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Explorando Preditores de Suicidalidade em Pacientes com Transtorno Obsessivo- Compulsivo: uma Abordagem com Machine Learning.

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Dissertação de Mestrado submetida ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito para a obtenção do grau de Mestre

Orientador: Dr. Ygor Arzeno Ferrão

Porto Alegre
2019

Dedico esse trabalho a meu filho, meu esposo, meus pais e minha irmã,

aqueles que tornaram-me quem sou hoje, com seus

grandes ensinamentos ao longo vida.

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Sumário

Lista de Abreviações

AUC – Área sob a curva

BAI - Inventário de Ansiedade de Beck

BDI - Inventário de Depressão de Beck

C-TOC – Consórcio Brasileiro de Transtornos do Espectro Obsessivo-Compulsivo

IC – Intervalo de Confiança

IS – Ideação Suicida

ML – Machine Learning

OR – Odds Ratio

SOC – Sintomas Obsessivos-Compulsivos

TOC – Transtorno Obsessivo Compulsivo

TS – Tentativa de Suicídio

Y-BOCS – Escala Yale Brown de Obsessões e Compulsões

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Resumo

Este estudo buscou identificar preditores de tentativa de suicídio em um grande banco de dados de pacientes com Transtorno Obsessivo-Compulsivo (TOC). O objetivo foi utilizar um algoritmo de machine learning para fazer a análise estatística dos dados e assim, ter maior acurácia na predição. Técnicas de machine learning têm sido cada vez mais utilizadas nas pesquisas psiquiátricas, pois apresentam diversas vantagens, dentre elas a capacidade de predizer desfechos a nível individual.

Novecentos e cinquenta e nove pacientes com TOC, oriundos de sete centros de atendimentos especializados, foram incluídos neste estudo. A taxa de prevalência de tentativa de suicídio encontrada foi de 10,8%. O algoritmo elastic net identificou quatro principais preditores de tentativa de suicídio em pacientes com TOC: história prévia de plano de suicídio, história prévia de pensamentos sobre suicídio, comorbidade com episódio depressivo ao longo da vida e comorbidade com transtorno explosivo intermitente. A acurácia do modelo foi de 85%, com uma curva ROC de 0.95.

Nossos achados sugerem que as tentativas de suicídio no TOC estiveram associadas ao espectro psicopatológico de suicidalidade e à presença de comorbidades psiquiátricas, e não à fenomenologia do transtorno por si só. Especialmente aqueles pacientes com sintomas depressivos comórbidos ao TOC e com história de pensamento suicida devem receber tratamento intensivo para redução de desfechos trágicos como o suicídio. Além disso, este trabalho mostrou que a utilização de técnicas de machine learning traz maior acurácia na análise de bancos de dados extensos e de patologias polimórficas como o TOC, gerando um modelo de predição de forte acurácia. Os resultados devem ser testados em outras populações, podendo se transformar em uma ferramenta de predição robusta do risco de tentativas de suicídio nos pacientes com TOC e também com outras psicopatologias.

Abstract

This study aimed to identify predictors of suicide attempts in an extensive database of patients with Obsessive Compulsive-Disorder (OCD). The objective was to use a machine-learning algorithm to do the statistical analysis of the data and thus, to have greater accuracy in the prediction. Machine learning techniques have been increasingly used in psychiatric research, since they have several advantages, among them the ability to predict outcomes at the individual level.

Nine hundred and fifty-nine OCD patients from seven specialized care centers were included in this study. The prevalence rate of attempted suicide was 10.8%. The elastic net algorithm identified four main predictors of suicide attempt in patients with OCD: previous history of a suicide plan, previous history of suicidal thoughts, comorbidity with a life-long depressive episode, and comorbidity with intermittent explosive disorder. The accuracy of the model was 85%, with a ROC curve of 0.95.

Our findings suggest that OCD suicide attempts were associated with the psychopathological spectrum of suicidality and the presence of psychiatric comorbidities, not the phenomenology of the disorder per se. Especially those patients with OCD comorbid depressive symptoms and a history of suicidal thinking should receive intensive treatment to reduce tragic outcomes such as suicide. Moreover, this work showed that the use of machine learning techniques brings greater accuracy in the analysis of large databases and polymorphic pathologies such as TOC, generating a robust accuracy prediction model. The results should be tested in other populations and can become a handy tool for predicting the risk of suicide attempts in patients with OCD and other psychopathologies.

1. Introdução

O transtorno obsessivo-compulsivo (TOC) é um dos transtornos neuropsiquiátricos mais prevalentes, afetando cerca de 2,5% das pessoas ao longo da vida (1) (2), sendo caracterizado pela presença de obsessões (pensamentos, impulsos ou imagens intrusivos, indesejados e repetitivos) e/ou compulsões (atos mentais ou comportamentais realizados a fim de evitar as obsessões e reduzir a ansiedade e o desconforto ou para prevenir desfechos temerosos). Esses sintomas devem ser excessivos, causar sofrimento, ocupar um tempo considerável do dia-a-dia e interferir na funcionalidade do paciente (3). De acordo com a Organização Mundial da Saúde, o TOC é considerado uma das dez doenças mais debilitantes e incapacitantes (4). Apresenta curso crônico, e os efeitos negativos dos sintomas na vida dos pacientes geram extremo sofrimento, considerável incapacitação, e prejuízos nos níveis social, econômico, familiar e ocupacional, trazendo piora na qualidade de vida (5) (6) (7) (8).

As taxas de prevalências de comorbidades psiquiátricas no TOC são extremamente altas, chegando a cerca de 91% (9) (10) (11). As principais comorbidades no TOC são transtorno de humor depressivo e transtornos de ansiedade, com taxas variando entre 12 até 80% (1) (12) (13), atingindo cerca de 25 a 75% (14), dos pacientes, respectivamente. Transtornos de controle de impulsos e uso de substâncias também parecem ser comuns em pacientes com TOC, com prevalências de 55.9% e 38.6% respectivamente (1). Essas comorbidades geram considerável impacto na apresentação clínica do TOC, já que os sintomas comórbidos podem mascarar os sintomas do TOC e dificultar o diagnóstico, gerando maior prejuízo, sofrimento e aumentando a gravidade da doença, acarretando também maior risco de suicídio aos pacientes (12). As comorbidades com transtornos de humor parecem ser aquelas que mais causam prejuízo, pois reduzem ainda mais a qualidade de vida dos pacientes, trazendo sentimentos de desesperança importantes, e até comportamento suicida (15). Além do grande impacto das comorbidades, os próprios sintomas obsessivos-compulsivos podem ser extremamente graves e incapacitantes, levando os pacientes a passarem muito tempo do seu dia-a-dia envolvidos na execução de compulsões, evitando situações e paralisados por dúvidas obsessivas (16). Até 60% dos pacientes com TOC não respondem adequadamente às intervenções disponíveis, com baixas taxas de

remissão e uma probabilidade relativamente alta de recaída (17). Alguns fatores associados à baixa resposta ao tratamento e pior prognóstico são: início precoce, família disfuncional, gravidade e conteúdo dos sintomas obsessivo-compulsivos, a presença de comorbidades (especialmente depressão maior) e comportamento suicida (16)(17)(18).

Apesar do alto grau de sofrimento, incapacitação e prejuízo associados ao transtorno, das altas taxas de comorbidades e baixa taxa de resposta ao tratamento, pouca atenção vinha sendo dada ao comportamento suicida em pacientes portadores de TOC. O suicídio no TOC já foi considerado um fenômeno raro, com taxas de morte por suicídio descritas na literatura clássica de cerca de 1 % (19) (20). Da mesma forma, taxas de tentativas de suicídio (TS) no TOC também eram consideradas similares às da população geral, entre 3–4% (21)(22), com alguns estudos chegando a encontrar uma associação negativa entre suicídio e TOC (23). Mas, recentemente, vários estudos têm mostrado que, apesar do suicídio consumado ter baixa prevalência nessa população, o fenômeno conhecido por suicidalidade não é raro em pacientes portadores de TOC (24) (25).

Então, esta dissertação pretende revisar a literatura vigente sobre suicidalidade em pacientes com TOC e, explorar o banco de dados do Consórcio Brasileiro de Pesquisa em TOC (C-TOC) para explorar fatores preditivos de tentativas de suicídio nessa população, utilizando para isso técnicas analíticas de machine learning.

2. Revisão da Literatura

2.1 Suicídio e suicidalidade

O suicídio é definido como um ato deliberado para terminar com a própria vida. Os fenômenos envolvendo comportamentos suicidas podem ser entendidos como um espectro psicopatológico, chamado de suicidalidade, sendo constituído por quatro desfechos contíguos: ideação suicida (IS) (pensamentos sobre morrer, morte e se matar), planejamento de suicídio, tentativa de suicídio (TS) e suicídio consumado (26) (27)(28)(29).

Suicídio é um grande problema de saúde pública, sendo uma das dez principais causas de morte e carga de doença no mundo todo, em todas as faixas etárias (30). A cada 40 segundos uma pessoa comete suicídio e, para cada pessoa que morre, existe um adicional de 10 a 25 em tentativas de suicídio (31), o que consome recursos de saúde pública, encarecendo o sistema de saúde em todo o mundo (32).

A carga global estimada de mortes por suicídio é de mais de 800.000 mortes por ano, o que representa cerca 1,4% de todas as mortes em todo o mundo (33). O suicídio é responsável por cerca de 50% das mortes violentas entre homens e de 78% entre as mulheres (31). Além disso, cerca de 90% das mortes por suicídio estão relacionadas diretamente a transtornos mentais (34) (35).

Tradicionalmente, estudos de suicidalidade tinham seu enfoque predominantemente em transtornos de humor, transtornos psicóticos, transtornos por uso de substâncias e transtornos de personalidade (34) (35). Contudo, um recente estudo, que buscou estimar a prevalência e as comorbidades psiquiátricas associadas à ideação suicida na população adulta, encontrou que transtorno depressivo maior e TOC foram as variáveis psiquiátricas mais preditoras de ideação suicida (IS) em ambos os sexos (36). Da mesma forma, um estudo epidemiológico na Dinamarca, concluiu que pacientes com TOC tinham três vezes mais chance de morrerem por suicídio do que a população geral (37). Diante disso, revisaremos na próxima seção, a ocorrência desse fenômeno na população de portadores de TOC.

2.2 Suicídio e suicidalidade no TOC

Historicamente, pacientes com TOC são considerados hipervigilantes em monitorar impulsos agressivos e extremamente evitativos a danos potenciais (20)(38)(39). Essa idéia reforçava a crença de que esses pacientes “evitavam” o suicídio como estratégia para lidar com seu sofrimento psíquico, o que foi reforçado por uma metanálise que mostrou um risco de suicídio aumentado em todos os transtornos de ansiedade, exceto TOC (Odds Ratio (OR) = 0,99) (23), e por outros estudos que chegaram a apontar associação negativa entre TOC e suicidalidade (40) (41).

Contudo, contrárias a esses achados, evidências recentes têm sugerido que as taxas descritas sobre suicidalidade no TOC eram subestimadas (12) (22)(24)(25)(38)(40)(42)(43)(44). Dentre essas evidências, estudos apontam taxas de TS no TOC que variam desde 3 até 27%, e de IS variando entre 15 a 63%. As atuais estimativas de suicidalidade no TOC mostram-se semelhantes às de outros transtornos mentais comumente associados a esses desfechos (38), como esquizofrenia e transtorno de humor (45), transtorno de déficit de atenção e hiperatividade (46), transtorno de estresse pós-traumático (47) e transtornos por uso de álcool (48).

Numa tentativa de integrar os dados divergentes e não sistemáticos, Angelakis et al. (2015) realizaram uma ampla revisão sistemática englobando 48 estudos, evidenciando taxas de IS entre 10 a 63,5% (média de 27,9%) e de TS entre 1.0 a 46.3% (média de 10.3%). Os autores salientaram que existiam questões metodológicas importantes, sendo a grande maioria dos estudos transversais, com diversos vieses e sem metodologia adequada nas investigações (43). Além disso, essa revisão incluiu estudos com pacientes com outros transtornos psiquiátricos (ex.: esquizofrenia e transtorno de humor bipolar), mas que apresentavam sintomas obsessivos compulsivos (SOC), o que pode ter causado um viés de interpretação das taxas de suicidalidade. Além disso, os autores não diferenciaram entre taxas de risco entre populações clínicas e entre a população geral (estudos epidemiológicos).

Fernández de la Cruz et al. (2017), em um estudo epidemiológico, analisou um grande banco de dados com mais de 36 mil pacientes diagnosticados com TOC

ao longo de 4 décadas (49). Os autores encontraram que esses pacientes tinham um risco aumentado de morrer por suicídio ((OR = 9,83), Intervalo de Confiança (IC) 95% = 8,72–11,08)), e também de TS (OR = 5,45 (IC 95% = 5,24–5,67)), quando comparados com a população geral. Após o ajuste para comorbidades psiquiátricas comumente associadas com suicídio, o risco foi reduzido mas permaneceu significativo para os dois desfechos. Os autores encontraram que, dentre aqueles que morreram por suicídio, 43% dos indivíduos tinham TOC sem comorbidades, reforçando a idéia de que o TOC por si só confere um risco aumentado de morte por suicídio. Já com relação a TS, houve maior associação com TOC comórbido, especialmente com transtornos por uso de substâncias e transtornos de humor.

Ainda nesse estudo, o principal preditor de morte por suicídio foi a existência de uma TS prévia. Também estiveram associadas a maior risco de suicídio a existência de um transtorno de personalidade ou transtorno por uso de substâncias comórbidos. Foram considerados fatores protetivos contra o suicídio: ter um transtorno de ansiedade comórbido, ser mulher e ter pais com maior nível educacional. Com relação a TS, os principais fatores de risco foram: ser mulher, comorbidade com transtornos por uso de substâncias, transtornos afetivos, transtornos de personalidade, transtornos de ansiedade e transtornos psicóticos (49).

Albert U., et al. (2018) fizeram uma nova revisão sistemática, incluindo estudos estudos mais recentes e com definição clara de diagnóstico de TOC, e também diferenciando amostras clínicas de estudos epidemiológicos (28). Os autores encontraram taxas de TS ao longo da vida de 14,2% e de IS entre 26,3 – 73,5% em amostras clínicas. Já em estudos epidemiológicos, o TOC pareceu aumentar a chance de ter IS ao longo da vida (OR 1.9 -10.3) e também de TS ao longo da vida (OR 1.6 – 9.9) quando comparado à população geral. Dentre os preditores de maior risco de suicidalidade, os autores encontraram: severidade do TOC, dimensão de pensamentos tabú (conteúdos que envolvem aspectos agressivos/catastróficos, sexuais ou morais), comorbidade com transtornos de eixo I, severidade de sintomas depressivos e de ansiedade, história prévia de suicidalidade e fatores cognitivos-emocionais como alexitimia e desesperança.

Os resultados desses estudos permitem questionamentos sobre a

suicidalidade no TOC ser decorrente de fatores intrínsecos à fenomenologia psicopatológica do TOC (relacionados a efeitos diretos de aspectos psicopatológicos nucleares do transtorno) ou ser resultado de fatores extrínsecos a esse núcleo psicopatológico, como a ocorrência comorbidades psiquiátricas ou de fatores sociodemográficos. Na revisão sistemática de Albert U., et al. (2018), os autores discutiram a hipótese de que a alta variabilidade nas taxas de comportamento suicida nos diferentes estudos pode não estar somente relacionada a variações populacionais/amostrais, metodológicas ou de gravidade do TOC (28). Desta forma, podemos conjecturar que a ampla heterogeneidade e o polimorfismo fenotípico do TOC, bem como as altas taxas de comorbidades psiquiátricas presentes, podem estar envolvidas na variabilidade das taxas relatadas de suicidalidade.

2.3 Preditores de suicidalidade em pacientes com TOC

Frente ao fato de que indivíduos com TOC parecem estar em maior risco de suicidalidade, muitos autores vêm buscando compreender quais seriam os fatores envolvidos nesses desfechos. Alguns estudos apontam que a severidade dos sintomas obsessivos compulsivos (9), a presença de determinados dimensões de sintomas obsessivos compulsivos (9) (44) e a presença de sintomas depressivos (25) (50) seriam as principais variáveis associadas à suicidalidade no TOC.

A comorbidade do TOC com outros transtornos mentais também parece mediar a relação do transtorno com a suicidalidade, já que traz atrasos no diagnóstico do TOC, agravando os sintomas obsessivos-compulsivos (SOC) e aumentando o sofrimento e prejuízo funcional (51). Hollander et al. (1996) encontraram que pacientes com TOC, mesmo sem comorbidades, tinham uma maior taxa de TS (OR=3.2), quando comparados com indivíduos sem transtornos mentais. Já pacientes com TOC com alguma comorbidade psiquiátrica apresentavam chance maior de tentarem suicídio (OR=2.2), quando comparados com pacientes com outros diagnósticos psiquiátricos (52). Outros estudos corroboram a noção de que pacientes com TOC comórbido a outros transtornos apresentam maior risco para desfechos envolvendo suicidalidade (43)(53)(54).

A alta prevalência de TOC com sintomas depressivos e ansiosos, aumentando sentimentos de desesperança, seria uma das razões encontradas para

fundamentar as altas taxas de suicidalidade em pacientes TOC (15)(24)(40)(43)(55)(56), incluindo maiores taxas de TS desses pacientes quando comparados a pacientes com TOC sem comorbidades (10)(52)(55).

O conteúdo dos pensamentos obsessivos e/ou das compulsões também parece estar relacionado à suicidalidade no TOC, mesmo que de forma controversa. Especialmente as dimensões de pensamentos envolvendo sexualidade/religiosidade/moralidade e de agressividade/catástrofes parecem ter uma relação no comportamento suicida entre pacientes com TOC (9)(25) (54). Obsessões envolvendo conteúdo sexual/religioso e agressivo são consideradas como "pensamentos tabú", muitas vezes sendo consideradas socialmente inaceitáveis. Portanto, pacientes com esse tipo de conteúdo obsessivo apresentam maior grau de culpa e responsabilidade pelo conteúdo de suas obsessões, o que pode levar a pensamentos de morte e ideação suicida(24)(43)(44)(55). A dimensão de simetria/ordenamento também foi associada como preditora de suicidalidade em portadores de TOC (53).

Porém, como apontado por Ching et al. (2017), poucos estudos incluíram as diferentes dimensões de sintomas consideradas de forma individual na avaliação de suicidalidade no TOC (54). Sendo o TOC um transtorno altamente polimórfico, com apresentação psicopatológica heterogênea, pode-se supor que o comportamento suicida e toda a gama de fenômenos de suicidalidade se expressam de formas diferentes dentro de cada uma das dimensões do TOC.

As tabelas 1 e 2 resumem os diversos fatores apontados como possíveis preditores de maior suicidalidade e suicídio em pacientes com TOC.

Tabela 1 – Principais fatores intrínsecos associados à suicidalidade em pacientes com Transtorno Obsessivo-Compulsivo.

Fatores extrínsecos relacionados a suicidalidade	**Estudos**
Gravidade de sintomas do Transtorno Obsessivo-Compulsivo	(9)(12)(14)(15)(24)(25)(28)(43)(44)(55)
Presença das dimensões de contaminação, simetria/ordenamento, agressividade, sexualidade/religiosidade, hoarding	(9)(25)(40)(44)(55)(60)
Insight pobre	(44)

Tabela 2 – Principais fatores extrínsecos associados à suicidalidade em pacientes com Transtorno Obsessivo-Compulsivo.

Fatores extrínsecos relacionados a suicidalidade no TOC	**Estudos**
Transtorno de personalidade	(49)(52)(57)
Comorbidades de eixo I	(9) (28) (43) (49) (51)
Transtorno por uso de substâncias	(25)(28)(49)(53)
Comorbidade com transtorno de humor bipolar	(13)(28)
Comorbidade com episódio depressivo maior	(13)(24)(25)(28)(40)(50)(51)(55)(58)(59)

Gravidade de sintomas depressivos	(9)(15)(24)(25)(28)(40)(43)(55)(60)
Comorbidade com outros transtornos de ansiedade e/ou transtorno de estresse pós-traumático	(25)(28)(49)(58)
Gravidade de sintomas ansiosos	(9)(15)(25)(28)(43(44)(5)
Comorbidade com transtorno dismórfico corporal	(61)
Comorbidade com transtornos alimentares	(62)
Outras comorbidades médicas	(53)
Ideação suicida prévia	(9)(14)(24)(43)
Tentativa de suicídio prévia	(9)(24)(28)(40)(43)(49)
História familiar de suicídio	(9)
História de hospitalização psiquiátrica	(53)
Piores índices na Escala de Qualidade de Vida (QoL)	(9)(24)
Sentimentos de desesperança	(15)(24)(40)(43)(55)(56)
Não ter filhos	(25)
Menor nível de escolaridade/ Baixo nível socioeconômico	(25)
Gênero Mulher: tentativa de suicídio / Homem: suicídio consumado	(49)

Não ser casado	(25)(38)(40)
Desemprego	(38)
Trauma na infância	(58)
Ansiedade evitativa e transtorno de personalidade esquizotípico	(25)

Contudo, até o momento, não existem variáveis consistentemente associadas à predição de TS em pacientes com TOC, especialmente a nível individual. Todos os estudos utilizaram análise estatística tradicional, apontando possíveis mecanismos e fatores de risco envolvidos no fenômeno da suicidalidade no TOC. Contudo, tais estudos não tornaram possível a integração de todas essas variáveis em uma ferramenta clínica que possa ser utilizada individualmente para prever suicídio em um paciente com TOC.

A heterogeneidade psicopatológica do TOC pode reduzir potencialmente o poder e obscurecer as descobertas destes estudos clínicos, pois sabe-se que existem várias limitações no uso de métodos tradicionais de teste de hipóteses para analisar dados multidimensionais e heterogêneos. A maioria das abordagens estatísticas tradicionais concentra-se em explicar uma proporção estatisticamente significativa de variação em um determinado conjunto de dados. Os métodos estatísticos tradicionais fornecem principalmente resultados a nível de grupo em uma determinada população. Essa abordagem não permite detectar diferenças a nível individual e, portanto, resultados estatisticamente significativos podem não representar uma diferença ou um benefício clínico real, especialmente em patologias polimórficas como o TOC, com diversas dimensões de sintomas e com altas taxas de comorbidades. Desta forma, técnicas de análise de dados que compreendam diferenças a nível individual são imprescindíveis (63) (64) (65). Por isso, passaremos a revisar na seção seguinte, alternativas de análises de dados que possam suprir esses aspectos.

2.4 O uso de algoritmos de machine learning

A era digital tem gerado um aumento exponencial no acúmulo e disponibilidade de dados. O termo “Big Data” é um termo amplo, que descreve dados adquiridos e criados em grande velocidade, variedade, quantidade e complexidade. Os bancos de dados, de modo geral, estão se tornando multimodais, incluindo dados clínicos, sociodemográficos, ambientais cognitivos, genéticos, epigenéticos, de neuroimagens, dentre outras infinitas possibilidades (66) (67). A análise de “Big data”, incluindo grandes bancos de dados, com muitos pacientes e muitas variáveis, oferecem desafios estatísticos para análise e interpretação dessa grande quantidade de informações (68).

Um campo oriundo da inteligência artificial, o machine learning (ML) utiliza algoritmos computacionais capazes de analisar “Big Data” de forma não linear e interativa, extraindo padrões e transformando dados em informações relevantes, de forma que excede a capacidade do cérebro humano de compreender (69). Apesar do uso de ML ter mantido-se restrito às ciências da computação e inteligência artificial desde a década de 50, recentemente essa tecnologia têm sido aplicada no nosso dia-a-dia. A ferramenta de busca do Google, por exemplo, sugere publicações mais relevantes para cada usuário; o serviço de streaming no Netflix sugere atrações com base em filmes já assistidos e avaliados; o algoritmo utilizado pelo Waze aprende com os usuários os melhores caminhos de um mapa; o Facebook utiliza esse recurso para reconhecer padrões faciais e marcar pessoas em fotos; após realizar uma compra online passamos a receber sugestões de outros produtos semelhantes, entre outros inúmeros exemplos da aplicação prática e corrente do que chamamos machine learning.

Os computadores utilizam os algoritmos de ML para aprender através de observações e determinar como realizar o mapeamento dos dados e características registrados, gerando um modelo que consiga abranger amplamente as informações, para que essa mesma tarefa possa ser realizada de forma correta com novas informações ainda não registradas. De forma resumida, os algoritmos são implementados nas seguintes etapas (70), conforme a Figura 1:

1. Colheita de dados: os dados são colhidos, podendo ser combinados em uma planilha de dados, ou em um banco, como uma única fonte;

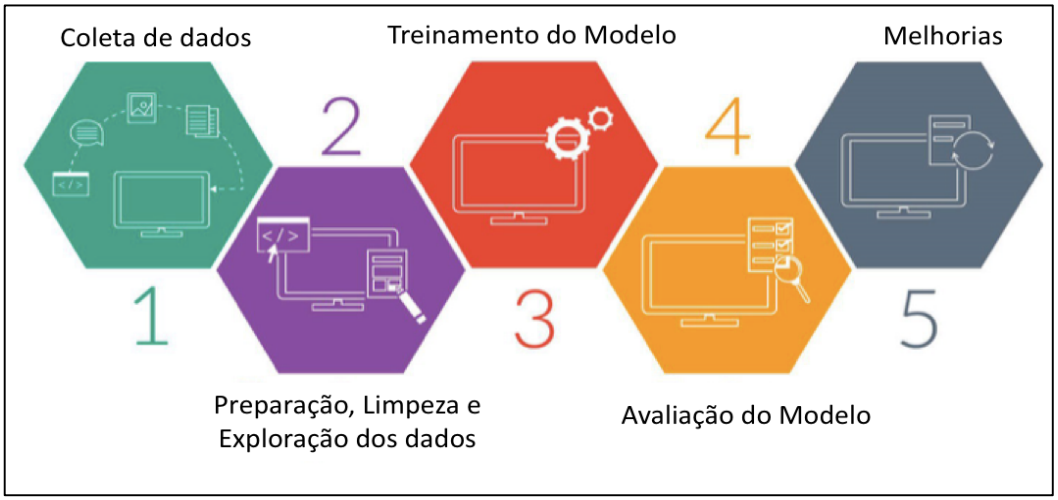
2. Exploração e preparação dos dados: Seguinte a etapa de colheita, os dados deverão ser preparados e explorados. Este processo envolve a limpeza e adequação dos dados que serão utilizados, com eliminação de informações desnecessárias e retificação de dados confusos;

3. Treinamento do modelo: Para uma tarefa específica de ML deverá haver a escolha adequada de um algoritmo e este representará os dados na forma de um modelo. Geralmente inicia-se por modelos mais simples, aumentando a complexidade se necessário. Na fase de treinamento, ocorre o ajuste do modelo ao banco de dados. Inicialmente os dados são separados em um grupo de dados de "treinamento" e outro grupo de “teste”, para que o algoritmo possa criar um modelo a partir do primeiro grupo, identificando diferenças individuais dentre os grupos;

4. Avaliação do modelo: Logo após a etapa de treinamento, o modelo é aplicado a um novo grupo de dados para avaliar o quanto o algoritmo aprendeu com a experiência e sua acurácia é então medida;

5. Melhorias do modelo: podem utilizar-se outras estratégias se houver necessidade de ampliar o desempenho do modelo.

Figura 1 – Fluxograma de implantação de modelos de Machine Learning



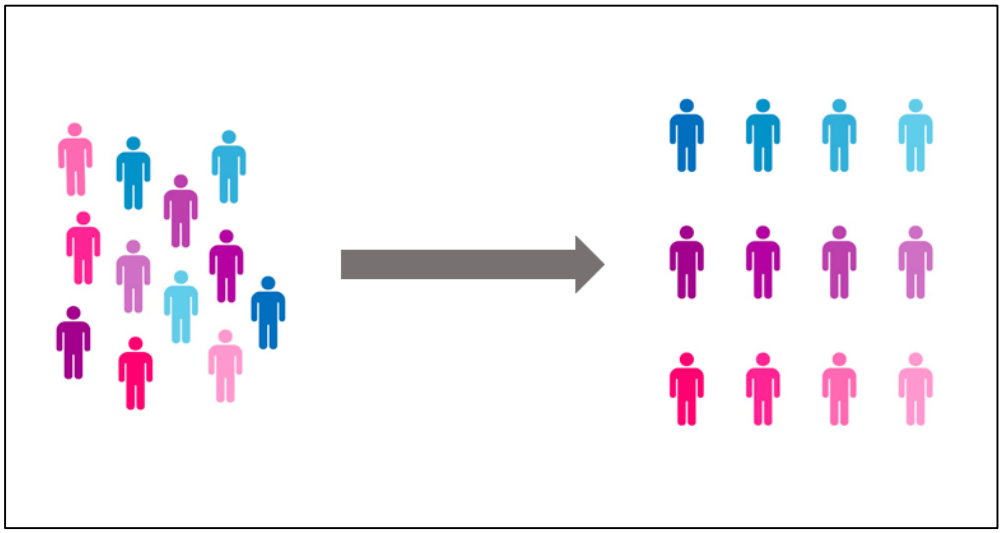
Fonte: Adaptada pela autora e disponível em: https://blog.usejournal.com/machine-learning-for-beginners-from-zero-level-8be5b89bf77c

O aprendizado em ML é classificado em duas categorias: aprendizado supervisionado e não-supervisionado (70). O primeiro refere-se à construção de um modelo preditivo, onde a máquina recebe instruções sobre o que e como necessitam aprender. Dessa forma, o algoritmo supervisionado aprende com o banco de treino e ganha experiência para analisar o banco de teste, tentando maximizar o modelo para encontrar o desfecho buscado. Um exemplo de aprendizado supervisionado é o que chamamos de "classificação", como quando um e-mail é classificado como importante ou "spam"; se determinado paciente é portador de determinado diagnóstico; se aquele indivíduo tem maior risco de envolver-se em um acidente de trânsito, entre outros.

Outra forma de aprendizado supervisionado são as regressões, sejam lineares ou não-lineares. Essas técnicas são utilizadas quando se necessita prever dados numéricos como renda, valores laboratoriais, resultados de testes ou contagens de itens, pois quantificam em termos exatos a associação entre preditores e o desfecho, incluindo a magnitude e a incerteza da relação entre eles.

Já no aprendizado não-supervisionado, o algoritmo deve identificar um padrão nas variáveis, sem instruções prévias apresentadas. A análise de "clusters" (ou conglomerados) é um exemplo clássico de aprendizado não-supervisionado, onde, por exemplo, o algoritmo agrupa indivíduos de acordo com espectros de diferentes psicopatologias, como mostra a Figura 2:

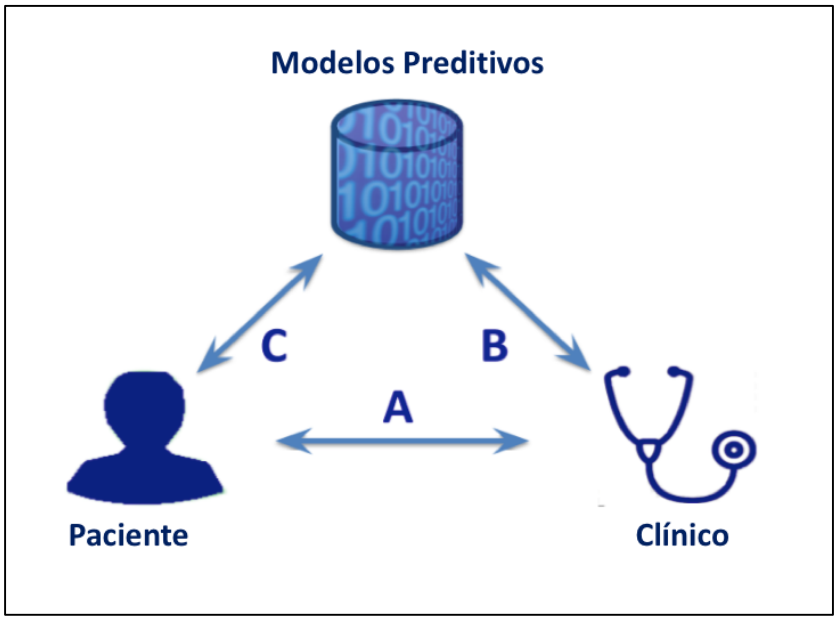
Figura 2 – Ilustração de análise de "clusters" em modelos não-supervisionados de Machine Learning



Fonte: Elaborada pela autora.

Na medicina, o ML tem sido destacado como sendo uma tecnologia fundamental, com a capacidade de processar grandes volumes de dados de forma significativa, trazendo novas compreensões a respeito de patologias polimórficas, trazendo resultados que podem ser extrapolados para “pacientes da vida real” (69). Uma recente revisão elencou diversos exemplos de aplicação de algoritmos de ML na medicina: predição de risco cardiovascular, detecção em tempo real de pacientes com piora clínica, diagnóstico de doenças oftalmológicas, identificação de metástases através de revisão de lâminas oriundas de biópsias, triagem de neuroimagens em busca de sinais de hemorragia intracraniana, dentre outros (69). Modelos preditivos com alta acurácia, utilizando algoritmos de ML, já começam a ser utilizados na prática médica, mudando a relação médico paciente, dando suporte a decisões clínicas de forma individualizada, conforme ilustrado na Figura 3.

Figura 3 – Ilustração do impacto na relação médico-paciente através da utilização de técnicas de machine learning



Fonte: Adaptada de Passos et al. (2019) (71).

Já na psiquiatria, o ML tem sido utilizado, por exemplo, na identificação de preditores de risco de suicídio (72), para predizer a resposta a tratamento através de neuroimagem (73), na identificação de padrões fenotípicos (74), e no uso de processamento de linguagem para identificar depressão resistente (75). O grande

avanço do uso da análise de “Big data” em psiquiatria deve-se ao potencial do ML para avaliar distúrbios multifatoriais, pois os modelos computacionais aprendem padrões de interação entre múltiplas variáveis e identificam desfechos individuais em grandes bancos de dados, bem como tornam possível a identificação de associações “não vistas” previamente (67) (72) (76). Isso possibilita que clínicos possam antecipar eventos futuros e prevenir desfechos graves e trágicos (como TS e suicídio consumado), a nível individual na clínica psiquiátrica (70) (76) – ao contrário dos métodos analíticos tradicionais que provêm resultados a nível de grupos (72).

2.5. O uso de algoritmos de machine learning na predição de suicidalidade

Apesar de várias estratégias científicas e intervenções públicas de saúde buscarem encontrar intervenções anti-suicídio, as taxas de suicídio não tem reduzido com o passar dos anos (77). Sabe-se que o suicídio é um desfecho que pode ser prevenido, mas a maioria dos pacientes não compartilha informações sobre suicidalidade com seus médicos (35) (78), tornando a tarefa ainda mais complexa.

A maioria dos estudos sobre comportamento suicida testou preditores isolados, contudo uma predição com boa acurácia necessita que diversos fatores de risco sejam combinados, o que não é possível com a utilização de análise estatística tradicional (77). Além disso, a grande maioria dos fatores de risco para comportamento suicida (como gênero, idade, história de psicopatologia) também são identificados dentre indivíduos que não apresentam desfechos relacionados à suicidalidade (79).

Então, para que uma maior acurácia na predição e identificação de indivíduos com real risco de apresentarem comportamentos suicida seja atingida, se faz necessário que uma complexa combinação de múltiplos fatores de riscos seja analisada, o que é possível através da utilização das técnicas de machine learning (77).

Diversas tecnologias envolvendo “smartphones”, aplicativos e dispositivos em mídias sociais que utilizam ML vêm sendo desenvolvidas atualmente, com o objetivo de predizer e prevenir comportamentos suicidas (80). Além disso, o uso de ML na

predição de suicidalidade já mostrou ter maior acurácia do que análises estatísticas tradicionais. Tais estudos produziram acurácias discriminativas de comportamento suicidas (AUCs = 0.60 a 0.80) que excedem aquelas que utilizam fatores de risco isolados (AUCs= 0.58) (82).

Um recente estudo utilizou algoritmos de ML para identificar variáveis clínicas e sociodemográficas associadas a suicidalidade em pacientes com transtornos de humor. O modelo utilizado encontrou que as variáveis mais preditoras para diferenciar aqueles que tentaram suicídio dos que não tentaram: hospitalização prévia por episódio depressivo, história de sintomas psicóticos ao longo da vida, comorbidade com dependência de cocaína e transtorno de estresse pós-traumático, atingindo uma acurácia de predição entre 65-72% ($p<0.05$) (72).

Até o momento, esse tipo de análise não foi utilizada para predizer o risco de tentativas de suicídio em pacientes com TOC em nível individual. Tendo em vista que a avaliação de um paciente com TOC é extremamente extensa, por tratar-se de uma psicopatologia heterogênea, com diversas apresentações e dimensões de sintomas, a identificação precisa de quais variáveis clínicas que podem predizer comportamento suicida a nível individual é extremamente importante, objetivando e personalizando a abordagem e tratamento terapêutico daquele paciente que está sendo avaliado.

3. Objetivos

3.1 Geral

- Investigar quais variáveis clínicas são preditoras de tentativa de suicídio em pacientes com TOC através da utilização de algoritmos de machine learning.

3.2 Específico

- Identificar um modelo de predição acurado de risco de tentativas de suicídio em pacientes com TOC e demonstrar como a análise com modelos de machine learning pode ter impacto em decisões clínicas e na prevenção de comportamento suicida nestes pacientes.

4. Hipóteses:

As nossas principais hipóteses para as variáveis implicadas em maior risco de tentativas de suicídio são:

- comorbidade com transtorno depressivo (episódico ou recorrente);
- gravidade dos sintomas depressivos (medidos pela BDI);
- gravidade de sintomas ansiosos (medidos pela BAI);
- gravidade de sintomas obsessivos (medidos pela Y-BOCS);
- presença de dimensão com conteúdo sexual/religioso/moral;
- presença de dimensão com conteúdo de agressividade/catástrofes;
- presença de dimensão de simetria/ordenamento/arranjos;
- idade de início precoce dos sintomas obsessivos compulsivos;
- sexo feminino;
- comorbidade com Transtornos por Uso e Abuso de Substâncias;
- maiores taxas de eventos traumáticos e/ou Transtorno de Estresse Pós-traumático.

5. Considerações Éticas

Os projetos de pesquisa do C-TOC foram submetidos e aprovados pelos Comitês de Ética locais dos centros envolvidos (Processo: USP-968/05; IPA-6600023; UFRGS-06/171; Unifesp-302/2006 e UFRJ-0024.0.249.000-06). Todos os participantes assinaram o Termo de Consentimento Livre e Esclarecido, após uma descrição detalhada dos objetivos e métodos de cada estudo, e a garantia de que sua decisão de participar ou não teria qualquer impacto sobre a disponibilidade do tratamento. Quando o sujeito tinha menos de 18 anos de idade, um termo de consentimento de informado foi assinado pelo sujeito e também por um dos pais ou responsável legal. Todos os projetos de pesquisa do C-TOC são consistentes com as Diretrizes e Normas Regulamentadoras de Pesquisa Envolvendo Seres Humanos (Resolução 466/12), seguindo os princípios éticos da Declaração de Helsinque.

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7. Artigo

Predictors of suicide attempt in patients with OCD at individual clinical level: an exploratory study with machine learning analysis.

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Abstract

Background: Patients diagnosed with Obsessive-Compulsive Disorder (OCD) are at increased risk for suicide attempt (SA) compared to the general population. However, it is unclear what are the significant risk factors associated with SA in this population –whether these factors are associated with the disorder itself or related to extrinsic factors, such as comorbidities and sociodemographic variables. This study aimed to identify predictors of SA in OCD patients using a machine learning algorithm. **Methods:** A total of 959 outpatients with OCD were included. An elastic net model

was performed to recognize the predictors of SA among OCD patients, using clinical and sociodemographic variables. **Results:** The prevalence of SA in our sample was 10,8%. Relevant predictors of SA founded by the elastic net algorithm were the following: previous suicide planning, previous suicide thoughts, lifetime depressive episode, and intermittent explosive disorder. Our elastic net model has a good performance and found an AUC of 0.95. **Conclusions:** This is the first study to identify factors associated with SA among OCD patients with machine learning. Our results demonstrate that an accurate risk algorithm can be created using clinical and sociodemographic variables. All aspects of suicidal phenomena need to be carefully investigated by clinicians in every evaluation of an OCD patient. Particular attention should be given to comorbidity with depressive symptoms. However, longitudinal studies must be performed to confirm the causal relationship between these predictors and SA among OCD patients.

Keywords: obsessive-compulsive disorder, suicide attempts, elastic net, machine learning.

Introduction

Obsessive-compulsive disorder (OCD) is one of the most prevalent neuropsychiatric disorders affecting about 2.5% of people throughout their lives (Ruscio et al., 2010) (Kessler et al., 2005). According to the World Health Organization, OCD is one of the debilitating and disabling diseases (Murray et al., 1996). Despite the high degree of suffering, disability and impairment associated with the disorder, high rates of comorbidities and low rate of response to treatment, little attention was paid to suicidal behavior in patients with OCD (Jacoby et al., 2014) (Eisen et al., 2006) (American Psychiatric Association, 2013).

Suicide is a major public health problem, being one of the top 10 causes of death and burden of disease worldwide, across all age groups ("WHO | Preventing suicide") (Lozano et al., 2012). Also, about 90% of suicide deaths are directly related to mental disorders (Arsenault-Lapierre et al., 2004)(Nock et al., 2010) (Hawton and van Heeringen, 2009). Suicide in OCD has long been considered a rare phenomenon, with suicide death rates described in the classic literature of about 1% (Goodwin et al., 1969) (Coryell, 1981), with some studies finding a negative

association results between suicide and OCD (Kanwar et al., 2013).

Contrary to these findings, recent evidence has suggested that rates reported on suicide in OCD were underestimated, with two systematic reviews indicating rates of suicide attempts (SA) in OCD ranging from 3 to 27%(Angelakis et al., 2015) and from 6 to 51.7% (Albert et al., 2018). The current estimates of suicide in OCD are similar to those of other mental disorders commonly associated with such as schizophrenia and mood disorders (Osborn et al., 2008), attention deficit hyperactivity disorder (Ljung et al., 2014), posttraumatic stress disorder (Gradus et al., 2010) and alcohol use disorders (Flensborg-Madsen et al., 2009).

However, the results of previous studies allow questions about whether suicide in OCD is due to factors intrinsic to the psychopathological phenomenology of OCD (related to the direct effects of the psychopathological nuclear aspects of the disorder) or to the result of factors extrinsic to this psychopathological nucleus, such as the occurrence of psychiatric comorbidities or sociodemographic factors. All studies until now used traditional statistical analysis, but the psychopathological heterogeneity of OCD can potentially reduce power and obscure the findings of these clinical studies, as it is known that there are several limitations in using traditional hypothesis testing methods to analyze multidimensional and heterogeneous data.

In light of this finding, techniques that comprise differences at the individual level are essential such as machine learning, a field of artificial intelligence. The use of machine learning focuses on algorithms that can analyze, learn and extract patterns from data in a non-linear and interactive way, thus transforming data into relevant information, exceeding the human brain's ability to understand (Rajkomar et al., 2019) (Greenhalgh et al., 2014)(Huys et al., 2016)(Passos and Mwangi, 2018).

Machine learning has shown to be more accurate in predicting suicidality than traditional statistical analysis in several studies (de Ávila Berni et al., 2018)(Leonard Westgate et al., 2015)(O'Dea et al., 2015)(Larsen et al., 2015)(Simon et al., 2018)(Niculescu et al., 2015) (Torous et al., 2018) (Passos et al., 2016) producing suicidal behavioral discriminators (AUCs = 0.60 to 0.80) that exceed those using isolated risk factors (AUCs = 0.58) (Franklin et al., 2017). A recent study used ML algorithms to identify clinical and sociodemographic variables associated with

suicidality in patients with Mood Disorders. The model used found that the most predictive variables to differentiate those who attempted suicide from those who did not try were: previous hospitalization for a depressive episode, history of life-long psychotic symptoms, comorbidity with cocaine dependence and posttraumatic stress disorder, reaching a prediction accuracy between 65-72% ($p < 0.05$) (Passos et al., 2016).

To date, this type of analysis has not been used to predict the risk of SA in patients with OCD at the individual level. In this sense, our objective will be to explore sociodemographic and clinical factors associated with SA in adult OCD patients. Considering that the evaluation of a patient with OCD is extremely complex due to its heterogeneity (diverse presentations and symptom dimensions), the precise identification of which clinical variables can predict suicidal behavior at the individual level is clinically essential, allowing intervention customization preventive and therapeutic.

Methods

Participants

The sample was initially formed by 1,001 OCD patients from seven university centers in six Brazilian cities, which made up the Brazilian OCD Consortium (C-TOC). Patients were interviewed between August 2003 and August 2009 and were included in the study because they met criteria for OCD confirmed by the Structured Clinical Interview for Axis Disorders I of DSM-IV (SCID-I) (First MB, et al., 1997). Patients with psychotic disorders or any other condition that impaired their understanding of the evaluation questions were excluded (e.g., Schizophrenia, Autism Spectrum Disorder, Intellectual Disability), and each local Ethics Committee of each university hospital approved the research protocol. The detailed description of the evaluation protocol is available in (Miguel et al., 2008). For this paper, 42 (4,2%) patients were excluded because of data missing concerning suicide information, resulting in a sample of 959 OCD patients.

Instruments

Subjects were directly interviewed by psychologists or psychiatrists trained in the application of the protocol and their structured interviews. In addition to sociodemographic data (sex, age, religion, marital status, occupation, socioeconomic classification, etc.), personal medical history, family psychiatric history, and several standardized instruments comprised the protocol of the C-TOC. Among them, the items below were relevant for this study:

- The Structured Clinical Interview for DSM-IV (SCID-I) and additional modules for tic and impulse control disorders were used to assess psychiatric comorbidities) (First MB, et al., 1997). Attention deficit hyperactivity disorder (ADHD) and separation anxiety disorder were investigated through a module of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997).

- The Yale Obsessive-Compulsive Brown Scale (Y-BOCS) was used to measure the severity of OCD symptoms. It has been translated into Portuguese by Asbahr et al. (Asbahr FR, Lotufo NF, Turecki GX, et al. and Miguel EC, 1996).

- The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos et al., 2006) evaluated the presence and severity of OCS according to specific six dimensions, including obsessions and related compulsions. Also investigated avoidance and the time spent with obsessive-compulsive symptoms (OCS), the level of anxiety and interference. Its scores range from 0 to 5 (maximum of 15 for each dimension). The negative impact of OCS is also measured (maximum score of 30), and the therapeutic response can be evaluated according to specific dimensions. This instrument was simultaneously validated in Portuguese and English.

- Beck Depression Inventory (BDI) (Beck et al., 1961) and Beck Anxiety Inventory (BAI) (Beck et al., 1988) two scales used worldwide to evaluate depressive and anxious symptoms respectively. Translated into Portuguese by Gorenstein and Andrade (Gorenstein and Andrade, 1996).

- The Yale OCD Natural History Questionnaire (Leckman et al., 2002,

unpublished manuscript, translated into Portuguese by Rosário et al., 2002). Used to look for OCS onset and course, including stressful life events.

A questionnaire about suicide behaviors was composed of 7 questions with categorical answers ("Yes," "No," "I do not know"), and included: "Have you ever thought that it was not worth living?"; "Did you ever wish you were dead?"; "Have you ever thought about taking your own life or committing suicide?"; "Have you planned to take your own life or commit suicide?"; "Have you ever tried to take your own life or commit suicide?"; "Did you need hospitalization/treatment at that time?"; "Have any of your relatives tried to commit suicide?"; "Have any of your relatives ever committed suicide?". These questions have already been used in other publications (Torres et al., 2011) (Velloso et al., 2016). The question about attempted suicide was chosen as the outcome in this study

Selection of predictor variables

The variables used in the model of this study were selected through a structured search on Pubmed. We searched for articles that had clinical relevance in finding risk factors for suicide in OCD. Thus, the predictors variables selected to be used in "training" the algorithm included demographic variables and clinical variables related to OCD and other psychopathologies that presented comorbidly in our database. This way of selecting the predictor variables is a method already used in previous studies that used machine learning (Perlis, 2013)(Passos et al., 2016). Given the extensive number of variables present in our dataset (n=1,680), we suggest that readers seek Miguel et al. (2008) for a more detailed description of all the data collected. According to our meticulous C-TOC original dataset review (two authors, NAA and YAF, reviewed each variable of the dataset separately and, after a best estimate diagnosis technique (Maziade et al., 1992), a consensus was achieved), 89 remained variables were entered into the analysis. Table S1 in the Supplementary Material resumes these remained variables.

Statistical Analysis

Continuous variables were reported as means (with standard deviations(sd)) and/or median (minimun-maximun values); categorical variables were described by

absolute(n) and relative frequencies (%). Descriptive analysis were performed with Statistics Package for Social Sciences 18.0 (SPSS) (SPSS Inc., 2009).

The machine learning analysis was performed with R software (Version R 3.3.1) (R Foundation for Statistical Computing., 2013) and R Studio (Version 0.99.902) with the R package caret (Version 6. 0-73) (Kuhn, 2008). We ran experiments with the elastic net method (Zou and Hastie, 2005). We used machine learning techniques to address two problems in conventional multiple regression: 1) coefficients are unstable when high correlations exist among predictors; this is the case for the predictors included in the present study, leading to low replication of predictions in independent samples (Berk RA., 2008); 2) traditional regression assumes additivity, whereas the predictors considered here might have non-additive effects (Ozer et al., 2003) (Tolin and Foa, 2006) (DiGangi et al., 2013).

The elastic net is a machine learning method that comprises both feature selection characteristics with regularization and classification. In statistics and, in particular, in the fitting of linear or logistic regression models, the elastic net is a regularized regression method that linearly combines the L_1 and L_2 penalties of the lasso(least absolute shrinkage and selection operator is a regression analysis method that performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces) and ridge (it is the most commonly used method of regularization of ill-posed problems. In statistics, the method is known as ridge regression, in machine learning it is known as weight decay) methods, turning the method able to remove predictors with low impact to the outcome while regularizing for improved generalization. As our dataset is composed of several attributes, identifying the most important ones permits for a wider applicability and more practical use of our risk calculators.

To handle missing data we first remove all variables with more than 5% missing. We then impute the remaining variables by the variable mean, for numerical variables, or by the variable mode, for categorical variables. For each analysis, we have split our data into training (75% of the whole sample) and test datasets (25%). We deployed a standard machine learning protocol with 10-fold cross-validation, feature selection, hyperparameter tuning, and class imbalance correction in the

training dataset (Figure S1 in the Supplementary Material),with model selection based on the area under the receiver operating characteristic (ROC) curve. Class imbalance usually leads to very different sensitivity and specificity scores in the model; to account for this, we balanced each class predominance with class weighting. Each class was weighted inversely proportional to its frequency in the training set, or:

$$W1=F0/N$$

where W1 is the weight for the positive class and F0 is the frequency of the negative class in the training set. Consequently, W0=1-W1. Class weighting allows us to use the whole training set instead of relying on downsampling techniques.

Individual-level predicted suicide attempt probabilities based on the elastic net algorithm were created, ROC curve generated, area under the curve (AUC) calculated to evaluate prediction accuracy. Additionally, we calculated sensitivity, specificity, balanced accuracy, positive predictive value (PPV), and negative predictive value (NPV) when the cut-off is selected as 0.5. Elastic net regularization predicted probabilities were then discretized into deciles (10 groups of equal size ordered by percentiles) and cross-classified with observed suicide attempts.

From those variables selected by the elastic net algorithm to distinguished suicide attempters from non-attempters only those with a importance weighting factor higher than 20% was considered as clinically and epidemiologically relevant.

Results

Among the 959 adult patients included, 413 were male (43.1%), and 546 were females (56.9%). The mean age (SD) was 34.95 (12.94), with a median of 32 and ranging from 9 to 82 years of age; the mean number of years studied was 14.51 (4.95), with a median of 14 and ranging from 1 to 31 years of study. Regarding marital status, 520 (54.2%) were single or without stable partners; 378 (39.4%) reported having children; 560 (58.4%) were Catholics, while 298 (31.1%) were from other religions and 101 (10.5%) said they had no religion. Of the 858 patients who had some religion, 521 (60.7%) admitted to being practitioners. From the

occupational point of view, 415 (43.3%) were working, 166 (17.3%) were students, 102 (10.6%) were housewives, 104 (10.8%) were retired, 22 (15.6%) were unemployed, and when questioned about paid employment, 457 (47.7%) had no remuneration. The socioeconomic class, according to ABIPEME, showed that 157 (16.4%) were of class A, 369 (38.5%) of class B, 341 (35.6%) of class C, and 92 (9.6%) were of classes D and E.

From the clinical point of view, 231 (24.1%) had never performed psychiatric or psychological treatment until the time of the interview. Of the 728 (75.9%) who had already performed specialized care, 675 (92.7%) had already used some serotonin reuptake inhibitor, 138 (19.0%) had already used some other type of antidepressant, 365 50.1%) had already used some type of benzodiazepine, 105 (14.4%) had used some mood stabilizer, 49 (6.7%) had used lithium and 192 (26.4%) had used some neuroleptic . Still, 609 (83.7%) had already performed some kind of psychotherapy (but only 148 (20.3%) had already performed cognitive-behavioral therapy for OCD), 65 (8.9%) had already been hospitalized for psychiatric disorders, and 12 (1.7%) had already undergone electroconvulsive therapy.

From the psychopathological point of view, Table 1 shows the descriptive results of phenomena intrinsic to the symptomatological core of OCD.

Insert table 1

Table 2 presents clinical characteristics extrinsic to the psychopathological nucleus of OCD.

Insert Table 2

Figure 1 shows the prevalence rates of suicidality in patients with OCD. Concerning the need to be hospitalized due to the SA, only 19 (1.99%) reported it occured [15 (78.9%) in general hospital, and 4 (21.1%) in a psychiatric unit].

Insert Figure 1

Machine-Learning Analysis

The model showed an accuracy of 87% in distinguishing individual attempters from non-attempters. The elastic net algorithm selected 18 variables that could predict the SA: 1) previous suicide plans; 2) history of suicidal thoughts; 3) lifetime

depressive episode; 4) lifetime intermittent explosive disorder; 5) lifetime substance use/dependence disorder; 6) lower economic class; 7)lifetime anorexia disorder; 8) lifetime attention deficit and hyperactivity disorder; 9)mulatto ethnicity; 10)lifetime kleptomania disorder; 11) any sensory phenomena; 12) lifetime simple phobia; 13) lifetime panic/agoraphobia disorder; 14) familial history of OCD; 15) familial history of alcohol dependence; 16) familial history of psychosis; 17) familial history of SA; and 18) no occupation. Thus, the most relevant (higher than 20% of importance weighting factor) predictor variables that remained in the model were: 1) previous suicide plans, 2) history of suicidal thoughts 3) the presence of a lifetime depressive episode, and 4) the presence of a lifetime intermittent explosive disorder. Figure 2 shows the weighting factors of each clinical variable that remained in the model.

Insert Figure 2

Sensitivity and specificity were 84.61 and 87.32%, respectively, with a balanced accuracy of 85.97% and significant at $\chi 2$ $p<0.0001$. The positive predictive value was 44,89% and the negative predictive value was 97.89% and an area under receiver operating characteristic curve of 0.95. (see Figure 3)

Insert Figure 3

All sample were ranked based on their probability of belonging to the positive class and separated in deciles. The percentage of positive and negative class samples was then analyzed at each decile based on their expected outcome. This demonstrates that over half of the OCD sample which had a SA were recognized to be at the highest risk of SA, and 85% were categorized as at highest or second-to-highest risk of SA deciles. Likewise, 100% of the sample was categorized in the first three deciles of predictive risk of having a SA. Figure 4 shows the concentration risk for suicide attempt based on model output probability.

Insert Figure 4

Discussion

Describing suicidality in patients with OCD

In our study, 104 (10.8%) patients with OCD attempted suicide throughout

their lives, a rate almost identical to the average of 10.3% found in the systematic review of Angelakis et al. (2015) and identical to the median of 10.8 % (mean of 14.2%) in clinical samples in the studies pointed out in the systematic review by Albert et al. (2018). Two previous studies of our group on suicide in OCD found SA rates of 11% in a subsample of 582 patients (n = 64) (Torres et al., 2011) and 19.4% in a sub-sample of 356 (n = 69) (Velloso et al., 2016). However, the sample size of these two studies was smaller than in the present study, since, according to their specific objectives, they excluded patients to analyze different variables, such as the scores of the quality of life instrument, for example (Velloso et al., 2016).

The study by Alonso et al. (2010), with 218 patients in a 4 years follow-up, showed lower rates of suicidality: suicidal ideation (SI) was 8.2% (n = 18); SA was 5% (n = 11) and 0.91% (n = 2) committed suicide in that period. Only 4,1% presented current SI, concluding that suicidal behavior would not be such a prevalent phenomenon in OCD, previous corroborating studies that indicated rates of SA in OCD of 3 to 4% (Goodwin et al., 1969) (Koran et al., 1996) (Khan et al., 2002) (Hollander et al., 1996). In fact, rates of SA in this present study were lower than those of other psychiatric disorders, which are already established to be highly related to suicidality: in schizophrenia, they are 30.2% (Radomsky et al., 1999); in the bipolar disorder are 29.2% and in the unipolar mood disorder of 15.9% (Chen and Dilsaver, 1996). However, in a Survey of Mental Health from the World Health Organization (WHO), in which 108.705 adults from 21 countries were evaluated, the prevalence of SA were 0.3% for developed countries and 0.4% for developing countries (Borges et al., 2010). Thus, our results confirm that suicidal behavior is prevalent in the OCD population when compared to the general population, according to previous findings (Angelakis et al., 2015) (Albert et al., 2018) (Fernández de la Cruz et al., 2017).

Predictive factors of suicide attempted in patients with OCD

This is the first study that uses machine learning techniques to explore possible predictive factors for individual SA in patients with OCD using demographic and clinical variables. It found 18 possible predictive variables of SA in our sample, but only 4 were clinically and epidemiologically important and deserving of discussion.

As regards sociodemographic variables, our negative finding is in agreement with previous studies, where the authors found no association between suicidality and marital status, family status, level of education, employment, religion, quality of life, clinical course, age of onset or family history of suicide or suicidality (Torres et al., 2011)(Torres et al., 2007)(Kamath et al., 2007).

Several studies have pointed out that suicidality in OCD may be associated with phenomena intrinsic to the psychopathological core of the disorder, which seems to have its effect mediated by the severity of OCD symptoms (Torres et al., 2007)(Hung et al., 2010), the sexual / religious / moral dimensions (Torres et al., 2011)(Fernández de la Cruz et al., 2017)(Dell'Osso et al., 2018), aggressiveness / catastrophe (Balci and Sevincok, 2010), and symmetry / organization and arrangement (Alonso et al., 2010). Obsessions involving sexual/religious/moral and aggressive/catastrophic content are considered as "taboo thoughts" and considered as socially unacceptable. Therefore, patients with this type of obsessive content could present a higher degree of shame, guilt, and responsibility for the content of their obsessions, which may lead to thoughts of death, SI, SA and suicide (Angelakis et al., 2015)(Kamath et al., 2007)(Balci and Sevincok, 2010)(Gupta et al., 2014). Our findings, however, point out that no variable intrinsic to OCD psychopathology is predictive of SA. Thus, suicidality in OCD does not appear to be related to the disorder itself. Concurrently, Sareen et al. (2005), in a population study with traditional statistical analysis, did not find an independent association between OCD and suicidality, after adjustment of sociodemographic variables and control for psychiatric comorbidities.

The only variable intrinsic to the nuclear phenomenology of OCD psychopathology that remained important in the machine learning model in our study was the presence of some sensory phenomenon but did not reach the importance value of pre-stipulated clinical-epidemiological relevance. Thus, we will discuss the two comorbidities and the two specific aspects of suicidal behavior, possible predictors of SA in patients with OCD.

Comorbidities

The two lifetime comorbidities that remained predictive of SA were those of

depressive episode and intermittent explosive disorder. In two previous systematic reviews, higher rates of suicidality were found in patients with OCD who presented concomitant comorbidities (especially greater severity of depressive and anxious symptoms), previous history of suicidal behavior and feelings of hopelessness (Albert et al., 2018) (Fernández de la Cruz et al., 2017). On the other hand, Torres et al. (2006) after controlling for variables such as the presence of comorbidities, found that the risk of suicidal behavior in OCD remained significant, reaching up to 25% of prevalence, with an independent effect of OCD symptoms in suicidality, since patients with OCD without comorbidities did not differ from those with comorbidities in terms of the prevalence of suicidal behavior. This divergence of results is possibly due to different samplings (clinical x epidemiological) or to the method of analysis instituted in each study.

Depression as comorbidity predictive of attempted suicide in OCD

The presence of depressive symptoms has an important impact on the expression of suicidality among patients with OCD (Kamath et al., 2007)(Maina et al., 2007)(Tükel et al., 2006). Depression alone is one of the major factors for the presence of suicidal behavior (Bertolote et al., 2005) and is associated with all suicidal outcomes (Scocco et al., 2008). It is known that depression is one of the most common comorbid codings in OCD and, in our sample, was the most frequent comorbidity, being diagnosticated in 67% of patients throughout life.

Apter et al. (2003), in a study of adolescents inpatients, found that among OCD individual the rates os SI was similar to those of non-OCD patients, but the incidence of SA was significantly lower in the OCD group compared with patients with psychotic, depressive, eating or personality disorders. The authors did not find an independent association between OCD, SI and SA after controlling for comorbidities and clinical variables. Besides, in this study, depressive symptoms were protective against SA in patients with OCD. Such a finding may be because adolescents with non-depressed OCD become more impulsive. Likewise, Gupta et al. (2014) found no difference between those patients with OCD with and without depression in terms of the presence of SI.

Nevertheless, we can hypothesize that the existence of comorbidity with

depressive symptoms results in more severe and incapacitating obsessive-compulsive symptoms, with a higher occurrence of suicidal behaviors compared to patients with non-comorbid OCD (Hollander et al., 1996). Depression (or severity of depressive symptoms) may be an indicator of OCD severity and is midway between OCD and suicide outcome. The depressive picture would therefore be a consequence of OCD, not only a confounding variable (Torres et al., 2007), since mood changes appear to be consequences of chronic stress and injury associated with the severity of OCD symptoms (Angst et al., 2004),. In fact, temporally depressive symptoms manifest about 10 years after the onset of OC symptoms (OCS) (de Mathis et al., 2013).

However, the vast majority of studies evaluating suicidality in OCD did not control the temporality relationship of depressive symptoms concerning the variability of the intensity of OCS. It is known that patients with OCD with comorbid depression tend to become more vulnerable and have more cognitive distortions about their thoughts, which would lead to a reflex worsening of OCS (Abramowitz et al., 2007). Likewise, the presence of depressive symptoms seems to worsen insight regarding the content of obsessions, which may precipitate the appearance of more severe conditions, such as psychotic symptoms (Fontenelle et al., 2011). This is a crucial point in the study of suicidality, since depressive symptoms associated with psychosis increased rates of suicidal behavior (Gournellis et al., 2018).

Also, depressive symptoms are associated with a significant worsening of quality of life, a greater impact on limitations and avoidance behaviors, as well as feelings of hopelessness and incapacity, resulting in the presence of the various outcomes of suicide in OCD (Angst et al., 2004) (Torres et al., 2013)(Viswanath et al., 2012). These feelings are significantly associated with the presence of SI in OCD (Kamath et al., 2007) and this is an independent association of the presence of comorbidity with depression (Alonso et al., 2010) (Torres et al., 2007). Unfortunately, our database did not evaluate the presence of of hopelessness. Another limitation of our study was the fact that we did not evaluate whether, at the time of SI and SA, there was presence of some stressor, as well as if the depressive and OCD symptoms were more severe and incapacitating, or if the presence of depressive symptoms impacted on the severity of OCD symptoms. Interestingly, however, Torres et al. (2007) and Sareen et al. (2005) reported that both depressive symptoms

and SOC severity were associated with prior SI but not with suicidal planning or SA.

Intermittent Explosive Disorder (IED) as comorbidity predictive of attempted suicide in OCD

In another study of our group, with a smaller sample (n = 582), the authors found, after the logistic regression model, that impulse control disorders were independently associated with SI, suicidal plans, and SA. This finding, even using traditional statistical analysis, is similar to our finding that IED is a predictive comorbidity of SA in patients with OCD (Torres et al., 2011).

The association of IED with suicidality has been found in other studies. In a community-based survey found that the group with impulse-control disorders were strongly associated with SA (Lee et al., 2007). Likewise, in a Turkish cross-sectional study, the authors described a prevalence of lifetime IED 2.7 times higher among those with lifetime SA (Gelegen and Tamam, 2018). Individuals with IED presents impulsive behaviors and incapacity of controlling their behaviors, especially in the face of life stressors. Besides, there is a high prevalence in comorbidity with depressive disorders (American Psychiatric Association, 2013). We hypothesized that this impulsive and disruptive behavior seems to contribute to the association with suicidal phenomena in this group of patients. Why this specific disorder was related to suicidality and not other impulse control disorder is subject to further investigation. In our sample, the lifetime prevalence of IED is higher (7,4%) than the 12-month prevalence in the United States (2,7%) (American Psychiatric Association, 2013), which may have impacted our results.

Psychopathological aspects of suicidality as predictive factors of suicide attempts in patients with OCD (suicidal ideation and planning)

In our study, the risk of SA in OCD can be predicted with high accuracy by SI and plans, which is emphasized by the fact that these two variables accounted for about 85% of the prediction of SA. As expected, the results corroborate the view that SI, SA and consummate suicide represent different aspects of the same psychopathological phenomenon: the specter of suicidality. In two other studies in

our group, which used traditional statistical analysis, it was also evidenced that there is continuity of severity of the phenomenon of progressive suicide in patients with OCD, evolving from ideation to planning and attempting suicide, culminating even in suicide (Torres et al., 2011) (Velloso et al., 2016).

Suicide ideation is a vital aspect in the suicidality dimension, since it is the initial route of SA, being the main predictor of future SA, and even of completed suicide among patients with different psychiatric diagnoses, which characterizes suicidality as a transdiagnosis phenomenon (Mann, 2002). In fact, 90% of suicides are committed by people with the most diverse pathologies (Nock et al., 2010) (Hawton and van Heeringen, 2009). The presence of a previous SA is a great predictor of suicide, and among patients with OCD, this finding has already been replicated (Meier et al., 2016).

In fact, risk factors commonly associated with suicide in the general population, such as depression and hopelessness, appear to be strong predictors of SI, but some data point out that there is insufficient accuracy to distinguish between those who try and those who do not attempt suicide (Bertolote et al., 2005) (Qiu et al., 2017) (Klonsky et al., 2016). Few studies have evaluated the specific risk factors associated with progression from SI to SA. An Italian study, for example, showed that the probability of an individual with SI to draw up a plan was 25%, and the probability of SA following a plan was 50% (Scocco et al., 2008). Already in a Chinese study, among those with SI, the probability of progressing to suicidal planning was 29.5% and of making a SA of 32.3% (Lee et al., 2007).

According to the systematic review of Albert et al. (2018), all the studies evaluated found that individuals with OCD were more likely to present lifetime SI, when compared to the general population, with an odds ratio ranging from 1.9 to 10.3. This risk remained significant even after controlling for confounding variables (AOR between 3.8 and 5.58). As for SA, the data from previous studies are more controversial, with some studies pointing out that individuals with pure OCD (without comorbidities) are more likely to have SA (Nock et al., 2010) (Fernández de la Cruz et al., 2017)(Torres et al., 2006) and others not finding this association (Sareen et al., 2005) (Angst et al., 2004). The systematic review of Angelakis et al. (2015) also corroborates the idea that OCD is associated with several suicidal phenomena of

moderate to severe intensity, but the authors pointed out a negative association between OCD and suicide. However, it is noteworthy that only two studies had been included in the systematic review that examined the impact on OCD of the suicide outcome, both of which had patients with psychotic symptoms and depressive symptoms (Pfeiffer et al., 2009) (Hantouche et al., 2003), which may have biased the interpretation of results.

In a prospective population-based study (36,000 patients with OCD) Fernández de la Cruz et al. (2016) reported that the risk of death from suicide was significantly higher than expected - about ten times higher than the general population. Most patients with prior SA had at least one comorbid psychiatric pathology, while about 40% of those with a history of completed suicide had OCD without comorbidities. Thus, the authors concluded that OCD without comorbidity is more associated with death by suicide, and OCD with comorbidities is more associated with SA. Also, the leading risk factor for death by suicide in this study was the presence of a previous SA (OR = 4.70). After controlling for the impact of different comorbidities, the risks remained significant, which would reinforce the idea that OCD alone poses a higher risk of suicidal behavior, contrary to our study. Likewise, Meier et al. (2016) in a prospective cohort on nationwide Danish registries found that OCD individuals are at greatest risk of suicide - a risk tripled in ten years of follow up. One of the probable explanations would be that there is a delay in the search for treatment and diagnosis in patients with OCD without comorbidities since a large percentage of the patients seems to be ashamed and not aware that OCD is treatable psychopathology. In a population-based study, 26% of OCD had a SA, only 40% of them were on psychiatric treatment. The authors also showed that only 14% of the patients with OCD without comorbidities seek treatment, against 56% of those with comorbidities, among those seeking treatment (Torres et al., 2006).

Thus, the risk factors for the presence of SI, SA and suicide in OCD appear to be different. In a prospective study of 218 OCD patients, although authors conclude that the phenomenon of suicidality is not so frequent in OCD, they found that 63.1% of patients with persistent thoughts of suicide or suicidal plans evolved into SA. Besides, the severity and the presence of depressive symptoms also seemed to predict the risk of suicidal behavior (Alonso et al., 2010).

In our study, SA in patients with OCD was not predictable by characteristics of the disorder itself, but by precursor aspects of SA (thoughts and suicidal planning) and two comorbidities: major depression and IED. Such a finding seems to diverge from previous studies, where OCD was associated with suicidal behavior even after control of confounding factors, due to the use of a different method of statistical analysis. The use of ML algorithms is better applied in scenarios where numerous variables must be considered simultaneously to estimate the probability of an event occurring. ML techniques do not ignore small effects to perform predictions or to identify patterns (Perlis et al., 2013) (Mwangi et al., 2012).

Limitations

The limitations of this study include the fact that the sample is made up of patients coming from tertiary care centers and not representative of patients with OCD in the community. It is a cross-sectional study, subject to memory bias, and is not ideal for the identification of predictors. Also, no control of potentially triggering variables at the time of SA was done, as well as interference of the severity of OCD symptoms and of psychiatric comorbidities to lead to SA. Another critical factor is that family members were not directly interviewed regarding suicide. Personality disorders, which may be an essential predictor of suicidality, as well as hopelessness, have not been evaluated. A smaller part of our sample had previously been evaluated in two other studies in our group; however, the methodology applied differs fundamentally. Finally, the predictor variables included in the algorithm were defined based on previous studies, and may not ideally represent all possible predictors, since the database was not specially constructed to study phenomena of the suicidality spectrum, and aspects such as intensity, duration, variability, and persistence of the behaviors were not measured.

Conclusions

This is the first study that uses an ML algorithm to explore predictors of individual risk of SA in patients with OCD. Studies of this nature have shown accuracy in suicidality discrimination (AUCs = 0.60 to 0.80), values that exceed those using isolated risk factors with traditional statistical analysis (AUCs = 0.58) (Franklin et al. 2017) (Passos et al. 2016).

Thus, this study adds to evidence that suicidality is a relevant phenomenon in OCD patients. It is important to note that questions about suicidality need to be inquired in all interviews. All aspects of suicidality need to be asked for, in a direct form, including thought about death, SI, plans about committing suicide, desire to be death, previous SA ou actual desire to make an attempt and family history of suicidality. Besides this, it is vital to investigate depressive symptoms and aggressively treat them, as previous recommend by Kamath et al. (2007).

Early recognition of depressive symptoms and soft signs about suicidality make it possible setting an appropriate treatment plan and prevention tragic disclosures as a suicide. Preventive strategies consist of initially identifying the main predictors of suicidality and intervening in modifiable risk factors. To date, there are only effective pharmacological treatments to reduce suicide risk for mood disorders and schizophrenia - lithium (Cipriani et al., 2013) and clozapine (Meltzer et al., 2003) respectively. Psychotherapeutic strategies are also useful in reducing the manifestation of suicidal behavior, regardless of the primary psychiatric diagnosis (Hawton et al., 2016). There is as yet no evidence of longitudinal studies demonstrating any pharmacological intervention in reducing the risk of suicide in patients with OCD.

Our results also indicate that suicidality appears as a continuum and that it is imperative to analyze and investigate manifestations of suicidality actively in all patients with OCD, but more aggressively among those with comorbid depressive symptoms. Those patients with thoughts and plans regarding suicide should receive intensive treatment to prevent outcomes such as SA and suicide death. Future studies should focus on understanding suicidality, with longitudinal design and specific and structured assessment measures to assess all aspects of suicidal behavior. Genetic evaluation measures, immunological markers, neuroimaging results in combination with clinical and sociodemographic variables should also be combined to provide a more accurate predictive model of risk for suicidal behavior. Also, predictive and intervention strategies should be given greater focus as suicide is an extremely tragic outcome, but it is possible to be prevented.

Finally, our study demonstrated that an algorithm of ML can predict SA among patients with OCD. These techniques are ideal for identification of the pattern of multiple variables with complex combinations and can be used to stratify risk of SA for a given person by comparing the probability of SA predicted by the algorithm for their variables as compared to those calculated from a dataset of subjects with known outcomes.

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Highlights

- We estimated risk for suicide attempt among patients with obsessive-compulsive disorder.
- The prevalence rate of attempted suicide was 10.8%.
- The accuracy of the elastic net algorithm was 85%, with a ROC curve of 0.95.
- Previous history of a suicide plan and suicidal thoughts, comorbidity with depressive episode and with intermittent explosive disorder were the most relevant predictor variables.
- Risk for suicide attempts can be estimated using demographic and clinical variables

Tables and Figures

TABLE 1 - Descriptive results of the psychopathological variables intrinsic to the phenomenology of Obsessive-Compulsive Disorder.

	Mean (SD)	**Median (Minimum – Maximum)**
Age of onset (in years)		
- Compulsions	13,2 (7,8)	11 (3-60)
- Obsessions	13,5 (8,0)	12 (1-59)
- Interference of OCS	22,3 (10,6)	20 (4-64)
- Looked for treatment	30,3 (12,7)	28 (6-75)
- Had OCD diagnose	31,9 (12,4)	29,5 (9-75)
Duration of OCD (in years)	23,2 (12,9)	22 (0-67)
Untreated time (in years)	17,6 (13,0)	15 (0-58)
Severity of symptoms (DY-BOCS)		
- Aggression / catastrophes	5,34 (5,0)	5 (0-15)
- Sexual / religious / moral	4,36 (4,9)	2 (0-15)
- Contamination / cleaning	6,22 (5,2)	7 (0-15)
- Symmetry / ordering	7,39(4,6)	8 (0-15)
- Accumulation	3,19 (4,1)	0 (0-15)
- Miscellaneous	7,56 (4,7)	9 (0-15)
- Total Score	21,25 (6,2)	22 (0-30)
Severity of symptoms (Y-BOCS)		
- Obsessions	12,75 (3,9)	13 (0-20)
- Compulsions	12,89 (4,2)	13 (0-20)
- Total Score	25,60 (7,5)	26 (7-40)
Insight Level (BABS)	6,88 (5,5)	6 (0-24)
	n	**%**
Symptom Dimension (DY-BOCS)		
- Aggression / catastrophes	644	67,2
- Sexual / religious / moral	554	57,8
- Contamination / cleaning	705	73,5
- Symmetry / ordering	832	86,8
- Accumulation	511	53,3
- Miscellaneous	837	87,3
Presence of sensory phenomenon	589	61,4
Course of OCS (n = 857)		
- Intermittent / episodic	417	48,7
- Continuous - stable gravity	62	7,2
- Chronic - gravity worsening	378	44,1
Family History		
- OCD	480	50,1

- Tics	178	18,6
Age of onset (n = 915)		
-Precoce (<11 years)	460	50,3
-Intermediate	320	35,0
- Late (> = 18 years)	135	14,7

SD = standard deviation; OCS – Obsessive Compulsive Symptoms; OCD = Obsessive Compulsive Disorder; DY-BOCS = Dimensional Yale-Brown Obsessive Compulsive Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; BABS = Brown Assessment of Beliefs Scale.

TABLE 2 - Descriptive results of the variables psychopathological extrinsic to the phenomenology of Obsessive-Compulsive Disorder.

	Mean (SD)	**Median (Minimum – Maximum)**
Severity of depressive symptoms (BDI)	16,6 (11,3)	16 (0-53)
Severity of anxiety symptoms (BAI)	16,2 (11,4)	14 (0-53)
	n	**%**
With some stressful life event	580	60,5
With some traumatic event throughout life	294	30,7
Psychiatric Comorbidities Throughout Life		
- Tics	267	27,8
- Tourette's Disorder	78	8,1
- Attention Deficit Hyperactivity Disorder	137	14,3
- Separation Anxiety	268	27,9
- Major Depression	643	67,0
- Dysthymia	110	11,5
- Bipolar Disorder Type I	37	3,90
- Bipolar Disorder Type II	39	4,10
- Alcohol Dependence	75	7,80
- Cannabis/ Cocaine Addiction	24	2,50
- Panic Disorder / Agoraphobia	191	19,9
- Social phobia	328	34,2
- Specific Phobia	297	31,0
- Generalized anxiety	329	34,3
- Post-Traumatic Stress Disorder	186	19,4
- Somatization Disorder	23	2,40
- Body Dysmorphic Disorder	109	11,4
- Eating Disorders	107	11,2
- Anorexia	23	2,40
- Bulimia	22	2,30
- Periodic Eating Disorder ("Binge")	78	8,10
- Skin Picking Disorder	162	16,9
- Intermittent Explosive Disorder	74	7,40
- Kleptomania	27	2,80
- Compulsive Buying	104	10,8

SD = standard deviation; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

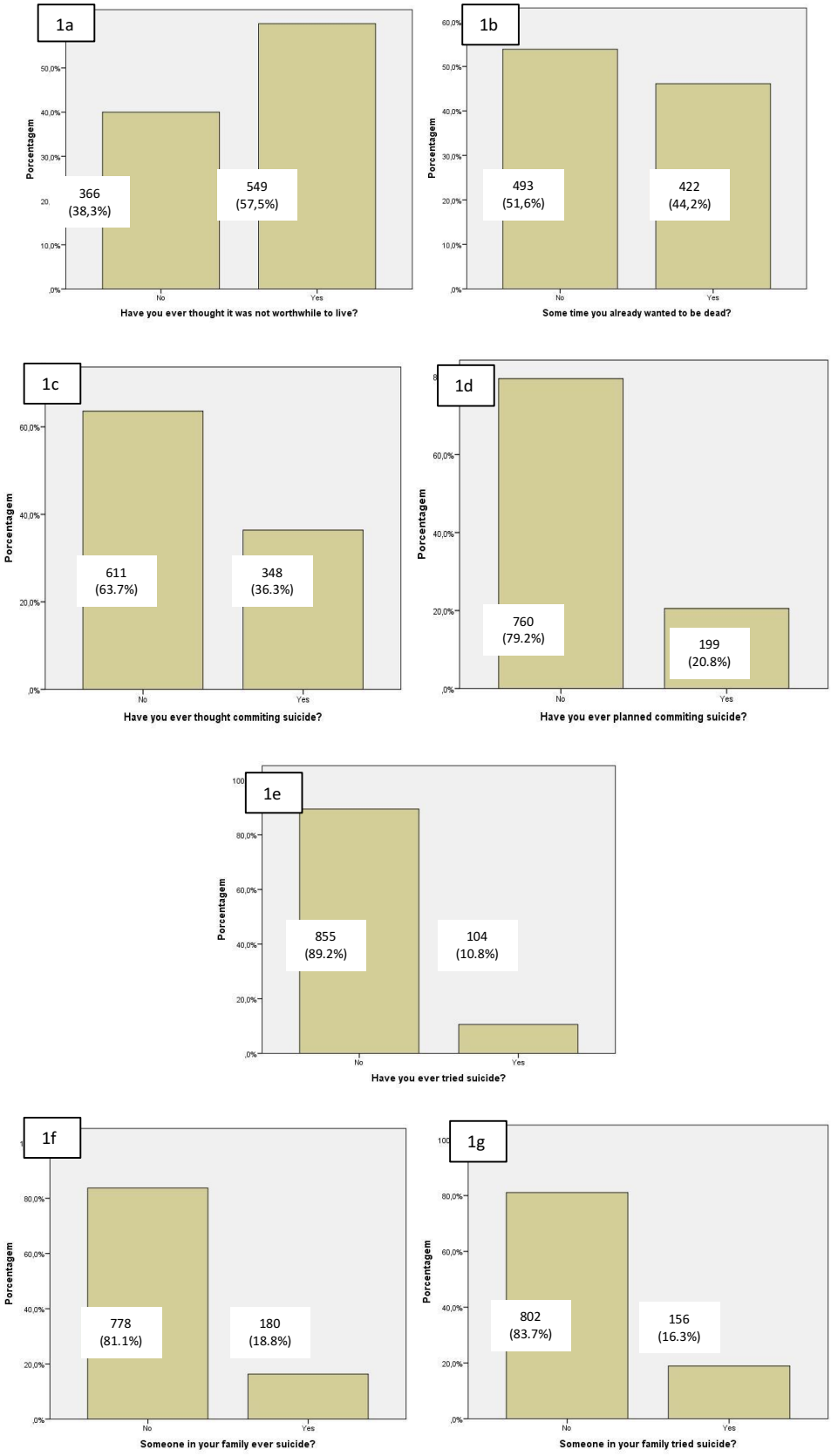

FIGURE 1– Prevalences of suicidality phenomena in the sample of 955 adults with Obsessive-Compulsive Disorder. Bar graphics from 1a to 1g shows the percentages of each of the aspects related to suicidality. Figs 1a and 1b – 915 patients with data available; Figs 1f and 1g – 958 patients with data available

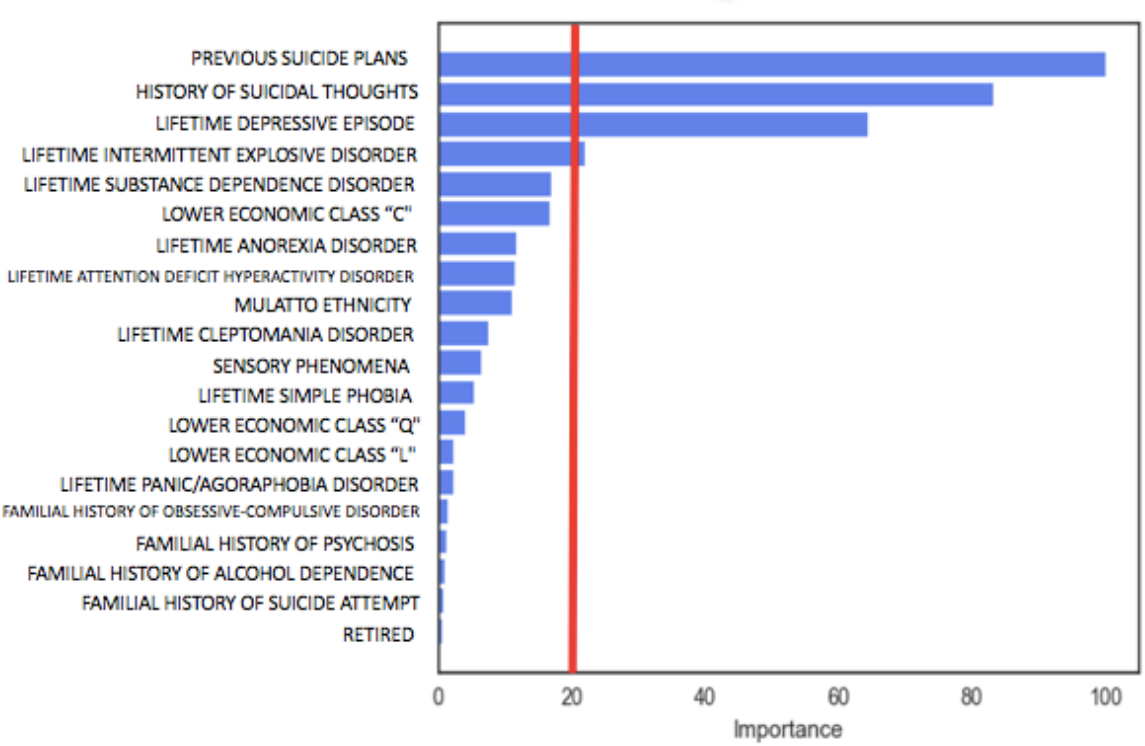

FIGURE 2 – Bar graph showing weighting factors assigned to each clinical variable by elastic net algorithm based on their relevance in distinguishing suicide attempters from non-attempters. The vertical red line "cuts" the importance weighting factors at the 20% level (considered clinically and epidemiologically relevant for this study).

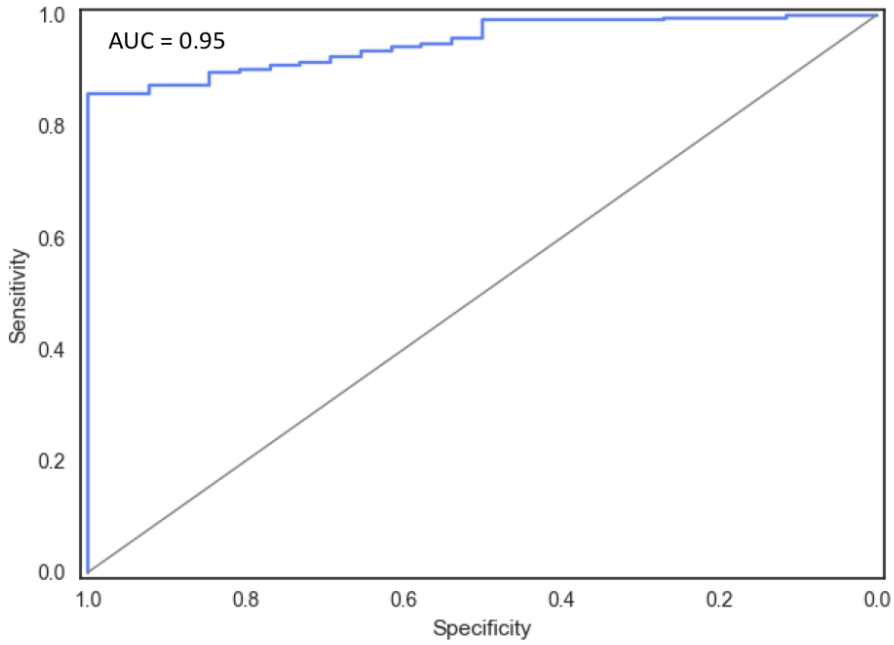

FIGURE 3 – Receiver operating characteristic curve of the predictive model

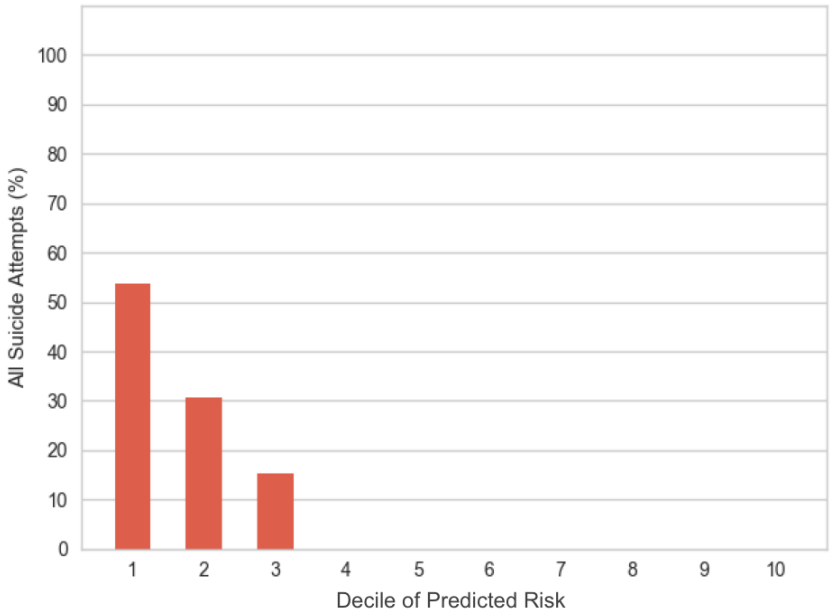

FIGURE 4 – Concentration of risk for suicide attempts among OCD patients

Supplementary Material

TABLE S1- Remained variables that entered the analysis after meticulous review of the CTOC dataset.

Remained variables that entered the analysis			
Subject number	Lifetime suicide thought	Presence of any sensory phenomena	Lifetime Somatization disorder
Age	Lifetime suicide plan	Course of OCS symptoms	Lifetime Body Dysmorphic disorder
Gender	Lifetime suicide attempt	Age at OCS onset	Lifetime Eating disorder
Body mass index	Familial history of suicide attempt	Depressive symptoms severity (BDI)	Lifetime Anorexia
Marital status	Familial history of suicide	Anxious symptoms severity (BAI)	Lifetime Bulimia
Offspring	Social Class	Insight level (BABS)	Lifetime Binge eating disorder
Live alone	DY-BOCS symptom dimension of aggressivity	Lifetime tics	Lifetime Intermittent Explosive disorder
Religion	DY-BOCS symptom dimension of sex/religion	Lifetime Tourette Syndrome	Lifetime Kleptomania
Practice religion	DY-BOCS symptom dimension of symmetry/order	Lifetime ADHD	Lifetime Compulsive Buying disorder
Occupation	DY-BOCS symptom dimension of contamination/wash	Lifetime Separation Anxiety	Lifetime “Grooming” behavior disorder (Trichotillomania + Skin Picking)
Ethnicity	DY-BOCS symptom dimension of hoarding	Lifetime Major Depression	Familial history of any psychiatric disorder
Number of studied years	DY-BOCS miscellanea symptom dimension	Lifetime Bipolar I disorder	Familial history of alcohol related disorder
Lifetime convulsion	DY-BOCS severity subscore of aggressivity dimension	Lifetime Bipolar II disorder	Familial history of other substance related disorder
Lifetime migraine	DY-BOCS severity subscore of sex/religion dimension	Lifetime Alcohol dependence disorder	Familial history of Panic/Agoraphobia disorder
Lifetime use of SSRI	DY-BOCS severity subscore of symmetry/order dimension	Lifetime canaabis dependence disorder	Familial history of Social Anxiety disorder
Lifetime use of Clomipramine	DY-BOCS severity subscore of contamination/wash dimension	Lifetime other substances dependence disorder	Familial history of Simple Phobia disorder
Lifetime use of other	DY-BOCS severity	Lifetime	Familial history of

antidepressants	subscore of hoarding dimension	Panic/Agoraphobia disorder	any Eating Disorder
Lifetime use of benzodiazepines	DY-BOCS severity subscore of miscellanea dimension	Lifetime Social Anxiety disorder	Familial history of ADHD
Lifetime use of neuroleptics	DY-BOCS severity total score	Lifetime Simple Anxiety disorder	Familial history of Major Depression
Lifetime use of mood stabilizers	Y-BOCS obsessions subscore	Lifetime PTSD	Familial history of Bipolar Disorder
Lifetime use of lithium	Y-BOCS compulsions subscore	Lifetime any trauma history	Familial history of any Psychotic Disorder
Lifetime electroconvulsive therapy	Y-BOCS total score	Lifetime General Anxiety disorder	Familial history of PTSD and Familial history of OCD

OCS – Obsessive Compulsive Symptoms; OCD = Obsessive Compulsive Disorder; DY-BOCS = Dimensional Yale-Brown Obsessive Compulsive Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; BABS = Brown Assessment of Beliefs Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; PTSD = Post Traumatic Stress Disorder; ADHD = Attention Deficit Hyperactivity Disorder.

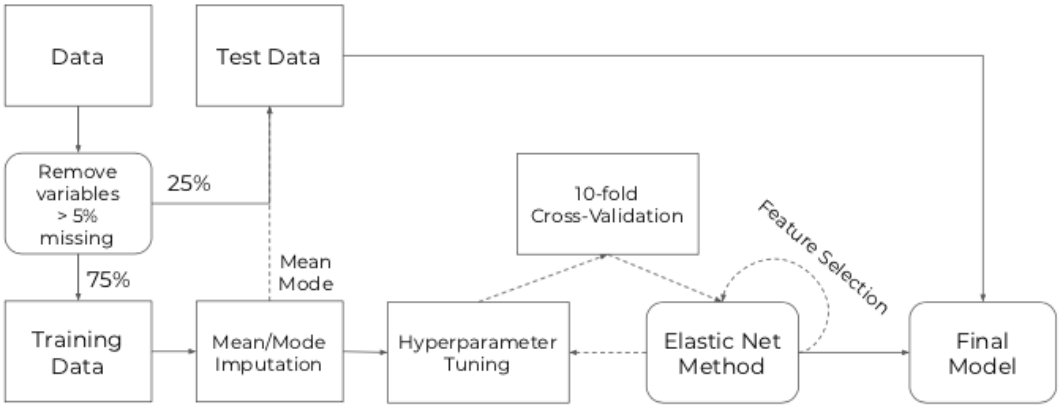

FIGURE S1 - Machine Learning protocol.

8. Conclusão

O objetivo do trabalho desenvolvido consistiu em analisar um grande banco de dados de pacientes com TOC para identificar variáveis preditores de tentativa de suicídio, utilizando um algoritmo de machine learning. Essa dissertação concluiu que, além de estarem associadas a fenômenos do espectro psicopatológico de suicidalidade, as tentativas de suicídio no TOC estão associadas a presença de comorbidades, especialmente depressão e transtorno explosivo intermitente, e não a aspectos intrínsecos a psicopatologia do transtorno.

Nossos resultados reforçam que o fenômeno da suicidalidade no TOC é mais prevalente do que na população geral, devendo ser ativamente investigado em todas as avaliações médicas. Além disso, nossos achados apontam que a suicidalidade comporta-se como uma continuum, evoluindo de pensamentos para planos e para tentativas de suicídio. A questão dos fatores de evolução para suicídio consumado permanece um tópico extremamente importante a ser investigado.

A comorbidade com depressão para exigir uma maior atenção e monitoramento intensivo em pacientes com TOC, especialmente pelas altas taxas de prevalência dessa comorbidade no TOC e pelo maior risco de suicidalidade dessa associação. Dessa forma, questões relacionadas a suicidalidade devem ser investigadas em todas as avaliações psiquiátricas, desde pensamentos, planos até tentativas de suicídio prévias e ideação suicida atual, especialmente se sintomas depressivos estão presentes.

Além disso, implementamos um algoritmo de machine learning, instrumento capaz de integrar informações de múltiplas variáveis de forma não linear para subsequentemente identificar a probabilidade ou o risco individual de um paciente com TOC ter uma tentativa de suicídio com alta acuracia. Este é o primeiro estudo que utiliza essas técnicas para identificar desfechos graves como o suicídio em pacientes com transtorno obsessivo compulsivo, mostrando ser possível construir uma ferramenta clínica útil para ser utilizada na prática clínica psiquiátrica.

A avaliação de pacientes com TOC é extremamente extensa, pois existem diversas apresentações fenomenológicas e de dimensões de sintomas. Somado a

isso, a suicidalidade também é um fenômeno complexo e multifatorial, que apresenta relações transdiagnósticas não lineares. Dessa forma, a utilização de machine learning para construir uma ferramenta clínica útil e precisa para a predição de suicidalidade em pacientes com TOC é o principal ponto forte deste estudo. O modelo de predicao gerado deve ser testado em outras amostras para corroborar os achados do presente em estudo.