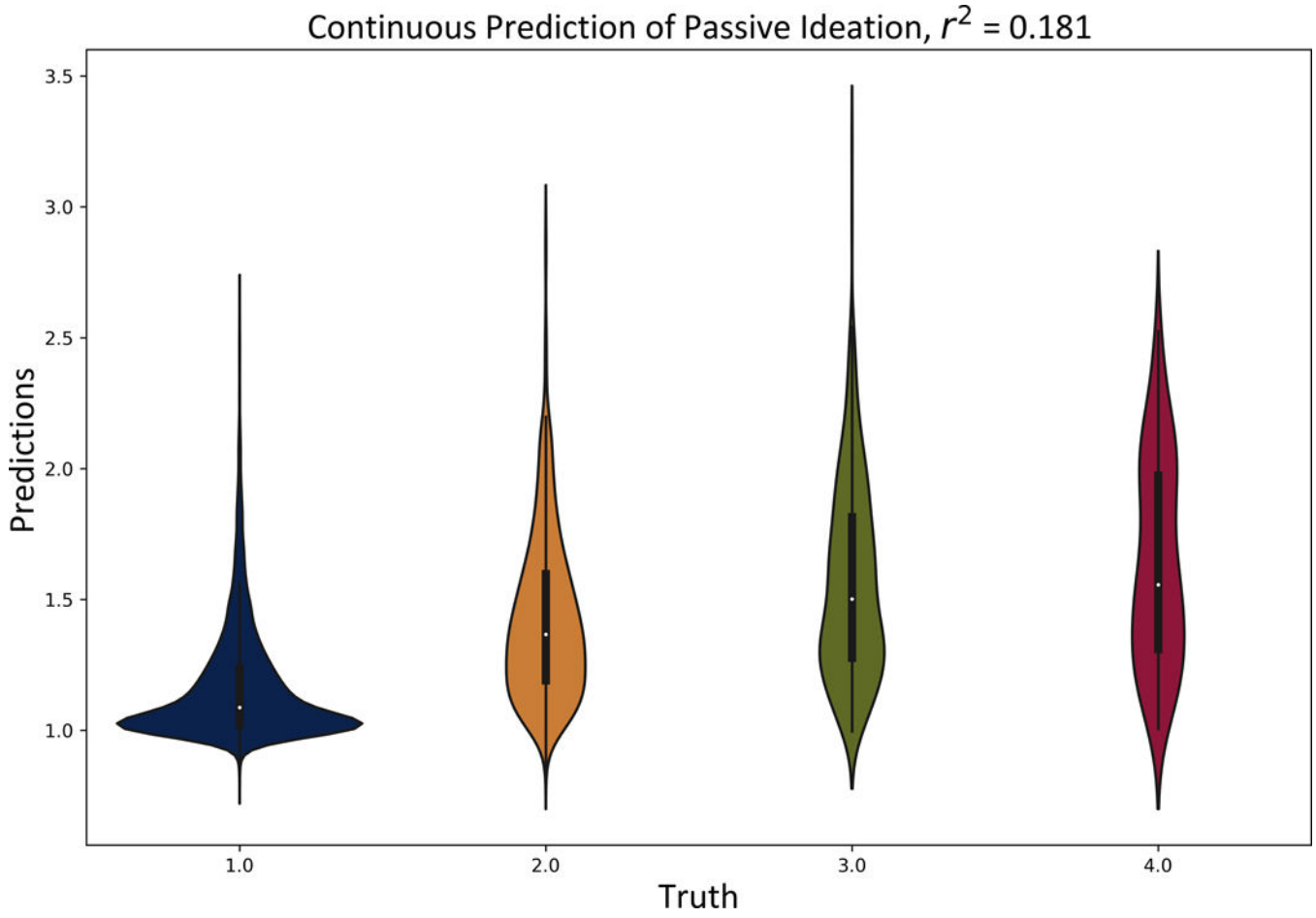

Figure 1.

This is a violin plot showing the distribution of predicted values for passive suicidal ideation (y-axis) for each true observed severity (x-axis). The median predicted value increased as true severity increased and the distribution of predictions trended higher as true severity increased.

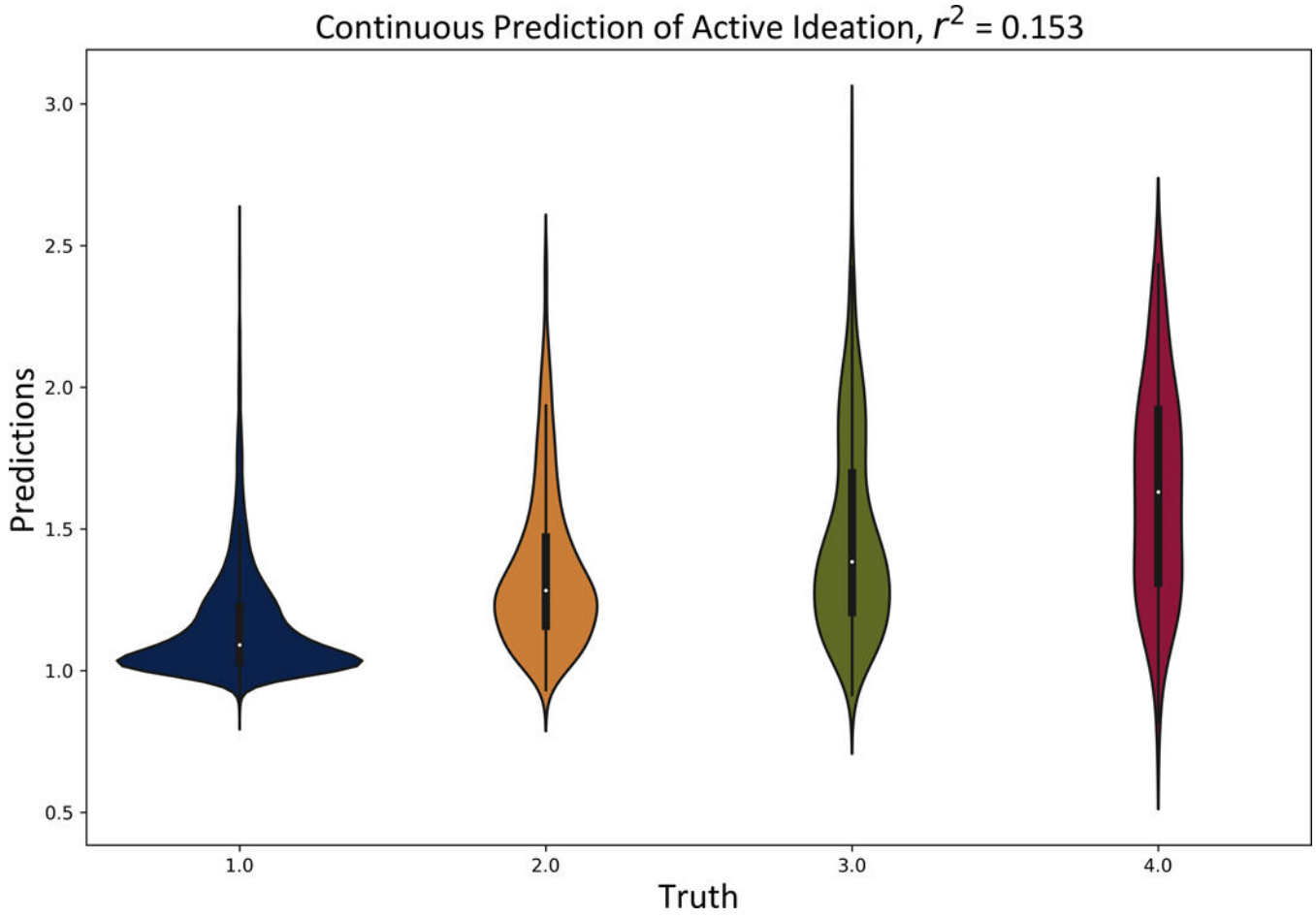

Figure 2.

This is a violin plot showing the distribution of predicted values for active suicidal ideation (y-axis) for each true observed severity (x-axis). The median predicted value increased as true severity increased and the distribution of predictions trended higher as true severity increased.

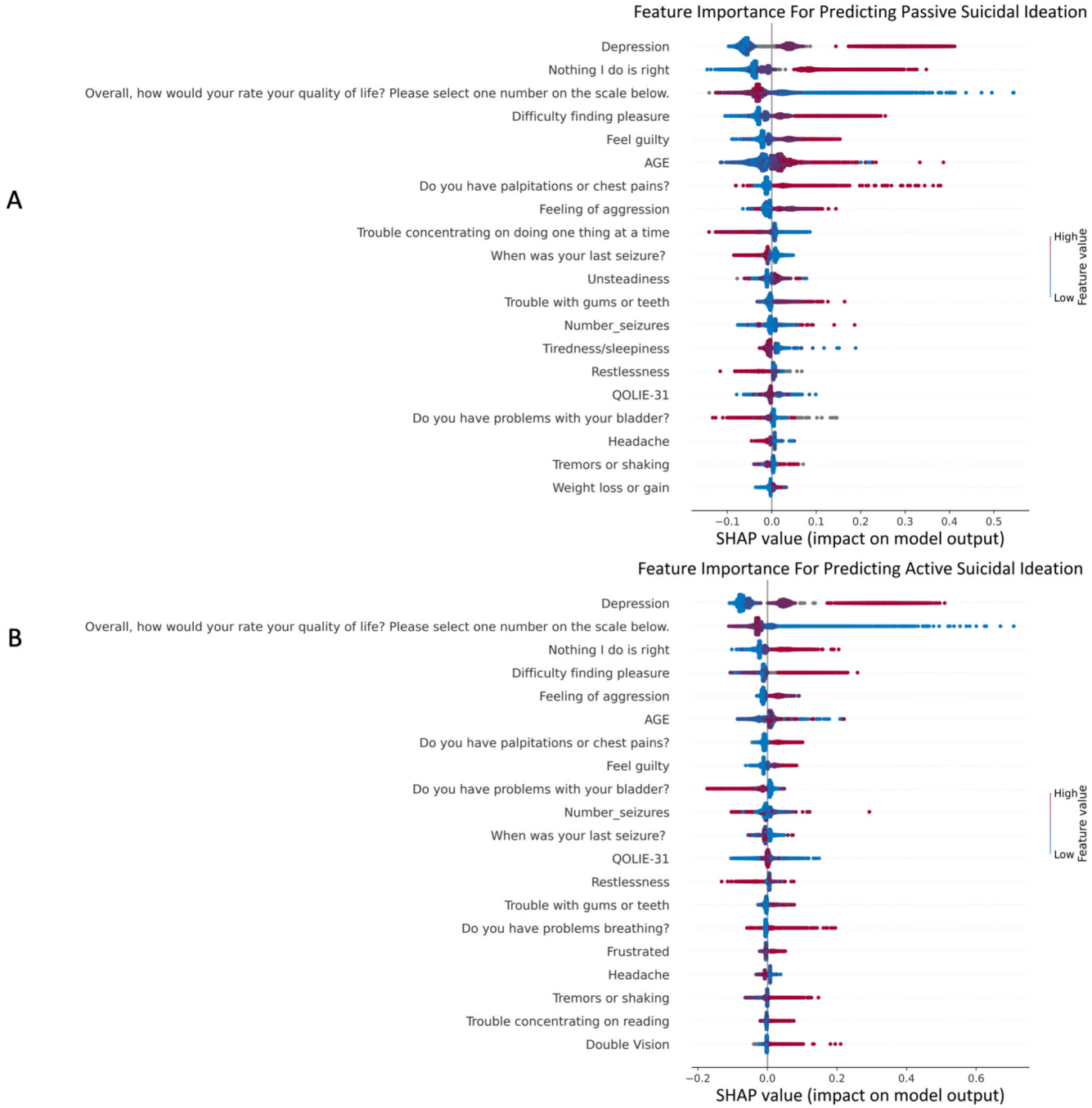

Figure 3.

This is a figure showing the relative importance of each independent variable and how that variable informed prediction for each given subject. The y axis shows the top 20 variables in order (from top to bottom) of most important to least important. The X axis indicates how that variable informed prediction (higher on the X axis meant more severe prediction). The color indicates the value for that independent variable for that subject (each dot corresponds to one subject). This can be interpreted as follows: “The most important

variable in prediction was depression. Typically, higher levels of depression led the model to predict more severe passive (or active in panel B) suicidal ideation.

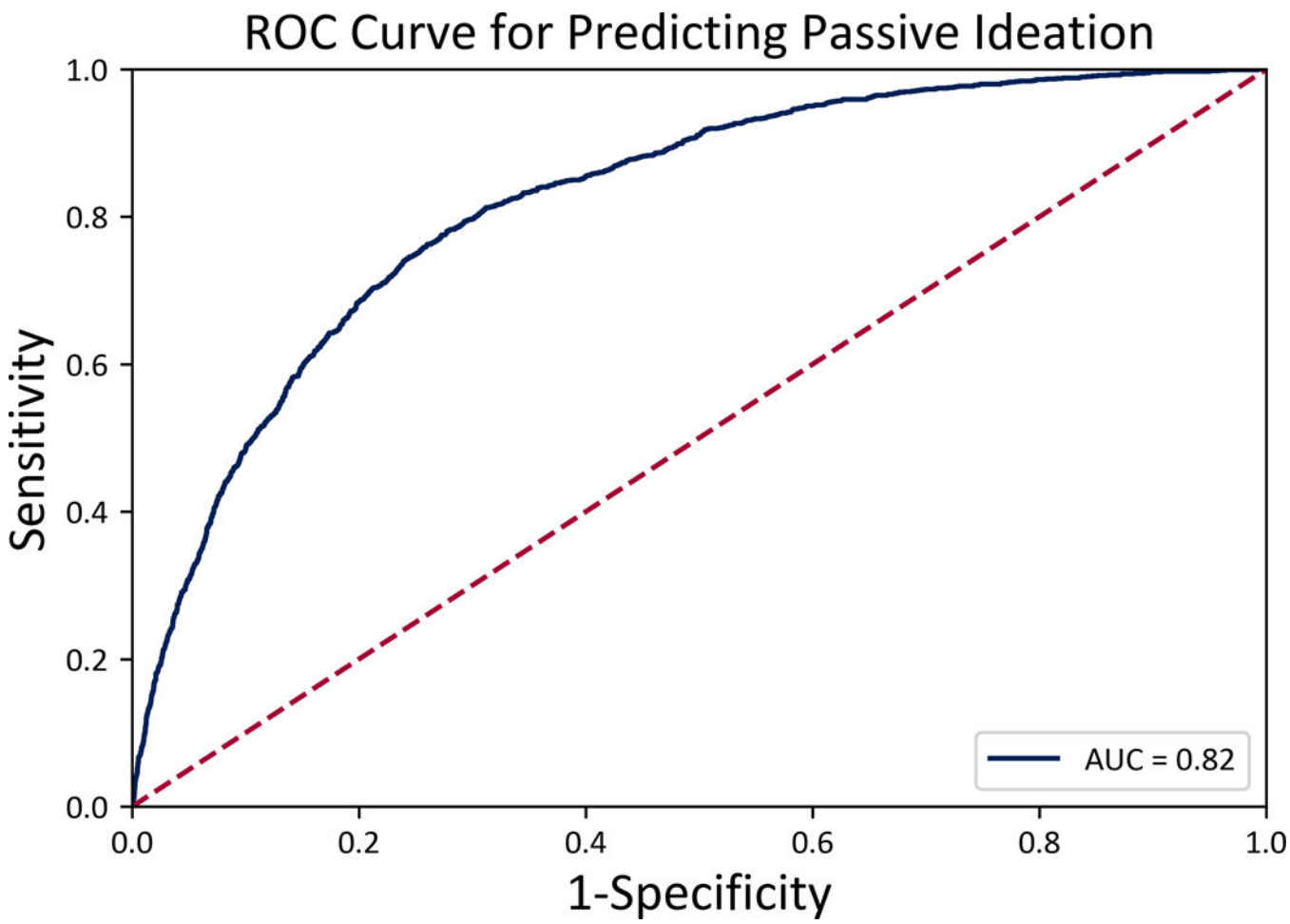

Figure 4.

This figure is the ROC curve for predicting passive suicidal ideation. The x-axis is 1-specificity and the y-axis is sensitivity. As you move along the curve from bottom left to top right, the threshold probability for determining predicted passive ideation decreases. In this way, as you move along the curve the number of false negatives that are acceptable increases.

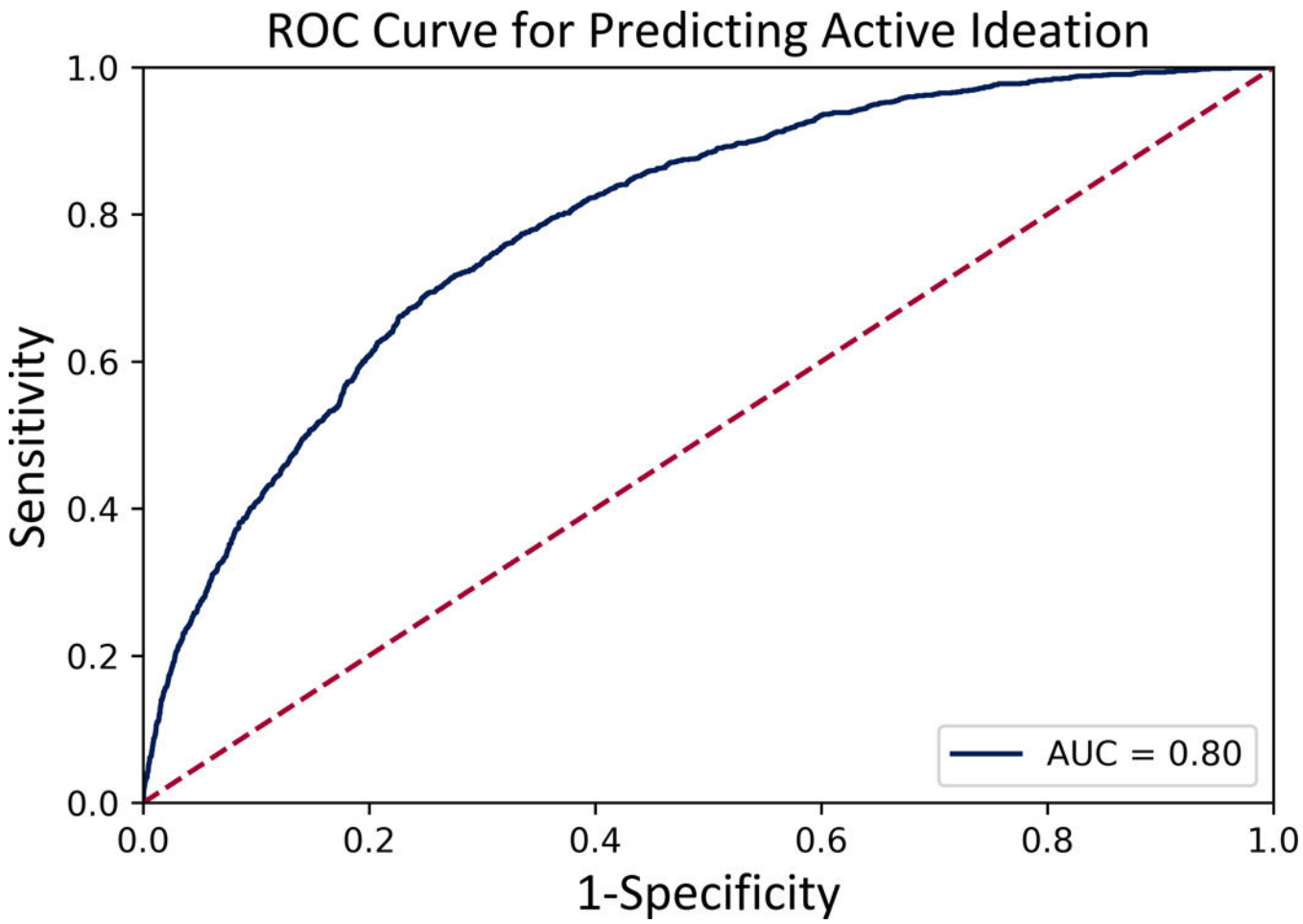

Figure 5.

This figure is the ROC curve for predicting active suicidal ideation. The x-axis is 1-specificity and the y-axis is sensitivity. As you move along the curve from bottom left to top right, the threshold probability for determining predicted active ideation decreases. In this way, as you move along the curve the number of false negatives that are acceptable increases.

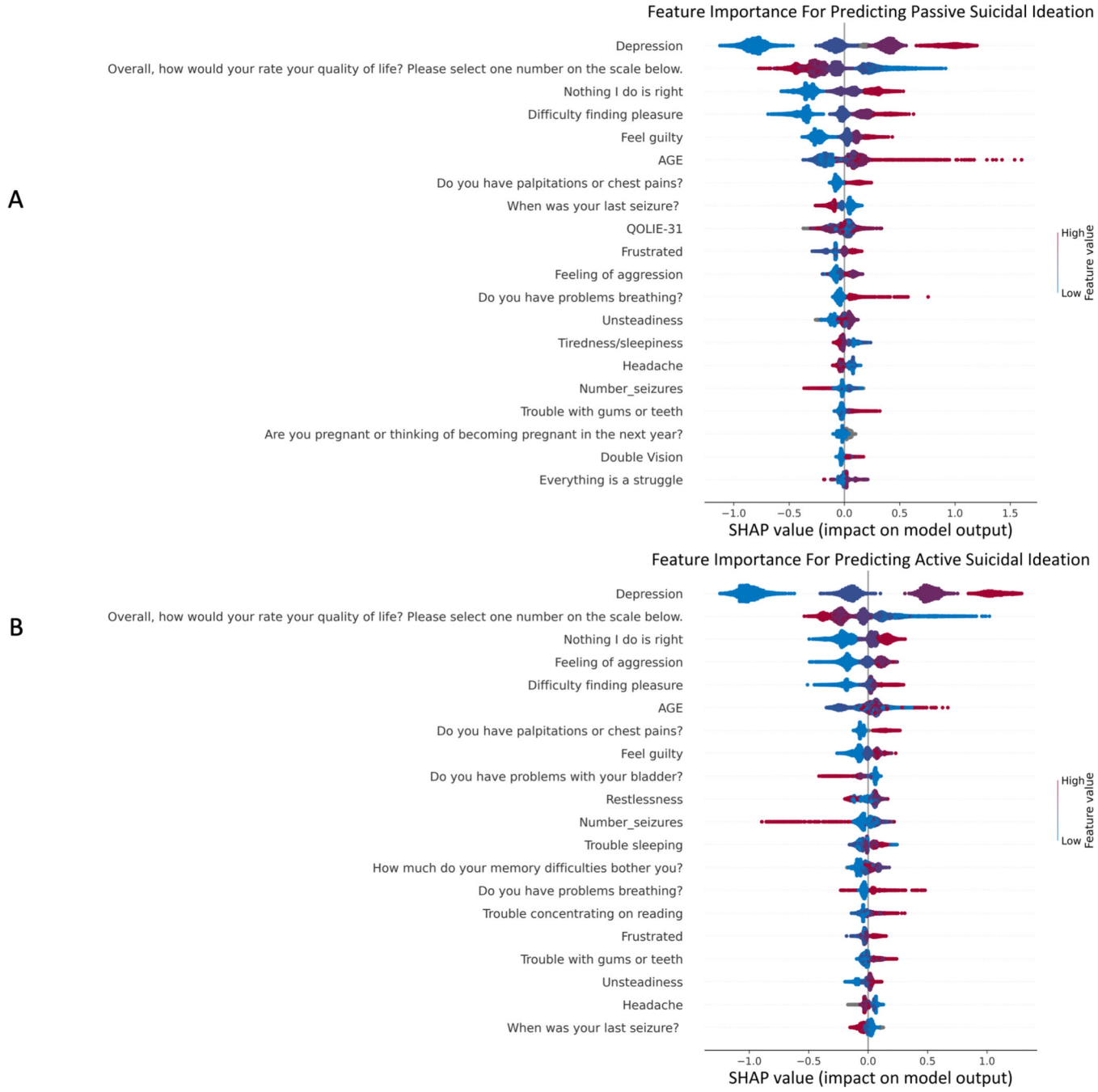

Figure 6.

This is a figure showing the relative importance of each independent variable for binary prediction and how that variable informed prediction for each given subject. The y axis shows the top 20 variables in order (from top to bottom) of most important to least important. The X axis indicates how that variable informed prediction (higher on the X axis meant more severe prediction). The color indicates the value for that independent variable for that subject (each dot corresponds to one subject). This can be interpreted as follows: “The most important variable in prediction was depression. Typically, higher levels

of depression led the model to indicate that passive suicidal ideation was more likely at the next encounter.”