UNDERSTANDING THE COMPLEX PHENOMENON OF SUICIDE: FROM RESEARCH TO CLINICAL PRACTICE, VOLUME II

EDITED BY: Domenico De Berardis, Massimo Di Giannantonio and Giovanni Martinotti

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UNDERSTANDING THE COMPLEX PHENOMENON OF SUICIDE: FROM RESEARCH TO CLINICAL PRACTICE, VOLUME II

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Meteorological Variables and Suicidal Behavior: Air Pollution and Apparent Temperature Are Associated With High-Lethality Suicide Attempts and Male Gender

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This study analyzed the impact of meteorological variables and high-lethality suicide attempts (HLSA) to assess a potential time shift of HLSA affected by climate evolution to predict the suicide attempt cases over different periods of the year. After attempting suicide, 225 subjects were admitted to the emergency ward of the IRCCS Ospedale Policlinico San Martino and later to the psychiatric unit from March 2016 to July 2018. Socio-demographic and clinical characteristics as well as the meteorological variables were collected. The Mann-Kendall test as well as redundancy and cross-correlation analyses were performed to analyze the trends, statistically correlations, and correspondence of the trends, respectively between suicidal behaviors and climatic factors. Sixty-seven (29.8%) committed a HLSA. Our findings indicate a significant association between HLSA and male gender and apparent temperature with a strong correlation of 75% with a phase shift of −1 month. Solar radiation and air pollution ($PM_{2.5}$) have a positive correlation of 65 and 32%, respectively, with a zero-time lag. Limitations include that the data are limited to a single hospital; psychological factors, or other clinical variables that could be ruled out as a trigger have not been considered. Meteorological variables may not mirror the temperature that the patient is exposed to due to the air conditioning systems. Exploring those environmental factors associated with HLSA in a more detailed manner could lead to early intervention and prevention strategies for such distressing admissions.

Keywords: suicide attempt, environmental parameters, apparent temperature, air pollution, hospitalization, suicide, suicidal behavior

INTRODUCTION

Suicide is a preventable public health issue causing more than 800.000 annual deaths globally; it is the second leading cause of death among 15- to 29-years-olds worldwide (1).

Climate changes based on extreme temperatures, floods, drought, tornadoes, hurricanes, and wildfire can lead distress symptoms, suicidal behaviors, and psychiatric disorders in the general population. Global warming fits into this context with possible negative influence of environmental parameters on mental health and psychiatric disorders through both indirect and direct factors (2, 3). Changes in temperature, especially during the transition between winter and spring, can have remarkable consequences on suicidal behavior trends. Mental disorders and rates of attempted and complete suicidal behaviors have been studied for years to understand their trends and triggers and identify the influence of external risk factors such as social, economic, and environmental factors (4–6). In a multicenter study, a strong association was reported between climate effects vs. economic factors on suicidal behavior. The authors found that suicidality in Europe followed the climate/temperature change, which was from south to north-east (6). On the contrary, it has been hypothesized that higher lithium levels in drinking water may be associated with a reduced risk of suicidal behaviors in the general population (7–9).

Therefore, some research suggested that environmental conditions might be potentially important trigger factors. Specifically regarding meteorological variables, a positive correlation between seasonality (10–14) or sunlight exposure, also called photoperiod (15, 16), or latitude (17), and suicidal behaviors has been shown. Recently, a significant association between hours of sunshine and violent completed suicides (18, 19) or high-lethality suicide attempts (HLSA) (20, 21) was reported. These findings were not confirmed by Veisani et al. (22) who showed seasonal trends in spring and autumn of suicides by violent methods and spring and summer for what concerns non-violent suicides.

The mechanisms underlying this association are still unclear and need further investigation. Therefore, other environmental variables such as increased ambient temperature or air pollution could be implicated in this complex phenomenon. A potential role of ambient or apparent temperature on suicidal behaviors has been studied with controversial results (15, 16, 23–28). Several data, however, showed that a 26.6–60% of variation in suicidal behaviors could be explained by temperature fluctuations (29–31) but not with sunlight exposure, especially in completed suicide (16). Some researchers found a relationship between the warmest temperatures and suicide rates, mostly involving older subjects (32) and men relative to females (33) while others (34) found no association between weather variables and suicides in Colombia highlighting the absence of association in a tropical country where seasonal changes are not marked.

Among the environmental factors, air pollution and ozone could also have a detrimental impact on mental health. For example, Bernardini et al. (35) considered daily admissions to psychiatric emergency services in two Italian hospitals over a period of 2 years and highlighted that exposures to ozone may be associated with increased psychiatric admissions. Recently, several studies reported that higher levels of particulate matters ($PM_{2.5}$ and PM_{10}) were linked to an increase in suicidal behaviors (attempts and deaths) worldwide (36–44), demonstrating both short- and long-term effects. Nevertheless, other studies report the absence of this association (34, 45). Although the specific mechanisms linking air pollution and suicide are uncertain, a growing body of research does suggest that the link is plausible.

Genoa has a population of about 600.000 inhabitants with an area of 240 km^2. Its territory is located in the Liguria Region, and it has typically a Mediterranean climate with relatively temperate winters (mean temperature 8°C in January) and hot summers (mean temperature 24°C in July). Rains are concentrated in autumn (annual mean precipitation 1,100–1,300 mm) (46). Genoa territory is ringed to the north by rugged mountains with wide gaps between them, which channel and control the movement of air masses. Therefore, despite the mild climate, these morphological characteristics combined with the fact that Genoa is located at the apex of the Ligurian sea on the northern side of one of the most active cyclogenetic areas in Europe, lead to frequent periods of unstable weather (47) that could affect the mental health of the population.

In recent decades, several climate changes have been reported in Genoa. For example, Faccini et al. (46) analyzed Genoa weather data between 1833 and 2014 and found that the annual mean temperature and rainfall rate (the ratio of annual rainfall and the number of rainy days) had a statistically positive trend (+0.15°C yr^{-1} and +0.28 mm yr^{-1}, respectively) while rainy days had a negative trend (−0.43 d yr^{-1}) suggesting a shift toward more extreme weather.

Data from the Italian National Institute of Statistics (ISTAT; www.istat.it) suggested that the province of Genoa has attempted and completed suicide rates of 17.2 and 10.0 cases per 100.000 inhabitants, respectively. On the contrary, the city of Genoa had a mean of 23 cases per year of death by suicide from 2007–2017; the victims were mostly males (71%).

To the best of our knowledge, no Italian study has yet reported data about meteorological parameters (including temperature and air pollution) and HLSA. Therefore, the aim of this study was to analyze the impact of several meteorological parameters such as air temperature, rain, solar radiation, and air pollutants, recorded by different measurement stations in Genoa (north-west Italy), on suicidal behaviors (especially HLSA). Second, we assessed a potential time shift of HLSA in a Mediterranean city characterized by a mild climate but affected by climate evolution such as the increase of flood events and temperature to predict the suicide attempt cases during the different periods of the year.

MATERIALS AND METHODS

Sample

We recruited individuals consecutively admitted for a suicide attempt (225 cases) and referred to the Emergency Department of IRCCS Ospedale Policlinico San Martino (Genoa) over a period of 2 years (from March 2016 to July 2018). This hospital works as for the whole Liguria region and the northwestern Italian area. It is the main hospital in Genoa and it is located in the eastern part of the city with a catchment area that extends to the neighboring municipalities. After clinical and medical evaluation, these individuals were admitted to the Psychiatric Unit.

The inclusion criteria were: (a) being hospitalized in an emergency psychiatric ward for a suicide attempt; (b) age > 18 years; and (c) the willingness to participate in the study by signing a written informed consent. The exclusion criteria were: (I) pregnancy or having just given birth; (II) having a positive history of acute neurological injuries such as neurodegenerative illnesses, intellectual disability, and loss of consciousness related to the presence of severe neurological conditions; (III) the assumption of melatonergic or lipid-lowering agents; (IV) the presence of acute or severe medical condition; and (V) the refusal or inability to provide a valid consent prior to participation in the study.

All participants received a detailed explanation of the study design and written informed consent was obtained from all respondents according to the guidelines provided in the current version of the Declaration of Helsinki. The study design was approved by the local Ethical Review Board.

Assessment and Procedures

Socio-demographic and clinical characteristics were investigated through the standardized clinical chart and lifetime computerized medical record used in our Psychiatric Unit. Age, gender, marital status, occupation, education level, suicide method, and psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria (48) at discharge were recorded and grouped as in previous research (49, 50). All available information have been cross-referred and revised by two senior psychiatrists (MA and GS).

Silverman's operative definition of "suicide attempt" was used in the present study: a kind of suicide-related behavior classified as a suicidal act and characterized by self-inflicted, potentially injurious behavior with the non-fatal outcome for which there is evidence – either explicit or implicit – of the intent to die (51). Moreover, our definition involved the presence of a lethal intent that may be of varying intensity but needs to be present in the decision to carry out the suicidal act (52).

The cases of suicide attempts were divided into two subgroups based on the severity of the suicidal behaviors. The term "suicidal lethality" has not yet been defined comprehensively and, in our study, we adopted the concept of lethality as defined by Shneidman's (53) and Joiner's (54) criteria even used in recently published reports (20, 21, 55, 56). Methods of suicide attempt were dichotomized in terms of lethality. Therefore, a HLSA was defined as a suicide attempt that warranted hospitalization for at least 24 h and either treatment in a specialized unit (including intensive care unit, hyperbaric unit, or burn unit), surgery under general anesthesia, or extensive medical treatment (beyond gastric lavage, activated charcoal, or routine neurological observations), including antidotes for drug overdoses, telemetry, or repeated tests or investigations. Conversely, a low-lethality suicide attempt (LLSA) was defined as a suicide attempt that did not meet these criteria (20, 21, 55, 56).

The environmental parameters included air mean temperature (T, °C), precipitation (P, mm), wind speed (WS, m sec^{-1}), and relative humidity (RH, %) data recorded by the Meteorological Observatory of the University of Genoa (MO-UNI). Solar radiation (SR, J cm^{-2}) and atmospheric pressure

(AP, hPa) data were recorded by the weather station of the Regional Agency for the Protection of the Ligurian Environment (W-ARPAL). Particulate matter with diameter $\leq 10\,\mu m$ (PM$_{10}$) and with diameter $\leq 2.5\,\mu m$ (PM$_{2.5}$; $\mu g\,m^{-3}$) as well as CO (mg m^{-3}), NO$_2$ ($\mu g\,m^{-3}$), and benzene ($\mu g\,m^{-3}$) were measured via an air pollution detection station of ARPAL (P-ARPAL) (Genoa – Latitude: 44°24′40″ N; Longitude: 008°55′58″ E).

Statistical Analysis

Starting from data recorded by the weather station, the apparent temperature (AT) was calculated according to the following formula:

$$AT = T + 0.33 * Wp - 0.70 * WS - 4.00 \qquad (1)$$

where T is the air temperature, WS is the wind speed, and Wp is the water vapor pressure, calculated as following:

$$Wp = RH/100 * 6.105 * exp(17.27 * T/(237.7 + T)) \qquad (2)$$

where RH is the relative humidity.

Distributions of monthly cases of attempted suicide and environmental parameters were statistically tested to find eventual significant trend: the Mann-Kendall trend test with a p-value = 0.05, was applied by the statistical software ProUCL (v. 5.1; U.S. Environmental Protection Agency).

Redundancy analysis (RDA) (57) was applied to data on suicide attempts (HLSA, LLSA, and total cases). Environmental parameters (T, P, WS, RH, SR, AP, PM$_{10}$, PM$_{2.5}$, CO, NO$_2$, benzene) were used to find potential statistically correlations. RDA investigates the presence of relationships between the explanatory variables (meteorological parameters) and the response variables (the lethality of suicide attempts and gender) of a data matrix. Given the diversity between the ranges of the considered parameters, the data were standardized before the analysis. RDA was performed using the Brodgar software (Highland Statistics Ltd., v. 2.7.5, 2017).

The cross-correlation analysis was applied to the number of cases (total cases, HLSA, and LLSA) and to the environmental parameters that in the RDA showed a correlation with suicide attempts. The cross-correlation is a mathematical function that allows the comparison of two series by measuring the level of similarity and the time lag between them. To facilitate the interpretation of the cross-correlation function, the systems are normalized and ranges between −1 and +1. If the value of the normalized cross-correlation is equal to 1 it means that the two series are identical (100% positive correlation). If the series are not similar, then it tends to approach 0. If a negative correlation is found, then they are anticorrelated and the value is −1 (100% negative correlation). The time to which the maximum value of the cross-correlation function represents the time lag between the two series. Cross-correlation was performed using PITSA software package (58).

RESULTS

Characterization of the Total Sample

We included 225 subjects admitted for suicide attempt, of which 29.8% ($N = 67$) presented a HLSA and 70.2% ($N = 158$) a LLSA. One hundred seventy five (75.6%) were females, half of the individuals was unmarried, and about a third was actively working. Distributions of the different diagnoses did not show statistically significant trends, except for "other diagnoses", which decreased trend. The greatest number of cases are concentrated in the spring-summer months for bipolar disorder. The most commonly used method of suicide attempts was drug intoxication. Further details about sociodemographic and clinical characteristics are summarized in **Table 1**.

Characteristics of Environmental Parameters

All environmental parameters showed typical values and variations in the Mediterranean climate that characterizes the Genoa area. However, the beginning of 2018 was characterized by some peculiarities from the meteorological point of view: a relatively warmer January (mean temperature of 11.2°C in January 2018 compared to 7.5°C in January 2017), the shift of the minimum winter temperature in February, and a spring with high cumulative precipitation, especially in March 2018 (178.8 mm).

Distributions of all the environmental parameters analyzed are reported in **Figure 1**. Only temperature and solar radiation show a clear seasonality in the period typical of the mean latitude.

Among the environmental parameters, only CO, PM_{10}, and $PM_{2.5}$ have statistically significant trends and all three have decreasing trends.

Influence of Environmental Parameters

Several tests with RDA, combining suicide lethality and gender (response variables) with the environmental parameters (explanatory variables), were made.

The **Figure 2** shows the results of RDA carried out with HLSA, LLSA, gender, and environmental parameters. These results are obtained by using AT instead of the individual parameters WS, T, HP, and WP to better summarize the results. Furthermore, AT has been proven to characterize the physiological experience better than just the temperature or the other parameters alone [Niu et al. (27)]. In our case, SR, AT, and $PM_{2.5}$ are very closely related to the HLSA and male subjects while LLSA and females are correlated to NO_2 concentration and precipitation. Therefore, most findings demonstrate how SR and AT can influence the distribution of cases.

Following the RDA results, we applied cross-correlation analysis between pairs of parameters to verify the degree of relationship between an environmental parameter and one relating to suicide attempts and highlight the time lag between the two; hence, there is a delay in response in patients following the environmental stimulus.

Considering HLSA and AT (**Figure 3**), a positive and strong correlation of 75% was found with a phase shift of −1 month, i.e., suicide attempts peak with HLSA 1 month before reaching the

TABLE 1 | Sociodemographic and clinical characteristics of the total sample ($N = 225$).

Gender (female), N (%)	170 (75.6)
Age, N (%)	
<40 years	82 (36.4)
40–60 years	72 (32.0)
>60 years	71 (31.6)
Education level, N (%):	
Primary school (1–5 years of school)	9 (4.0)
Secondary school (6–8 years of school)	66 (29.3)
High school (9–13 years of school)	112 (49.8)
Graduation and post (>14 years of school)	38 (16.9)
Marital status, N (%)	
Unmarried	109 (48.4)
Married	43 (19.1)
Separated/divorced	47 (20.9)
Widowed	26 (11.6)
Working status, N (%)	
Unemployed	150 (66.7)
Employed	75 (33.3)
Primary diagnosis, N (%):	
Bipolar and related disorders	72 (32.0)
Schizophrenia and related disorders	21 (9.3)
Depressive disorders	72 (32.0)
Others	60 (26.7)
Lethality of suicide attempt, N (%)	
High-lethality suicide attempt	67 (29.8)
Low-lethality suicide-attempt	158 (70.2)
Modality of suicide attempt, N (%)	
Drug intoxication	147 (65.3)
Cuts	35 (15.6)
Defenestration	17 (7.6)
Weapon	1 (0.4)
Stabbing	3 (1.3)
Burn/gas/caustic	14 (6.2)
Strangling	8 (3.6)

AT maximum in the phase of AT increase. Considering HLSA and solar radiation, a positive correlation of 65% is obtained with a zero-time lag: therefore, the monthly increase in solar radiation corresponds to a tight monthly increase in cases of HLSA and a decrease in light corresponds to a decrease in violent suicide attempts. Between HLSA and $PM_{2.5}$, there is a 32% of correlation without time shift. Therefore, the increase in $PM_{2.5}$ corresponds with an increase in suicide attempts albeit with a relatively low degree of correlation.

DISCUSSION

To our knowledge, this is the first Italian study investigating the correlation between HLSA and several meteorological variables. We found a significant association between three weather parameters (apparent temperature, solar radiation and $PM_{2.5}$)

FIGURE 1 | Monthly distribution of **(A)** solar radiation (pale yellow bars) and temperature (red line); **(B)** precipitation (gray bars) and wind speed (blue line); **(C)** atmospheric pressure (green bars) and relative humidity (black line); **(D)** particulate matter concentrations (PM_{10}-dark green line and $PM_{2.5}$-orange line); **(E)** CO (gray line) and NO_2 (violet line) concentrations; **(F)** benzene concentrations (dark blue line).
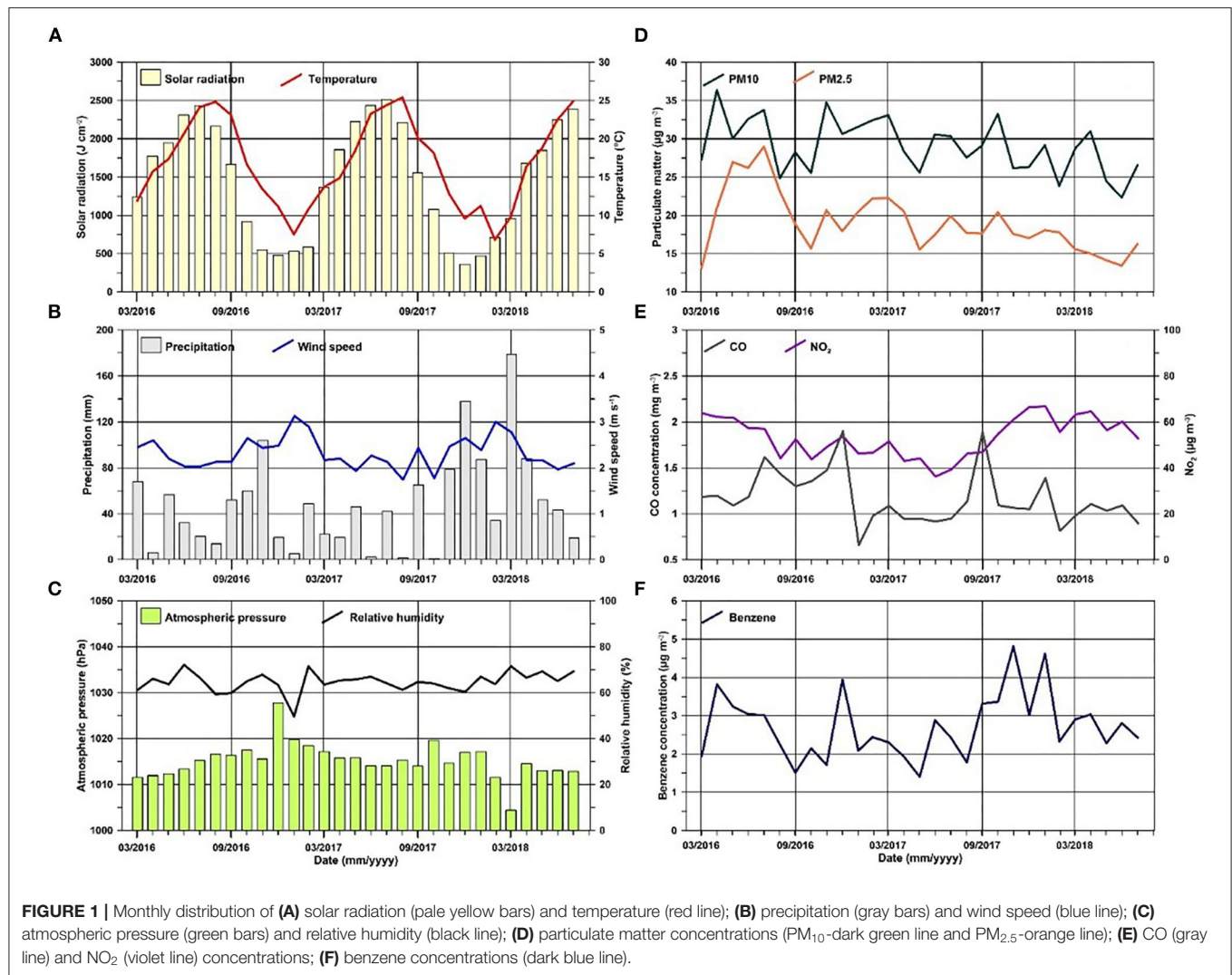
and both HLSA and male gender. This is confirmed by Dumenčić et al. (33) that demonstrated, in a sample of 478 suicide attempts in Croatia over 10 years, a significant influence of temperature on males more than females.

It has been widely reported in literature that these variables influence not only the mental health but also suicidal behaviors. Nowadays, with global warming and a greater focus on climate issues, several efforts have been made in this direction. A recent meta-analysis (16) demonstrated a significant positive association between temperature rises and incidence of suicidal behaviors, while the potential role of solar radiation is more controversial (59), confirmed previously (15, 16, 23–28, 60, 61). The innovative aspect of our study was the significant association of meteorological variables with HLSA.

As observed by Postolache et al. (62), several neurotransmitters (e.g., dopamine, norepinephrine, and serotonin) affect both mood and thermoregulation. Specifically, serotonin is a neurotransmitter regulating emotion that is sensitive to weather variability and light exposure, so springtime

changes in expression might be associated with increased suicidal behavior (63, 64). Regarding biochemical mechanisms underlying this phenomenon, it has been proposed that warming temperatures enhance the responsiveness of $5\text{-}HT_{2A}$ receptors of the central nervous system (CNS) (65). The activation of $5\text{-}HT_{2A}$ receptors increases the sympathetic outflow to brown adipose tissue (BAT) (66) and hyperactivity of BAT impairs heat tolerance, and it could enhance the risk of suicidal behaviors. As proposed by Helama et al. (29): a potential association exists between psychiatric condition (i.e., anxiety and/or depressive symptomatology or disorders leading to suicidal behaviors) and altered transmission in the CNS projecting from BAT through the hypothalamus to the periaqueductal gray areas. Regarding structural brain findings, some authors have recently reported that individuals who commit HLSA could show larger pre-frontal cortex, caudate, and insula volumes compared to LLSA and individuals without suicidal behaviors. Furthermore, suicide attempters with familiarity for suicidal behavior reported smaller volumes in temporal regions, dorso-lateral pre-frontal
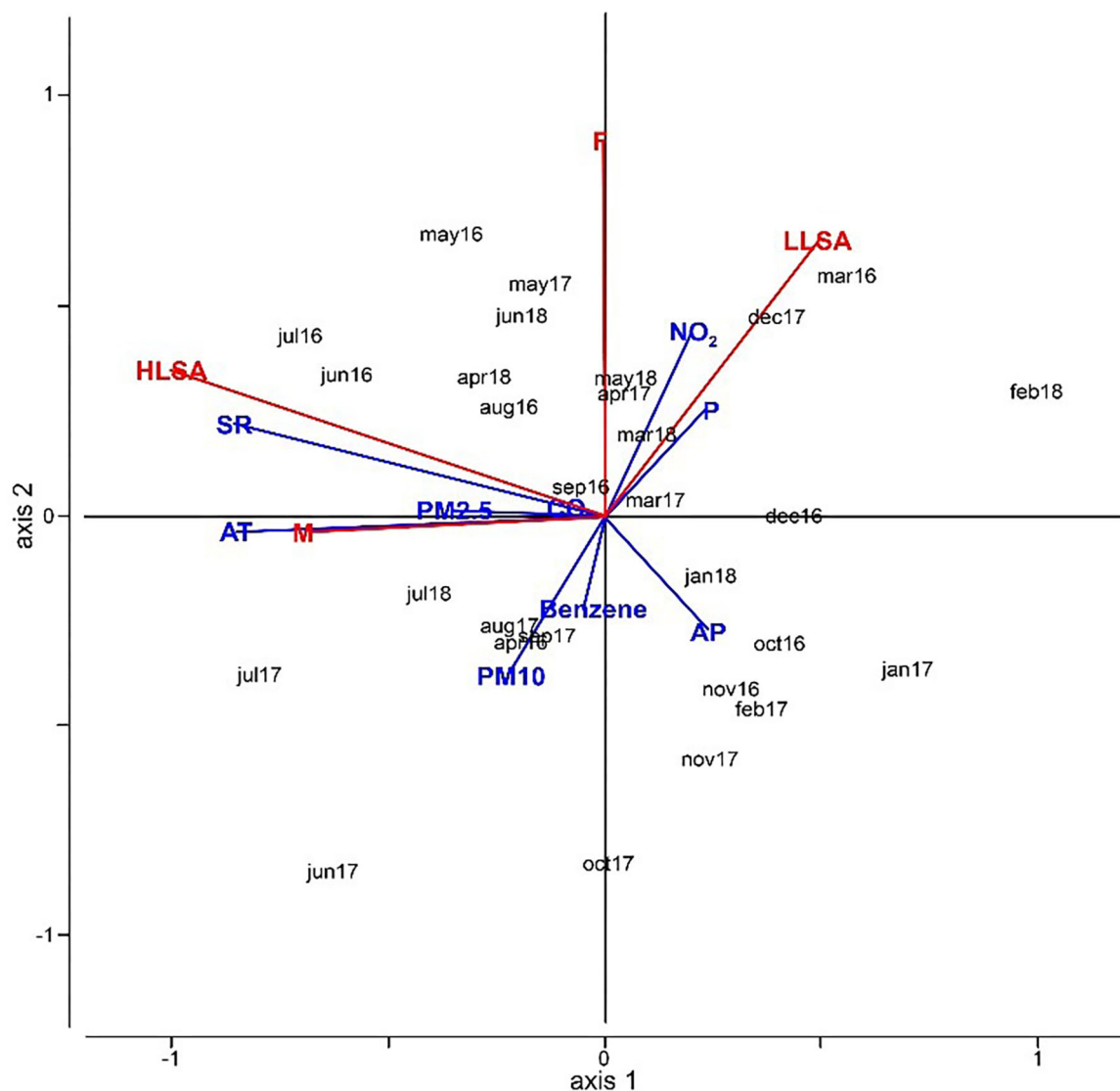
FIGURE 2 | RDA analysis combining suicide lethality and gender (response variables) with environmental parameters. The sum of all canonical eigenvalues is 0.42.

cortex, and putamen. These cerebral structures play a role in cognitive process like decision making, inhibition, emotional dysregulation, and risk perception, and when compromised because of several factors (i.e., heat, climate change, sleep-deficiency), they could lead to more impulsive decisions and acts (67). Lastly, based on the assumption that similar areas of the insular cortex are activated during recall of feelings and sensation of pain and temperature (68), we assumed a link between the perception of significant heat and emotional correlation of discomfort, which could lead to suicidal behaviors in subjects at risk. Maes et al. (69) found a trend in L-tryptophan levels inversely related to the seasonal variation of violent suicides in the Belgian population. Furthermore, a correlation between peripheral dysfunctions of serotoninergic transmission, assessing metabolic, such as cholesterol and triglycerides, and hematologic,

such as platelet-lymphocyte ratio and mean platelet volume, parameters and HLSA was demonstrated by recent findings (55, 56). A very recent review on the complex phenomenon of suicidal behaviors, conducted by Mann et al. (67) confirmed these findings and concluded that there is deficient serotonin release in HLSA. This is not likely due to serotonin biosynthesis, but seems to be associated with up-regulated serotonin$_{1A}$ (5-HT$_{1A}$) auto-receptors located on serotonin neuron cell bodies and proximal dendrites (70) or postsynaptic cortical serotonin$_{2A}$ receptors (5-HT$_{2A}$) that correlate with lifetime aggression severity (71). Serotonin dysfunction is more prominent in high-lethality suicidal behavior.

In our study, we found a positive correlation between HLSA and PM$_{2.5}$. Recently, several studies confirmed our findings, reporting short- and long-term effects of higher levels of PM$_{2.5}$
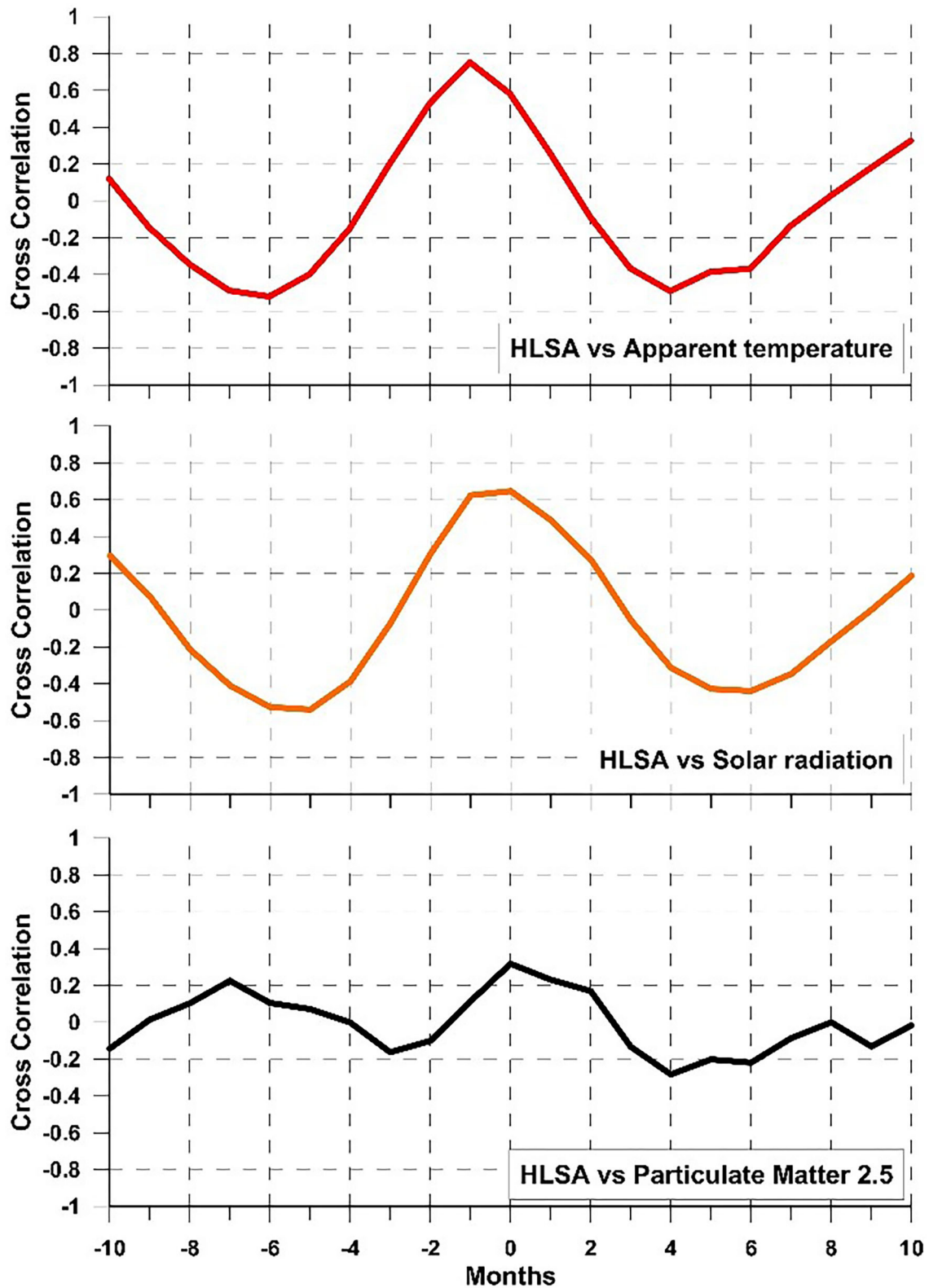
FIGURE 3 | Cross-correlation results: HLSA *vs.* apparent temperature (red); HLSA vs. solar radiation (orange); HLSA vs. PM₂.₅ (black).

and PM_{10} on suicidal behaviors, including attempted and completed suicides (36–44). However, the concentration and composition of air pollutants and population-level features (i.e., age and race) vary across countries.

The possible biological explanation of the observed association between air pollution and HLSA has not been clarified. A link between suicidal behaviors and inflammation was recently reported (6). Therefore, it is hypothesized that $PM_{2.5}$ and PM_{10} could induce systematic inflammation/oxidative stress or impair hippocampal neurogenesis and neurotrophic factor expression, leading pollutants to play a causative role in the occurrence of psychological problems or suicide attempts. So, $PM_{2.5}$ enters the olfactory bulb and reaches the basis nuclei (substantia nigra and striatum), causing a release of pro-inflammatory factors and cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1beta (IL-1β). Besides, air pollution causes a chronic activation of brain capillaries, astroglia, and, particularly, microglia, leading to inflammation and oxidative stress (72). Recently, Baharikhoob and Kolla (73) proposed the following relationship between microglial dysregulation and suicidal behaviors: pro-inflammatory cytokines (i.e., IL-1β, TNF-α, interferon-gamma (IFN-γ), and IL-6) would provoke neurotoxicity by increased glutamate (dependent on loss of inhibition in glutamatergic neurons). This hypothesis is confirmed by literature evidence, in which a significant correlation between higher IL-6 levels and suicide attempters' impulsivity was demonstrated (74). Furthermore, a recent study reported that high IL-6, IL-10, and C-reactive protein levels and activated microglia-related alterations were associated with greater suicidal ideation severity (75). Therefore, neuroinflammation seems to be one of the most involved factors in the pathogenesis of suicidal behavior and neurotoxicity and disrupted blood-brain barrier leads to impulsive, aggressive, and self-destructive behaviors.

Our study has several limitations. First, our data are limited to a single hospital. Second, psychological factors (e.g., life events, no compliance to treatment, and poor social support) that could be ruled out as triggers have not been considered. Furthermore, the effect of other clinical variables has not been investigated. Therefore, the generalization from our results should be made with caution. No structured interviews were performed to formulate psychiatric diagnoses and evaluate the lethality of suicide attempts (such as the Columbia Suicide Severity Rating scale). We preferred to rely upon Shneidman's and Joiner's definitions of lethality, although we acknowledge that using a specific instrument might provide adjunctive relevant data. Lastly, meteorological variables measured outdoor might not mirror the temperature the patient is exposed to, due to the increasing number of air conditioning systems. This might be responsible for the well-known ecological regression bias.

In conclusion, we found that apparent temperature, solar radiation and $PM_{2.5}$ exposures were associated with an increased risk of HLSA in the Italian population. Our study extended prior results of an acute effect of seasonality and photoperiod on HLSA. Based on our findings, an increase in HLSA is expected within a month after a heatwave. Therefore, clinicians should monitor strictly high-risk subjects when hot temperatures occur and between the seasons (i.e., from spring to summer), playing a key role in predicting and preventing risky behaviors based on the knowledge of climatic variables. Furthermore, the correlation between multiple suicide attempters and climatic variables throughout the year is a crucial issue in the field of suicidology, assuming that a history of multiple attempters could be more vulnerable to heat stress. It is also necessary to evaluate the change in concentrations of air pollutants, as well as the degree of health damage, especially in areas of the world where air pollution is highest, and search potential biochemical mediators that could explain the greater influence of climatic and environmental factors in males than females.

Future prospective or cohort studies with a larger sample, exploring in a detailed manner these environmental factors, are warranted to further test the topic and clarify the impact of climatic factors on HLSA to reduce or prevent health damage, implementing early intervention for mental health promotion, especially focusing on vulnerable at-risk populations. Therefore, for suicidologists and their organizations, the potential rise in suicides is troubling and should lead to our support for those arguing for climate change policies. The organizations involved in suicide prevention should make public position statements, lending support to the growing demand for action on climate change (76).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, upon request.

ETHICS STATEMENT

The study was reviewed and approved by the Ethics Committee (IRCCS Ospedale Policlinico San Martino). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AAg and LC designed the study and wrote the first draft of paper. AE and AAm participated to the first revision of original article and revised the English language. GG, AC, and EM collected the data and managed the literature searches. DS, LC, and GF undertook the statistical analyses and wrote the result section. GS, MA, and MC supervised the study design, search strategy reviewed, and edited the original draft. All Authors contributed to and approved the final version of the manuscript.

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Depression and Suicidal Ideation in a Sample of Malaysian Healthcare Workers: A Preliminary Study During the COVID-19 Pandemic

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Objective: The burden of suicidal behavior is anticipated to increase as a sequela of the COVID-19 pandemic. However, there is limited evidence on suicidal behavior among healthcare workers, an at-risk population. Our study aimed to investigate suicidal ideation in terms of the rate and associated factors in a sample of Malaysian healthcare workers during the early-phase of the COVID-19 pandemic.

Methods: A subpopulation analysis ($N = 171$) was conducted within a larger, nation-wide cross-sectional study of Malaysian healthcare worker psychological distress from March 18–21, 2020. Current suicidal ideation was measured with item 9 of the Patient Health Questionnaire-9 (PHQ-9). The following independent variables were assessed: socio-demographic profile, occupation and service-related factors, health-anxiety (Health Anxiety Inventory, HAI), lifetime anxiety disorder and severity of depression (PHQ-9).

Results: The proportion of healthcare workers with current suicidal ideation (19/171) and clinical depression (17/171) were 11.1 and 9.9%, respectively. Multivariable analysis showed that clinical depression was the most significant factor associated with current suicidal ideation ($p < 0.001$, OR = 55.983, 95% CI = 9.015–347.671) followed by mild (subthreshold) depression ($p = 0.001$, OR = 115.984, 95% CI = 2.977–85.804). Service duration of more than 10 years was associated with significantly less suicidal ideation ($p = 0.049$, OR = 0.072, 95% CI = 0.005–0.993).

Conclusions: Depression (subthreshold and especially within the clinical range) and early-career status (<10 years in service) may be target areas of early intervention for reduction of suicidal ideation amongst healthcare workers who have served during the COVID-19 pandemic. Further research is warranted to elucidate specific occupational stressors related to COVID-19 work conditions to tailor appropriate suicide preventive strategies in this population.

Keywords: suicidal ideation, health-care workers, early phase, COVID-19 pandemic, Malaysia

INTRODUCTION

Suicidal behavior has been projected to increase globally (1) as a sequela of the anticipated mental health crisis stemming for the COVID-19 pandemic. The mental health needs of frontline healthcare workers (HCWs) have been highlighted as a global priority (2). Medical-related occupational groups have been established as an at-risk population for suicide. A pre-pandemic meta-analysis showed that physicians who are female, United States-based, and in disciplines such as anesthesia, psychiatry, general practice, and general surgery may have higher suicide risk compared to the general population (3).

The myriad stressors faced by HCWs worldwide in their personal and professional spheres are currently compounded by unprecedented challenges due to the COVID-19 pandemic. A meta-analysis showed that the mental health impact of the COVID-19 pandemic on healthcare workers was more severe compared to the general population (4). Significant levels of stress, depression, anxiety, psychological distress, post-traumatic stress symptoms, poor sleep quality, and insomnia have been demonstrated in this frontline population. Majority (92%) of the meta-analyzed studies were conducted in China, with the rest from Iran, Italy, Singapore, and Vietnam (4). Spanish and American healthcare workers' high levels of psychological distress were significantly correlated with fears of being infected or infecting others, especially family and friends, and clinical challenges i.e., perceived uncertainty/lack of control and inadequacy of PPE (5, 6).

Nepalese healthcare workers who felt stigmatized, had a history of receiving psychiatric medication, and reported insufficient preventive measures at work seemed to be at higher risk of experiencing mental health problems (7). Among a sample of Malaysian HCWs, depression, stress, and anxiety were shown to be significantly associated with being unmarried, experiencing fear and uncertainties surrounding COVID-19 infection risk via work-exposure to COVID-19 patients, and being in communities with high transmission rates (8). Potential psychological buffers for HCWs include perceived social recognition (5), perceived peer support and having more than three children (8).

Published systematic research in terms of the pandemic's effect specific to suicidal behavior (ideation, non-fatal and fatal attempt) in this high-risk population (HCWs) is limited. Anecdotal reports have linked the recent suicide deaths amongst frontline HCWs with the collective experience of fear, hopelessness, helplessness, and moral injury in the line of duty during the COVID-19 pandemic (3, 4). These authors speculated that multiple factors contributed to HCW suicide, such as social isolation from support networks and the experience of vicarious traumatization when caring for dying patients. In addition, the perceived risk of infection and transmission of the SARS-COV, compounded by uncertainties surrounding equitable allocation of personal protective equipment (PPE), were postulated to have increased HCW suicide risk. On the contrary, an online survey of 834 HCWs and 2,554 general population participants in Bangladesh did not show any significant association between patient care or PPE-related factors with suicidal behavior (ideation, intent, plan, and attempt) (9). Anxiety is a known

risk factor for suicidal behavior (10). The potential impact of health anxiety on the behavioral response to COVID-19 has been highlighted by researchers (11). Therefore, the relationship between suicidal behavior and health anxiety pertaining to HCWs' fear of contracting SARS-CoV-2 is an important area for further research. In terms of gender, female HCWs seemed to be at higher risk of suicidal behavior compared to their male counterparts during this current pandemic (9).

With regards to the spectrum of suicidal behavior, it is important to identify risk factors of suicidal ideation which can be distinct from predictors of more severe spectrum of suicidal behaviors (planned, non-fatal, and fatal attempts) (12–15). Though suicide is a devastating fatal outcome, it is a rare occurrence relative to suicidal ideation or suicide attempts (3, 16). A meta-analysis showed that 17% of physicians experienced suicidal ideation while one percent had previously attempted suicide. Identification of HCWs with suicidal ideation is clinically relevant for implementation of early intervention and prevention of suicide (15). The evidence-base is currently mixed on whether there is a definite increase in suicidal behavior around the world as a sequela of the current pandemic (17). A significant knowledge gap exists in terms of the burden of suicidal ideation and its related factors amongst HCWs within the context of the COVID-19 pandemic, especially in low and middle income (LMIC) countries.

Therefore, the objectives of this study are to investigate the rate of suicidal ideation and the association between suicidal ideation with the following factors: socio-demographic profile, depression, health anxiety and lifetime anxiety disorder, and occupation and service-related factors, amongst a heterogenous and culturally diverse sample of Malaysian HCWs during the early phase of the COVID-19 pandemic.

METHOD

Study Design, Setting and Population

This paper is based on a subpopulation analysis of 171 consecutive participants whereby data on depression and suicidal ideation were available from a larger ($N = 763$) nationwide, cross-sectional study on psychological distress among Malaysian HCWs; during the early phase of the COVID-19 pandemic. Ethics approval was obtained from the Medical Research and Ethics Committee, MREC: NMRR-20-1036-53864 and The National University of Malaysia Ethics Committee, UKM: FF 2020-130). According to the Malaysian Ministry of Health (MOH), frontliners are defined in the context of the COVID-19 pandemic as "individuals with high risks of contracting and transmitting Covid-19 infection i.e., those who are directly exposed to an infected individual, an individual at high risk of being infected, a patient sample or an environment that has the potential to be the source of the infection." Healthcare workers (HCWs) are categorized by the Malaysian health ministry as frontline essential workers during the pandemic (18). This population comprises of clinicians who are involved directly in providing medical treatment to patients as well as HCWs who are involved in patient care in healthcare facilities i.e., handling of patients' specimens, public health control on the

field etc. Thus, our study's operational definition of a health care worker in the frontline of the COVID-19 pandemic includes physicians and clinical medical trainees/students, dental practitioners, pharmaceutical officers, science officers, nurses, occupational/physiotherapists, paramedics, X-ray technicians, medical laboratory technicians, healthcare treatment assistants, public health assistants in government and private healthcare settings (18, 19).

Malaysia is a developing, upper-middle-income country in Southeast Asia with a population of 32 million (20). The health care system consists of 154 government hospitals, 210 private hospitals, 1,090 government health clinics, and 7,718 private clinics. Twenty-seven COVID hospitals were designated for admissions of patients under investigations (PUI) or confirmed case of COVID-19 in Malaysia during the pandemic (21). This study was conducted from 18 March 2020 until 21 March 2020. The study start date coincided with the commencement of the Malaysian Movement Control Order (MCO), which is synonymous with a national lockdown in other countries. Malaysia reported the first case of COVID-19 on 25 January 2020. Our study period captured the exponential rise of COVID-19 in Malaysia with cases increasing from 238 (zero mortality) to 1,183 cases (4 deaths) on 14 and 21 March 2020, respectively (22–24). At that time, Malaysia ranked the highest in South-East-Asia (SEA) and 18th globally with regards to the total number of COVID-19 cases (25). The spike in COVID-19 cases in Malaysia and significant spread to neighboring SEA countries was attributed to a cluster originating from a 4-day religious mass gathering with 16,000 people (including 1,500 foreign participants) held from 27 February to 1 March 2020 in Malaysia (26).

All HCWs working in Malaysia were invited to participate in the study. The inclusion criteria for this study include (i) aged between 18 and 60 years-old and (ii) able to read and write in the English language. Data collection was done through an online survey (Google Form). Advertisements for recruitment were sent or posted via email, social media platforms (e.g., WhatsApp, Twitter, etc.) among the networks of the research team, and via organizational/institutional email listserv/mailing lists/websites. The online survey Google Form included a study information sheet, informed consent form, declaration of anonymity and confidentiality as well as information on how to access crisis helplines. Participants were also given the option of including their contact information if they agreed to be contacted and offered online psychological support. Eligible Malaysian health care workers who gave informed consent were subsequently directed to the self-report questionnaire section in the online survey.

Measures
The self-report questionnaire section consists of four components: socio-demographic and occupational/service-related data, Health Anxiety Inventory (HAI), presence or absence of lifetime anxiety disorder, and severity of depression (PHQ-9).

Socio-Demographic and Occupational/Service-Related Data
The following data were collected from respondents: age, gender, ethnicity, educational level, marital status, type of HCW occupation (physician/non-physician), working hours, and duration of service. Self-reported data on the absence or presence of lifetime anxiety disorder was also collected.

Health Anxiety Inventory (HAI)
For this study, the very-short version of HAI was used. This screening instrument assessed health anxiety independently of physical health status with 14 items. Items assess worries about health, awareness of bodily sensations or changes, and feared consequences of having an illness. The very-short version HAI has demonstrated good reliability, criterion validity, and sensitivity to treatment (27). A cut-off point of ≥ 18 signifies hypochondriasis, and a cut-off point of ≥ 15 represents high health anxiety (28).

Patient Health Questionnaire (PHQ-9)
The PHQ-9 is a self-administered questionnaire which measures the frequency of symptoms of depression using nine items on a 4-point Likert-scale ranging from 0 (not at all) to 3 (nearly every day). It has demonstrated good construct validity (29). A total score ranging from 0 to 27 is obtained by the summing of all item scores. A Malaysian version of the PHQ-9 score ≥ 10 had a sensitivity of 87% specificity of 82% for detecting clinical depression (major depression according to the DSM-IV: Diagnostic and Statistical Manual of Mental Disorders) in a primary care setting (30). For item 9 of the PHQ-9 (suicidal ideation), respondents reporting "not at all" will be scored 0 ("no" for current suicidal ideation in the past 2 weeks), while respondents reporting "several days," "more than half the days," and "nearly every day" will be scored 1 ("yes" for current suicidal ideation in the past 2 weeks). Previous research showed that respondents who reported suicidal ideation in PHQ-9 had a significantly increased risk of non-fatal or fatal suicide attempt than those who did not have suicidal ideation (31).

Statistical Analysis
Data was analyzed using STATA software, version 12.0. Descriptive data were generated for all variables. Bivariate analysis was performed using chi-squared and t-tests. The dependent variable of suicidal ideation (PHQ item 9) was analyzed as a dichotomous (yes/no) variable. The following variables were analyzed as categorical independent variables: gender, relationship status (single vs. married), lifetime anxiety disorder (yes/no), ethnicity (Malay/non-Malay), education level (low: diploma level and below/high: degree level and above), occupation (physician/non-physician), severity of depression (PHQ-score range: 0-4 = minimal, 5–9 = mild, ≥ 10 = moderate to severe (clinical depression), working hours per week (<40 h/40 to 50 h/> 50 h) and service duration (years: 1–3/4–6/7–10/>10). Health anxiety (HAI) scores were analyzed as a continuous independent variable (assumption of linearity was met for HAI scores with the outcome dependent variable). Values for 10 cases with missing data on continuous predictors were

TABLE 1 | Association between socio-demographic, occupational, and clinical factors with current suicidal ideation among health care workers (*N* = 171).

Factors	Current Suicidal Ideation				*p*-value
	Yes	**95% CI**	**No**	**95% CI**	
	n = 19		**n = 152**		
Age, *n* (%)					0.756*
18–30	8 (42.11)	(19.13, 65.08)	45 (29.61)	(22.27, 36.94)	
31–40	10 (52.63)	(29.40, 75.86)	93 (61.18)	(53.36, 69.01)	
41–50	1 (5.26)	(−5.13, 15.65)	9 (5.92)	(2.13, 9.71)	
51–60	0 (0.00)	–	5 (3.29)	(0.42, 6.15)	
Gender, *n* (%)					0.812
Male	6 (31.58)	(9.95, 53.21)	44 (28.95)	(21.66, 36.23)	
Female	13 (68.42)	(46.79, 90.05)	108 (71.05)	(63.77, 78.34)	
Ethnicity, *n* (%)					0.768*
Malay	16 (84.21)	(67.24, 101.18)	118 (77.63)	(70.94, 84.33)	
Non-Malay	3 (15.79)	(−1.18, 32.76)	34 (22.37)	(15.67, 29.06)	
Relationship status, *n* (%)					0.017
Married	7 (6.60)	(14.40, 52.29)	99 (93.40)	(57.48, 72.79)	
Single	12 (18.46)	(40.71, 85.60)	53 (81.54)	(27.21, 42.52)	
Education level, *n* (%)					0.478
Diploma or lower	7 (36.84)	(14.40, 59.29)	44 (28.95)	(21.66, 36.23)	
Bachelor's degree or higher	12 (63.16)	(40.71, 85.60)	108 (71.05)	(63.77, 78.34)	
Occupation, *n* (%)					0.744
Physician	10(52.63)	(29.40, 75.86)	86 (56.58)	(48.62, 64.54)	
Non-physician	9 (47.37)	(24.14, 70.60)	66 (43.42)	(35.36, 51.38)	
Anxiety, *n* (%)					0.234*
Yes	4 (21.05)	(2.08, 40.02)	15 (9.87)	(5.08,14.66)	
No	15 (48.95)	(59.98, 97.91)	137 (90.13)	(85.34, 94.92)	
Working hours per week, *n* (%)					0.584*
<40 h	1 (5.26)	(−5.13, 15.65)	22 (14.47)	(8.82, 20.13)	
40–50 h	11 (57.89)	(34.92, 80.87)	85 (55.92)	(47.95, 63.90)	
>50 h	7 (36.84)	(14.40, 59.29)	45 (29.61)	(22.27, 36.94)	
Service duration (years), *n* (%)					0.013*
1–3	8 (42.11)	(19.13, 65.08)	21 (13.82)	(8.27, 19.36)	
4–6	3 (15.79)	(−1.18, 32.76)	35 (23.03)	(16.26, 29.79)	
7–10	7 (36.84)	(14.40, 59.29)	56 (36.84)	(29.09, 44.59)	
>10	1 (5.26)	(−5.13, 15.65)	40 (26.32)	(19.24, 33.39)	
Severity of depressive symptoms (PHQ-9), *n* (%)					<0.001
Minimal	2 (10.53)	(−3.75, 24.81)	112(73.68)	(80.76, 66.61)	
Mild	8 (42.11)	(65.08, 19.13)	32 (21.05)	(27.60, 14.50)	
Moderate and severe (clinical)	9 (47.37)	(70.60, 24.14)	8 (5.26)	(1.67, 8.85)	
Health Anxiety (HAI score) (mean ± SD)	20.32 (8.53)		17.16 (6.44)		0.027 ~

*Bivariate analysis based on Chi squared test except for * & ~.*
*Fischer exact test.
~T-test.

imputed using median. After deletion of 4 cases with missing values either on gender, relationship status, ethnicity, occupation, and having anxiety disorder, data from 171 respondents were available for analysis. Likelihood ratio test was used to determine which independent variables were included into the multivariable logistic regression model. According to Peduzzi et al. (32), sample size calculation for logistic regression is based on event per variable as $n = 100+5i$, where i refers to the number of independent variables. As the total sample size in this study was 171, 14 or fewer independent variables were considered adequate to be included in the final regression model.

RESULTS

Majority of the participants were within the 31–40 years age group, female (70.8%), Malay ethnicity (78.4%), married (62%), and with an educational level of a bachelor's degree or higher

TABLE 2 | Factors associated with current suicidal ideation based on multivariable logistic regression (N = 171).

	S.E.	p	O.R.	95% C.I. for O.R.	
				Lower	Upper
Married (vs. single)	0.725	0.948	0.952	0.214	4.233
Service duration (years)					
1–3 (baseline)	–	–	–	–	–
4-6	0.208	0.113	0.211	0.031	1.448
7-10	0.267	0.176	0.297	0.051	1.723
> 10	0.096	0.049	0.072	0.005	0.993
Total HAI score	0.044	0.822	1.010	0.928	1.099
Severity of depression					
Minimal depression (baseline)	–	–	–	–	–
Mild depression	13.705	0.001	15.984	2.977	85.804
Moderate to severe depression	52.163	<0.001	55.983	9.015	347.671

(70.2%). Most of the participants were physicians (56.2%), mainly working between 40 and 50 h per week (56.1%), and with a service duration of 7–10 years (36.8%). Eighty-three percent of study participants were healthcare workers in hospitals or healthcare facilities that were designated as COVID-19 treating or screening healthcare facilities. Cronbach alpha for HAI and PHQ were 0.879 and 0.873, respectively. Current clinical depression and lifetime anxiety disorder were present in 9.9% (17/171) and 11.1% (19/171) of participants, respectively. Nineteen out of 171 healthcare workers (11.1%) reported current suicidal ideation in the past 2 weeks. Fifty three percent (10/19) of those with suicidal ideation did not meet criteria for clinical depression (no or subthreshold depressive symptoms). Fifty three percent (9/17) of healthcare workers with clinical depression reported suicidal ideation. There was no multicollinearity between the independent variables. The correlation between the independent variables was 0.45 (<0.8).

From bivariate analysis (**Table 1**), factors significantly associated with current suicidal ideation were single status (p = 0.017), higher levels of health anxiety (p = 0.234), and higher severity of depression (p < 0.001). Participants with more than 10 years of service duration had a significantly lower rate of current suicidal ideation (p = 0.013). Multivariable logistic regression model (**Table 2**) showed that moderate to severe (clinical) depression was the strongest independent variable significantly associated with current suicidal ideation (p < 0.001, OR = 55.983, 95% CI = 9.015–347.671) followed by mild depression (p = 0.001, OR = 15.984, 95% CI = 2.977–85.804). Service duration of more than 10 years was associated with significantly less suicidal ideation (p = 0.049, OR = 0.072, 95% CI = 0.005–0.993).

DISCUSSION

The burden and risk factors of suicidal behavior among health care workers in low- and middle-income countries have not been well-established (33). Our present study showed that 11.1% of

healthcare workers in Malaysia reported current suicidal ideation (past 2 weeks) during the early phase of the COVID-19 pandemic and lockdown. Based on Zunin and Meyers' model of phases of disaster, our study period coincides with phase 2, whereby the psychological impact of the initial rapid spread of COVID-19 and environment of unpreparedness can encompass a wide range from shock, overt panic, initial confusion, disbelief, focus on self-preservation and family protection (34). The prevalence rate for current suicidal ideation (past 1 month) was 1.7% in the general population from the 2011 Malaysian National Health Morbidity Survey (35). Malaysian HCWs appear to have a higher rate of suicidal ideation during the early phase of the COVID-19 pandemic compared to available pre-pandemic data among medical students (7%) and the general population in Malaysia (36). Our reported figure of 11.1% is lower than the prevalence of 17% for suicidal ideation among physicians in Dutheil et al. (3) meta-analysis of 61 predominantly Western studies (3). Nevertheless, direct comparison of trends in suicidal behavior (including ideation) among HCWs pre- and post-pandemic is challenging due to limitations of methodological heterogeneity from published data in Malaysia and globally.

Depression is a well-established risk factor for suicidal behavior (ideation, attempt and suicide) among medical physicians and nurses (37, 38). Our study showed that the severity of self-reported depressive symptoms was associated with suicidal ideation, with the clinical range of depression being the most significant factor. Nevertheless, a substantial proportion of HCWs who experienced suicidal ideation (50%) did not meet criteria for clinical depression, i.e., having no or subthreshold depressive symptoms. This finding underscores the importance of understanding other factors that contribute to suicidal ideation beyond depression.

Our study demonstrated that a longer duration of service (more than 10 years) appeared to be protective against suicidal ideation in Malaysian HCWs during the early phase of the COVID-19 pandemic. This finding remained significant after controlling for age, gender, marital status, ethnicity, educational level, type of health care occupation and medical specialty, working hours as well as self-reported clinical depression, health anxiety or other anxiety disorders. Previous research findings have been somewhat mixed in terms of the significance of seniority and suicidal behavior among physicians. The level of seniority was not significantly associated with suicide among physicians in England and Wales (39). Being in practice for more than 30 years seemed to be protective against suicidal ideation in a previous study of 7,905 American surgeons. However, service duration was no longer significant after controlling for burnout and depressive symptoms (40).

Findings from our study echo a signal of increased vulnerability to suicidal ideation in early career compared to senior HCWs. The exact mechanisms underlying the interaction between suicidal behavior and stressors (professional and personal) encountered by HCWs in tandem with their level of work experience; are beyond the scope of this study. Nevertheless, previous research highlighted that physician burn-out can contribute to the complex issue of suicidal behavior in the medical profession (41).

Burn-out has been conceptualized as an occupational phenomenon that is separate from a medical condition (42). This is an important distinction to address in terms of interventional implications and suicide prevention among HCWs. Physicians who were younger in age appear to be more susceptible to burn-out in Malaysian and Chinese populations (43, 44). Being at the frontline of the COVID-19 pandemic increased the risk of severe psychological distress such as insomnia, depressive, and anxiety symptoms among HCWs in China, especially among mid-career compared to senior clinicians (45). In Malaysia, findings from a small descriptive study seemed to suggest that residents experienced more stress, anxiety, and depressive symptoms compared to medical specialists (46). A qualitative study in Egypt identified the following COVID-related stressors faced by psychiatry residents: (i) inadequate precautions to guard against the outbreak, (ii) high exposure risk, (iii) the conflict between family and work, and (iv) the postponement of personal and career plans (47).

Often, clinicians in the early phases of their careers inadvertently end up at the frontline of critical health care provision as part of their training. A study from Singapore reported that COVID-19 frontline HCWs mainly comprised of residents (48). The hierarchical nature of medicine and health care service is also a likely exacerbating factor. Three quarters of the nurses working at the frontline of the COVID-19 pandemic epicenter in Wuhan, China were in the junior category of service (49). The perception of having to practice beyond one's level of competency without adequate supervision may contribute to burn-out in a sample of Australian junior physicians (50).

Data from the general population during the current pandemic have shown that British young adults (18–29 years) have a heightened risk for suicidal ideation compared to middle-aged and older adults (51). In the U.S., young adults (18–29 years) were also a high-risk population for serious psychological distress (52). In that study, stressors included fear of contracting COVID, issues with employment, financial, and educational interruptions. In Spain, financial and occupational stressors such as the perception of lack of supervision, communication, coordination and personnel were associated with suicidal ideation and behavior among health-care workers during the 1st wave of the COVID-19 pandemic. These environmental factors remained significant after accounting for pre-existing mood and anxiety disorders as well as level of exposure to COVID-19 (53). Early- to mid-career healthcare workers in Malaysia may have to contend with a heightened sense of unpreparedness during the initial critical phase of the COVID-19 pandemic and lockdown. This population may be in a more vulnerable position compared to senior, better-resourced colleagues in terms of financial stability, job insecurity and disruptions to career progression and advanced training (e.g., postgraduate, specialty/sub-specialty). Therefore, we postulate that such a scenario may contribute to an increased risk of suicidal ideation in less experienced, junior healthcare workers. Further evidence beyond our study is needed to substantiate these hypotheses.

Study Implications and Recommendations

In view of depression being a significant factor associated with suicidal ideation, early identification of depression as a target for intervention is a potential suicide preventive strategy (54) among HCWs during this current pandemic. There are unique challenges posed by the current pandemic with regards to the logistics of accessible in-person mental health services. Even before the COVID-19 pandemic, multiple barriers to help-seeking and mental health service pathways existed amongst HCWs. The majority (61%) of a sample of American junior and mid-career physicians acknowledged the benefit of psychiatric services (55). However, these authors showed that only a quarter of that population accessed mental health treatment. Individual and institutional/structural level barriers have been reported, such as lack of time, stigma, fear of loss of confidentiality impacting career advancement and medical licensure, as well as lack of formal HCW-centered wellness programs and counseling/therapy, and treatment cost (55, 56). These issues have been reported to impede the accessibility of much needed mental health care services for HCWs including in Malaysia (57). Solutions to overcome these challenges are strikingly critical in the face of the current pandemic. This is imperative not only to address the obvious mental health care burden and risk of suicide among HCWs, but also to sustain the integrity of health care service systems and optimum patient care as medical errors have been associated with untreated depression in residents (58). Hence, creative implementation of online psychological support and crisis interventions may be a way forward during this pandemic. This would minimize infection risk of in-person mental health service provision, particularly among frontline medical staff as a target population (59). Examples of digital applications (apps) designed specifically to support the mental health of HCWs during this pandemic include TEN – The Essential Network for Health Professionals during COVID-19 (60) and an e-package developed by University of Nottingham (61).

Healthcare workers with less seniority in service appear to be a more at-risk population for suicidal ideation during this pandemic. Current models have recommended pre-frontline deployment training that emphasize resilience building, especially for medical staff that are more junior and less experienced in frontline crisis and disaster health services (59, 62). Previous research during the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic in Taiwan showed that implementation of a SARS prevention program significantly reduced the levels of depression in nursing staff from moderate to minimal or mild (63). The program encompassed infection control and patient care protocols and training, adequate PPE supplies, and access to a mental health clinic specific for HCWs. In order to better understand the risk and protective factors for suicidal behavior amongst HCWs, further quantitative and qualitative research is required to elucidate the trajectory of moral injury (64) and specific COVID-19-related work conditions faced by HCWs, i.e., adequacy of PPE, implementation of training protocols, formal infrastructural and organizational support as well as the impact of social isolation. Future longitudinal studies

focusing on the long-term impact and sequelae of the ongoing pandemic on healthcare workers are warranted.

Limitations

This study is susceptible to type II error due to the relatively small sample size. We acknowledge that our study is limited by cross-sectional design which is unable to determine causality of suicidal ideation found in healthcare workers in the context of the COVID-19 pandemic. The generalizability of findings from this study is limited by the non-random sampling of HCWs in Malaysia. Item 9 of the PHQ was used to assess current suicidal ideation in this study. Previous research has supported the utility of Item 9 of the PHQ-9 as an initial screening measure for risk of suicidal acts at the individual patient-level (31). However, caution has to be exercised with regards to its use as the sole self-reported measure of suicidal behavior without more comprehensive clinical assessment of suicide risk to minimize false-positives or false-negatives (65). Our study was limited to a relatively short duration during the initial critical phase of the COVID-19 pandemic and lockdown in Malaysia. Thus, it was beyond the scope of our current study to detect the mid to long-term effects on HCWs which warrants further research. Previous studies among healthcare workers in heterogenous settings have shown mixed findings in terms of the association between the level of COVID-19 exposure and psychological distress i.e., anxiety (66) suicidal behavior (53). The level of exposure to SARS-CoV-2 was not measured in our study. Nevertheless, the vast majority (83%) of healthcare workers in our study were in designated COVID-19 healthcare facilities. Thus, we have interpreted our study findings in the context of the overall significant risk of exposure to SARS-CoV-2 in our study population, while recognizing that individual level data of exposure to SARS-CoV-2 is a significant confounding variable.

CONCLUSIONS

Our study has highlighted that depression, both at the subthreshold level and particularly in the clinical range, may be associated with suicidal ideation, while a longer service duration is potentially protective against suicidal ideation amongst Malaysian HCWs. Identification and treatment of depression, as well as a focus on early-/mid-career HCWs as a target population for early intervention may be potential areas for suicide prevention amongst HCWs who have been exposed to the COVID-19 pandemic working environment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research and Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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Suicidality Presented to a Child and Adolescent Psychiatry Emergency Service: Increasing Rate and Changing Characteristics

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Background: Children and adolescents who present to child and adolescent psychiatric emergency departments show a variety of reasons for their presentations. Suicidality, in particular suicidal thoughts and suicide attempts, as well as non-suicidal self-injury (NSSI) play a large and important role. In this context, inpatient admissions frequently serve as crisis intervention.

Methods: In this study, face-to-face emergency presentations to the emergency department at our Clinic of Child and Adolescent Psychiatry (CAP) were analyzed over the years 2014-2018, the 4th quarter (October-December) of each year. Data from 902 emergency presentations were evaluated, primarily with regard to suicidal thoughts, suicide attempts, and NSSI as reasons for presentation.

Results: Data demonstrated that the number of emergency presentations increased in general and especially for suicidal thoughts and NSSI as reasons for presentation. In addition, suicidal thoughts, suicide attempts, and NSSI as reasons for emergency presentation were more likely to result in crisis-related inpatient admissions. Furthermore, reporting suicide attempts at emergency presentation was associated with longer inpatient stays. Finally, cases with multiple diagnoses increased independent of the general increase in emergency presentations.

Conclusion: The increase of utilization of clinics with CAP outpatient emergency patients and following admissions to the inpatient units for crisis intervention poses a major challenge for the future. It is important to prepare for the assessment and treatment of suicidality, which is of extraordinary importance in the care of emergency patients.

Keywords: suicidal thoughts, suicide attempt, emergency, non-suicidal self-injury, adolescents, children, mental health, crisis intervention

INTRODUCTION

According to a large epidemiological study 16.9% of children and adolescents living in Germany show mental health problems (1), comparable with rates in other European countries (2). It is of particular relevance that only between 20% (3) and 50% (4) of those affected receive treatment. Many children and adolescents who meet the criteria for mental illnesses have an unmet need for

support and especially those affected, even with mild symptoms, should receive prompt treatment (5). It is estimated that about 10% of children and adolescents suffer from their mental disorders to such an extent that they are not only affected on a daily basis, but the disorders can continue into adulthood if they remain untreated (6). Unfortunately, targeted treatment often begins years after the first onset of initial symptomatology (7).

Emergency child and adolescent psychiatric care is often the entry point to mental health care (8, 9). The number of emergency-related child and adolescent psychiatric visits has been growing in recent years (10–12). A study from the largest child and adolescent psychiatric hospital in the Paris area investigated emergency presentations over a long period of time and, as a result, found an annual increase by 3.85 times between 1981 and 2017, with the largest increase in the 1980s and then less pronounced over time (13). Context for emergency presentations varies from minor issues to life-threatening crises (14). Numerous reasons are given for emergency presentations, but most commonly the goal is the assessment of self-injurious thoughts and behaviors (SITB) (15). In addition to non-suicidal self-injury (NSSI), which is carried out without the intention to die, suicidal behavior, in which the person has at least to some degree the intention to die, is defined as SITB (16). Since the intention to die is often times ambivalent in patients, there is an overlap between NSSI and suicidal behavior (17), which is the reason why both aspects should be focused on in an emergency setting. Suicide attempts and NSSI represent distinct behaviors that differ in intent, form, and function, yet the two behaviors frequently occur simultaneously in adolescents as well as adults (18); the same can be concluded for suicides (19).

The prevalence of SITB reported by parents in children younger than 11 years was very low (20). However, in a representative sample of 12,068 adolescents from 11 European countries, an overall lifetime prevalence of direct self-injurious behavior (regardless of suicidal intent) of about 27.6% could be detected (17). The 12-month prevalence of NSSI in a clinical sample of inpatients was even higher with 60% and nearly 50% who engaged in it repeatedly (21). In a representative sample of 44,610 students in the 9th grade of different school types in Germany, the rate of suicide attempts (lifetime prevalence) was 9% and the prevalence of suicidal ideation was 39.4% (5.2% often, 10.4% sometimes, and 23.8% rarely) (22). Suicide is one of the leading causes of death among youth worldwide (23). In this respect, risk assessment but also, in general, clinical assessment of the mental health problems of children and adolescents presenting in an emergency plays a prominent role, including the crucial decision whether to proceed with inpatient admission for crisis intervention (24).

A study in a Clinic of Child and Adolescent Psychiatry (CAP) in Germany showed that utilization through crisis admissions increased by 219% between 2005 and 2015, compared to a simultaneous 23.7% increase in regular admissions (15). However, there are studies in Europe that show a different trend of inpatient admissions after psychiatric emergency consultation in adolescents, for example a study conducted in France (13). Here, admission to an inpatient unit immediately after an emergency consultation accounted for three-quarters of the total

annual number of consultations in 1981, but only 15.6% in 2017 (13). In a study from Denmark, the inpatient admission rate decreased from 19.2 to 15.7% between 2003 and 2006 (14). In this context, it would be interesting to examine how the trend in inpatient emergency admissions has developed in recent years.

This present study aimed at investigating the rate and possibly changing demographic and clinical characteristics of the outpatient emergency consultation of our clinic over a time course of 5 years. In particular, we analyzed the reasons given for the presentations with a focus on acute crises in connection with suicidal thoughts, suicide attempts, and NSSI. We expected a significant increase in emergency presentations over time. Furthermore, according to our clinical impression, we anticipated an increase in the presentation of reasons due to suicidal thoughts, suicide attempts, and NSSI over time. We also proposed that these reasons for emergency consultation were more likely to result in crisis-related inpatient admissions. In addition, we generally assumed a higher proportion of cases with multiple diagnoses over time. We also conceived of a higher number of psychiatric diagnoses among emergency presentations that presented for NSSI or suicidality. For example, it has already been shown that substance abuse can have a significant impact on suicidality (25), especially during the adolescent phase (26, 27). Specifically, patients with substance-induced psychosis have been shown to have a higher prevalence of suicidal ideation during the past year (28). In general, but also especially in emergency presentations, possible comorbid diagnoses (e.g., substance disorders) should not be overlooked, as these should be considered in treatment and often manifest in higher symptom severity (29, 30). Analyzing child and adolescent psychiatric emergency presentations is crucial in order to provide sufficient and appropriate resources for adequate emergency care. With additional knowledge of the clientele and the changes in recent years, emergency service in child and adolescent psychiatry can be adapted to future needs.

MATERIALS AND METHODS

The Clinic of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy at the University of Regensburg, Germany, is a typical child and adolescent psychiatric hospital of maximum care. It includes three full inpatient units (40 beds), three day-care units (22 patients) and offers a comprehensive outpatient care unit. The catchment area of our CAP service includes around 178,000 children under the age of 18 years. In this report, face-to-face emergency presentations in the emergency outpatient department 24 h for 7 days a week of the years 2014-2018 of the respective fourth quarter are examined, i.e., from October 01 to December 31. The fourth quarter for each year was chosen because clinical experience showed that these are the most demanding months of the year. Thus, a longer time period could be considered and seasonal fluctuations in the frequency of selected mental disorders [e.g., seasonal affective disorders (31)] could be excluded a priori. Patients from rural areas or large and medium-sized cities throughout the Upper Palatinate (Oberpfalz) were treated during regular

consultation hours, on weekends and holidays. During regular consultation hours, it serves the area of the city of Regensburg, the districts of Regensburg, Neumarkt and Schwandorf as well as the entire area of the Upper Palatinate after regular consultation hours. The Upper Palatinate is a government district of the Free State of Bavaria and has 1,106,269 inhabitants, with Regensburg being the only major city with 168,876 inhabitants. The sample described here includes patients of the emergency presentations in Regensburg as well as patients of the branch offices for whom an inpatient admission had to be assumed or was already indicated. This results in a sample size of 927 emergency presentations in the observation period, of which 902 were finally included in the data evaluation due to lack of information (for example, no detailed information about the reason for presentation).

The evaluation was based on the charts and electronic documentation records filled in by the physicians on duty and the physicians who continued the treatment. Clinical notes, doctor's letters, outpatient and inpatient treatment documentation stored in the electronic hospital information system were used to evaluate the amount and clinical characteristics of the emergency presentations. The parameters were collected to the best of our ability from the above-mentioned documentation. No specific scales were used, for example, to elicit the presence of suicidal thoughts or suicide attempts, as this was a purely retrospective analysis of existing data. Clinical psychiatric diagnoses were based on chapter V (F) of the International Classification of Diseases (ICD-10). Furthermore, compulsory presentations and the reasons for the presentation (e.g., suicidal thoughts, suicide attempts, non-suicidal self-injury, psychosocial stress factors, and aggression by others) were also obtained in this context.

Statistical Analyses

To test the relationships between the main variables time (in months), number of emergency presentations (specific to suicidal thoughts, suicide attempts, and NSSI) and number of diagnoses, non-parametric Kendall's τ correlations were calculated for each hypothesis, as the τ coefficient is less susceptible to deviations in distributions and possible outliers. When a Kendall's τ correlation did not show a significant result, an exploratory partial correlation was calculated in reasoned cases in order to control for a possible intervening variable. If a significant correlation with time (in months) was found, it was entered into a simple linear regression as an independent variable in order to compute the trend of cases over time. The relationship between suicidality, NSSI, and inpatient admissions was investigated through Chi-Square tests, particularly whether presenting with suicidality or NSSI as a reason was more likely to result in an inpatient admission than not. Additionally, to investigate whether suicidality and NSSI as reasons for emergency presentations resulted in longer inpatient stays, Mann-Whitney U-tests were conducted. Finally, the rate of "cases with multiple diagnoses" over the years was computed, with "cases with multiple diagnoses" defined as cases in which a patient received equal/more than two diagnoses. The rate was used to determine the increase of cases with multiple diagnoses over the years without a bias of a general increase in emergency presentations. In case of a significant correlation, a simple linear regression was computed to determine how much variance in the rate of cases with multiple diagnoses to cases with single diagnose can be explained by time alone. In cases with several tests for a single hypothesis, the false discovery rate (FDR) was used to correct for multiple comparisons (32). Reported p-values already correspond to the correction. All major statistical analyses were conducted using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and the statistical significance level was set to $\alpha = 0.05$.

RESULTS

Sample

Detailed sociodemographic and clinical characteristics of patients presented to the outpatient emergency service is presented in **Table 1**. A total of 902 cases of emergency presentations were included in the sample. Children and adolescents up to an age of 18 years, in exceptional cases up to 21 years were included in the study. The average age was about 15 years ($M = 15.4$, $SD = 2.6$). Slightly more than half of the presentations were female (57.8%). Among the reasons for presentation given by the patients, we focused on the reasons suicidal thoughts, suicide attempts, and NSSI. Suicidal thoughts were found to be the most common reason for emergency presentation ($N = 489$, 54.2%). NSSI was given as a reason for presentation by a quarter of emergency presentations ($N = 231$, 25.6%). Suicide attempt was given as reason for presentation in nearly 5% of emergency presentations ($N = 42$, 4.7%). It should be noted here that patients were able to provide multiple reasons for emergency presentations and that some of the patients presented more than once within a quarter. Patients who presented repeatedly were not excluded from analyses as they constitute a particularly relevant patient group that requires crisis intervention and resources. As the current paper is concerned with the sum of emergency presentations independent of whether these presentations are due to the same individuals or not, a single patient reappearing was not considered as "repeated measure." Each presentation was considered as an independent occurance that required emergency care and resources. On average the patients received about two psychiatric diagnoses ($M = 2.07$, SD = 1.14) with the maximum number of diagnoses reaching eight in a few cases. Of the emergency presentations and including patients of the branch offices, 47.1% were admitted to the inpatient units of the hospital. In total there were 424 inpatient admissions during the observation period, with the average length of stay reaching almost 12 days ($M = 11.62$, $SD = 28.86$) as presented in **Table 2**.

Development of Numbers of Consultations Over the Years

Figure 1 shows an overview of cases within each year, additionally split according to the main reasons under consideration. A significant positive correlation between time (in months) and number of emergency presentations was found [$\tau_{(13)} = 0.54$, $p = 0.005$]. To determine the influence of time on the number of emergency presentations, a simple linear regression was computed. The model was significant

TABLE 1 | Demographic and clinical characteristics of the sample per 4th quarter over the years of observation.

Variables	Years of Observation					Total
	2014	2015	2016	2017	2018	
Number of cases	134	174	138	234	222	902
Age (years; months)						
M	15;5	15;7	15;6	15;2	15;5	15;4
SD	2;8	2;6	2;4	2;7	2;4	2;6
Range	1;11 – 18;4	6;5 – 19;1	8;3 – 20;5	1;10 – 19;11	4;4 – 20;4	1;10 – 20;5
Female Patients n (%)	78 (58.2)	87 (50.0)	73 (47.1)	132 (43.6)	151 (32.0)	521 (57.8)
Inpatient admissions						
Total Sample n (%)	58 (43.3)	89 (51.1)	70 (50.7)	111 (47.4)	96 (43.4)	424 (47.1)
Suicidal Thoughts n (%)	45 (53.6)	53 (58.2)	45 (60.8)	76 (59.8)	65 (57.5)	284 (58.1)
Suicide Attempts n (%)	8 (88.9)	10 (83.3)	5 (71.4)	3 (50.0)	6 (75.0)	32 (76.2)
NSSI n (%)	16 (51.6)	25 (56.8)	23 (53.5)	32 (60.4)	30 (50.0)	126 (54.5)
Compulsory Presentations (police or court) n (%)	10 (7.5)	29 (16.7)	21 (15.2)	23 (9.8)	39 (17.6)	122 (13.5)
Diagnostic groups						
F1 n (%)	11 (8.2)	18 (10.3)	21 (15.2)	63 (26.9)	39 (17.6)	152 (16.9)
F2 n (%)	3 (2.2)	1 (0.6)	7 (5.1)	2 (0.9)	1 (0.5)	14 (1.6)
F3 n (%)	51 (38.1)	84 (48.3)	84 (60.9)	120 (51.3)	131 (59.0)	470 (52.1)
F4 n (%)	65 (48.5)	85 (48.9)	57 (41.3)	82 (35.0)	100 (45.0)	389 (43.1)
F5 n (%)	9 (6.7)	7 (4.0)	8 (5.8)	25 (10.7)	9 (4.1)	58 (6.4)
F6 n (%)	8 (6.0)	22 (12.6)	8 (5.8)	12 (5.1)	14 (6.3)	64 (7.1)
F7 n (%)	–	–	–	–	–	–
F8 n (%)	2 (1.5)	7 (4.0)	4 (2.9)	2 (0.9)	2 (0.9)	17 (1.9)
F9 n (%)	55 (41.0)	61 (35.1)	58 (42.0)	112 (47.9)	85 (38.1)	371 (41.1)
Multiple Diagnoses n (%)	68 (50.7)	107 (61.5)	93 (67.4)	147 (62.8)	148 (66.7)	563 (62.4)

NSSI, Non-suicidal Self-injury. F-diagnoses do not add up to 100 % as multiple diagnoses were possible.

TABLE 2 | Description of total sample and subsamples for duration of inpatient stay and number of psychiatric diagnoses according to ICD-10.

Variable	M (SD)	Range	n
Duration of inpatient stay			
Total Sample	11.62 (28.86)	0-381	423
NSSI	7.38 (12.97)	0-92	126
Suicidal Thoughts	9.36 (25.17)	0-381	284
Suicide Attempts	18.41 (24.32)	0-92	32
Number of diagnoses			
Total Sample	2.07 (1.14)	0-8	901
NSSI	2.06 (0.96)	1-6	231
Suicidal Thoughts	2.01 (1.14)	0−8	489
Suicide Attempts	2.02 (1.00)	0-5	42

NSSI, Non-suicidal Self-injury.

$[F_{(1,13)} = 15.70, p = 0.002]$ and explained a total of 54.7% of the variance in the dependent variable. Additionally, time was a significant predictor of the number of emergency presentations ($t = 3.96, p = 0.002$) (see **Table 3**). A closer look at suicidality and NSSI as reasons for emergency presentations revealed significant correlations between the variables time (in months) and suicidal thoughts [$\tau_{(13)} = 0.43, p = 0.028$]

and NSSI [$\tau_{(13)} = 0.48, p = 0.014$], respectively. There was no significant relationship between suicide attempt as a reason for presentation and time [$\tau_{(13)} = -0.13, p = 0.538$]. In order to analyze the influence of time on suicidal thoughts and NSSI, two simple linear regressions were performed. The regression model was significant for both, suicidal thoughts [$F_{(1,13)} = 6.66, p = 0.023$] and NSSI [$F_{(1,13)} = 10.40, p = 0.007$] and explained 33.9 and 44.5% of the variance for suicidal thoughts and NSSI, respectively. Time was a significant predictor in both cases (suicidal thoughts: $t = 2.58, p = 0.023$; NSSI: $t = 3.23, p = 0.007$). An overview of regression analyses with time as an independent variable and number of emergency presentations as well as NSSI and suicidal thoughts as reasons for emergency presentations as the dependent variables is presented in **Table 3**.

Relationship of Suicidality and NSSI With Admissions and Duration of Inpatient Stay

Chi-square tests were computed to determine whether emergency presentations due to suicidal thoughts, suicide attempts or NSSI were more likely to result in inpatient admissions. All three were significant with $\chi^2(1, N = 890) = 48.43, p < 0.001$, $\chi^2(1, N = 890) = 14.52, p < 0.001$ and $\chi^2(1, N = 890) = 6.16, p = 0.013$, respectively. To compute the impact of reasons for emergency presentations on the inpatient stay durations, Mann-Whitney U-tests were computed.
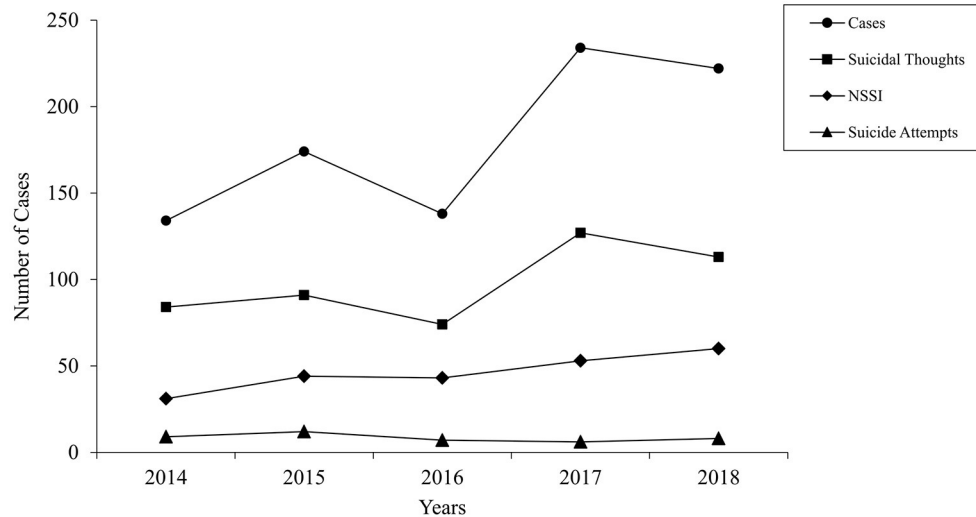
FIGURE 1 | Total number of emergency presentations between 2014 and 2018, fourth quarter of each year. Emergency presentations due to suicide attempts, suicidal thoughts, and NSSI are depicted separately. NSSI, non-suicidal self-injury.

TABLE 3 | Results of linear regression models with time predicting number of cases, NSSI, suicidal thoughts and rate of multiple diagnoses.

Dependent variables	Predictor	B	SE	β	t	p	R²
Number of cases	Time	2.54	0.64	0.74	3.96	0.002	0.55
NSSI	Time	0.74	0.23	0.67	3.23	0.007	0.45
Suicidal thoughts	Time	1.08	0.42	0.58	2.58	0.023	0.34
Rate of multiple diagnoses	Time	0.02	0.01	0.78	4.47	0.001	0.61

There was no effect of NSSI ($U = 17,565.00$, $p = 0.315$) and suicidal thoughts ($U = 17494.00$, $p = 0.08$) as a reason for the emergency presentation on inpatient stay duration, however, suicide attempts ($U = 4539.00$, $p = 0.03$) resulted in longer inpatient stays (see **Table 4**).

Relationship of Suicidality and NSSI With Number of Psychiatric Diagnoses or Rate of Cases With Multiple Diagnoses

There was no significant correlations between time and number of diagnoses [$\tau_{(13)} = -0.28$, $p = 0.151$]. Mann-Whitney U-tests were computed to determine whether patients who gave suicidal thoughts, suicide attempts and NSSI as reasons for their emergency presentation had more diagnoses on average. None of the tests were significant, indicating no difference in the average number of diagnoses in relation to suicidal thoughts, suicide attempts and NSSI as reasons for the emergency presentation (see **Table 4**).

Due to the strong clinical impression that cases are becoming more complex, patients were grouped into those that had equal/more than two diagnoses ("multiple diagnoses") and those that had <2 diagnoses ("single diagnose"). There was a significant positive correlation between time and the number of cases with multiple diagnoses [$\tau_{(13)} = 0.52$, $p = 0.007$]. However, this relationship did not remain significant when controlling for the general number of cases in a partial correlation [$r_{(13)} = 0.40$,

$p = 0.153$]. Since the strength of the relationship remained strong, a rate of cases with multiple diagnoses vs. cases with single diagnose was computed over the years, thereby determining the percentage of cases with multiple diagnoses without the bias of fluctuations in number of cases over the years. Since there was a significant correlation between time and the rate of cases with multiple diagnoses [$\tau_{(13)} = 0.54$, $p = 0.005$], a simple lineal regression was calculated. The regression model was significant [$F_{(1,13)} = 19.98$, $p = 0.001$] and explained 61.0% of the variance in the rate of cases with multiple diagnoses. Time was a significant predictor [$t_{(13)} = 4.47$, $p = 0.001$] (see **Table 3**).

There was a significant correlation between cases in which suicidal thoughts and NSSI were reasons for emergency presentations and the rate of multiple diagnoses, $\tau_{(13)} = 0.70$, $p < 0.001$ and $\tau_{(13)} = 0.56$, $p = 0.004$, respectively. This relationship was not present for suicide attempts as a reason for the emergency presentation, $\tau_{(13)} = 0.00$, $p > 0.999$.

DISCUSSION

The main purpose of this present study was to examine the frequency and possible changes in demographic and clinical characteristics of emergency outpatient presentations at our hospital over a 5-year time course. We were particularly interested in suicidality and NSSI as reasons that led to

TABLE 4 | Group differences in the duration of inpatient stay and number of psychiatric diagnoses for the different reasons of emergency presentations (Results of Mann-Whitney U-tests for dependent variables).

Dependent variables	Group variable	Mean rank	U	p
Duration of inpatient stay	NSSI	no = 215.86 yes = 202.91	17565.00	0.315[a]
	Suicidal thoughts	no = 228.14 yes = 204.10	17494.00	0.08[a]
	Suicide attempts	no = 207.61 yes = 265.66	4539.00	0.03[a]
Number of diagnoses	NSSI	no = 442.31 yes = 454.60	74013.00	0.513
	Suicidal thoughts	no = 461.69 yes = 432.22	91551.00	0.075
	Suicide attempts	no = 445.47 yes = 446.06	17784.50	0.988

$N = 890$; NSSI, Non-suicidal Self-Injury; [a]p-values have been corrected according to the False Discovery Rate (FDR).

emergency presentation. In addition, we also investigated crisis-intervention inpatient admissions from emergency consultations and the number of psychiatric diagnoses among patients.

By means of a retrospective data evaluation, we analyzed the rate and changing demographic and clinical patterns of face-to-face emergency presentations at our child and adolescent psychiatric emergency service. To depict the time course over the years 2014-2018, we examined the 4th quarter of each of the determined years using the hospital's documentation system. Overall, 57.8% of the emergency presentations in our clinic were female and the average age of presentations was 15;4 years. With regard to the sex distribution and mean age during the emergency consultation a previous study in Germany (33) revealed approximately similar findings (14.5 years, 56.2% females), whereas a recent study in France (13) which captured a longer time period starting from 1981 found a younger age (13;10 years) and a slightly higher rate of male children and adolescents (aggressive behavior as a frequent reason for presentation is likely to explain the higher proportion of boys).

The increase in the development of emergency consultations is of great importance for a clinic in order to be able to estimate the demand and the challenge associated with the growing number of patients. Data from this present study showed a significant increase in the number of cases for the last years in the investigated time span (2014-2018). According to the computed regression model, each additional month resulted in an increase of 2.54 cases. A study in France has also found a constant growth in the use of emergency consultations over the study period, albeit with the greatest growth during the 1980s (13). An analysis of emergency presentations in Denmark between 2001 and 2010 demonstrated an annual average increase of 15%, from 2009 to 2010 the number of consultations had declined by 12% (14). We were able to observe this effect of slowing or reversing the trend in our survey when comparing 2017 and 2018 (see **Figure 1**). Here it would be informative to observe the further time trend of emergency presentations. Nevertheless, the current course shows the increasing burden to clinics for child and adolescent psychiatry. The increase in emergency presentations is challenging for clinicians, as far-reaching and difficult decisions often have to be made within a short time. In addition, it is important to be well-prepared structurally and organizationally for this clientele in order to be able to provide high quality mental health care.

We were able to confirm that for every additional month the frequency of suicidal thoughts as reason for an emergency presentation increased by 1.08 cases and the frequency of NSSI by 0.74 cases. Contrary to our expectations, suicide attempts had fortunately not increased as a reason for emergency presentation. In Denmark, a survey between 2003 and 2006 found a doubling in prevalence of suicidal ideation as the single cause of not-admitted emergency presentations (6 vs. 13.1%); suicidal ideation was present in combination with other symptoms (e.g., social problems) in about one third of emergency contacts (14). In this Danish survey, suicide attempts were also unchanged as a reason of presentation (14). A survey of pediatric psychiatric emergency department visits in 2002 found that 47% of presentations reported suicidality (alone or in combination) as a main symptom (34). Primary indication for psychiatric consultation was suicidal ideation at 39% in another survey from a pediatric emergency department in the USA (35). NSSI led to 36.6% of emergency presentations in a retrospective chart review of a clinic for child and adolescent psychiatry in Germany (33). Suicidal ideation was the most common reason for emergency presentation in our study, accounting for 54.2%. NSSI was reported as the reason for presentation in 25.6% of emergency presentations and suicide attempt was obtained as reason for presentation by 4.7%. In our study, several reasons for emergency consultations were collected and evaluated. This could partly explain deviating results. An important research topic, but one that was not included in our survey, is the issue of alexithymia and resilience. Both alexithymia and low resilience were significant predictors of increased suicidal thoughts (36). These aspects would be exciting to consider in future surveys, especially since suicidal ideation was the most common reason for emergency presentation in our study. In general, our results are in line with previous studies on this topic. Our data clearly show an increasing burden to the CAP clinics. For the treatment of suicidal thoughts and NSSI in childhood and adolescence, special interventions must be chosen that pay attention to the risk of self-endangerment of the child.

We could show that emergency presentations due to suicidal thoughts, suicide attempts or NSSI were more likely to result in an admission to the inpatient units. Furthermore, suicide attempts resulted in longer inpatient stays. Former findings from another clinic for child and adolescent psychiatry in Germany showed that half of the crisis admissions were at risk of suicide

at the time of admission, while this was the case in only 5.1% of the planned admissions (15). The results for self-injurious behavior were not quite as clear, but similar; self-injury was present in 56.1% of crisis admissions, in planned admissions, this was the fact in 30.9% (15). The previous study showed a decrease in inpatient stay duration for crisis admissions from 40.4 days (2005) to 19.2 days (2015) (15). However, between 2005 and 2015, there was an increase of 571% in treatment episodes lasting <10 days (15). Thus, before 2009, most patients admitted in crisis almost automatically received regular treatment on the occasion of their crisis, whereas in 2015 the majority of patients received only crisis-focused treatment (15). We explain our finding of longer inpatient stays by the fact that inpatient admissions after psychiatric emergency consultations due to suicide attempts require a respective duration of inpatient treatment, which can hardly be limited further. Most patients admitted to our clinic for crisis intervention are also treated with a crisis focus. However, care must also be taken to ensure that patients are not discharged too quickly and that sufficient intervention and improvement has occurred that readmissions are not required.

The hypothesis that the presence of a greater amount of number of psychiatric diagnoses increases over time could not be confirmed. In further exploratory analyses the data was split according to cases with two or more diagnoses ("multiple diagnoses") and cases with single diagnosis. A rate of multiple diagnoses was computed in order to avoid the bias of generally increasing number of cases and observe multiple diagnoses in relation to single diagnoses. In this reduced data, a positive association between time and the rate of multiple diagnoses was found, indicating that cases with multiple diagnoses increased independent of the general increase in emergency presentations. This increasing number of emerging cases constitutes a constantly growing challenge for the clinic, in terms of personnel, structure and organization. Either, it suggests that additional psychiatric disorders will have to be examined diagnostically in the future, especially since the emergency presentation is partly the gateway to child and adolescent psychiatric treatment (8, 9). Or it suggests that the burden of multiple diagnoses on patients is likely to be increased and, accordingly, multiple aspects need to be considered in the emergency consultation. This in turn can make the evaluation of the crisis situation more difficult. Multiple psychiatric diagnoses often manifest themselves in higher symptom severity and also have to be taken into account in following treatment (29, 30). In the overall spectrum of self-harming behaviors, the context of substance use should not be neglected. Past research has shown a strong relationship between suicidality and substance use, especially among adolescents (25–27). In a study in France, substance use disorder as a main psychiatric diagnosis was four times more common among youth admitted to the emergency department in 2017 compared to 1992 (13). In our sample, the overall proportion of patients with an F1 diagnosis was 16.9%, whereby we surveyed all available diagnoses and not only the main diagnosis. The proportion of F1 diagnoses among emergency presentations with suicidal thoughts were 11.5% whereas a total of 37.6% of individuals with F1 diagnoses presented with suicidal thoughts. This was not examined in detail

as the main question was concerned with suicidality independent of specific diagnoses. However, from our point of view, accompanying substance disorders should be taken into account in the crisis intervention of adolescents. Despite providing an extensive overview of clinic emergency presentations and detailed numbers specifically relating to suicidality and NSSI as reasons for presentations, this study has several limitations. Because this is a retrospective analysis of medical records, the data were not originally collected for research purposes, so we may have underestimated or overestimated certain patient characteristics because of differences in data availability (such as differences in documentation by treating physicians). Our study reports emergency presentations from a maximum-care child and adolescent psychiatric hospital in Germany. It may be that our data cannot be generalized to other pediatric or CAP-settings or hospitals.

Nevertheless, especially with the analysis of over 900 emergency presentations, we have achieved a remarkable sample size and results indicate specific profiles in children and adolescent with suicidality. The daily care of patients presenting to a psychiatric emergency service who require outpatient care or, if necessary, crisis intervention inpatient care, has a high priority in child and adolescent psychiatric clinics. In this context, the risk assessment and management of suicidal crises remain an important and urgent task. All centers providing care should adapt to this topic in terms of content and organization and establish special intervention and treatment programs. In addition, future research should also examine the effectiveness of crisis intervention as it is currently offered in child and adolescent psychiatric clinics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by institutional examination board for the Medical Faculty of the University of Regensburg (Ethics Commission No.: 19-1428-104). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

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Applying Machine Learning Approaches to Suicide Prediction Using Healthcare Data: Overview and Future Directions

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Objective: Early identification of individuals who are at risk for suicide is crucial in supporting suicide prevention. Machine learning is emerging as a promising approach to support this objective. Machine learning is broadly defined as a set of mathematical models and computational algorithms designed to automatically learn complex patterns between predictors and outcomes from example data, without being explicitly programmed to do so. The model's performance continuously improves over time by learning from newly available data.

Method: This concept paper explores how machine learning approaches applied to healthcare data obtained from electronic health records, including billing and claims data, can advance our ability to accurately predict future suicidal behavior.

Results: We provide a general overview of machine learning concepts, summarize exemplar studies, describe continued challenges, and propose innovative research directions.

Conclusion: Machine learning has potential for improving estimation of suicide risk, yet important challenges and opportunities remain. Further research can focus on incorporating evolving methods for addressing data imbalances, understanding factors that affect generalizability across samples and healthcare systems, expanding the richness of the data, leveraging newer machine learning approaches, and developing automatic learning systems.

Keywords: suicide prevention, mental health, predictive analytics, machine learning, neural network analysis

BACKGROUND

According to the World Health Organization, approximately 800,000 people die by suicide annually worldwide, making it the 18th leading cause of death (1)[1]. In the United States, 48,344 people died by suicide in 2018 (2)[2], making it the tenth leading cause of death and contributing to decreasing average United States life expectancy (3). Ultimately, the first step of suicide prevention can be viewed as a classification task to accurately identify individuals at risk for suicide in a specified time horizon, thereby allowing preventive intervention. However, the largest meta-analysis of suicide prediction (4) analyzed 365 studies and concluded that predictions based on individual risk or protective factors have led to weak predictive accuracy showing little improvement over time.

Several factors contribute to this prediction failure. Most notably, suicide is an uncommon event, even among those considered at high risk, such as individuals who have been psychiatrically hospitalized, making it inherently difficult to predict. In addition, suicide results from a complex interaction of numerous factors, each having small but meaningful contributions, rather than a handful of powerful stable predictors. Complicating matters, many suicide drivers are time-varying. Some might change slowly, such as major depressive episodes, while others may change quickly, such as acute alcohol or other substance intoxication (5, 6) or feelings of rejection following a relationship breakup. Prior studies were often limited to small samples and examined a limited number of factors, measured at a single time point, and focused predominately on stable or enduring factors. Consequently, previous efforts have not collected sufficiently comprehensive chronic and transient risk factors over time within a sufficiently large sample to produce accurate prediction models.

Another limitation lies in traditional analysis of suicide data. Until recently, classical statistical approaches predominated, primarily focusing on inference, which includes estimation and hypothesis testing for model parameters. This approach yields relatively simple models, emphasizing interpretability over prediction accuracy, and is not well-suited to handle data with many correlated, interacting factors, or programmed to incorporate new data to iteratively update the models.

However, two recent developments have transformed the suicide prediction landscape. First, large, complex, longitudinal databases, often referred to as "big data," have been developed. For instance, adoption of electronic health record (EHR) systems has become ubiquitous (7), leading to an exponential data expansion: an estimated 2,314 exabytes (exabyte = one billion gigabytes) have been produced through 2020 (8)[3]. EHR data contains both structured and unstructured (text) data from multiple sources, is longitudinal, and can be linked with other sources, such as vital statistics and census data. Access to large, rich datasets containing substantial numbers of suicide cases is making it possible to overcome low occurrence rates.

Second, flexible mathematical and statistical models, referred to collectively as machine learning, have emerged, showing promise in addressing many problems inherent in previous approaches. Machine learning is well-suited to capitalize on emerging big data and enhanced computer processing capacity, making it feasible, easier, and cheaper to run massive analyses (9).

METHODS

This paper provides an overview of machine learning applied to suicide prediction, summarizes exemplar published studies for illustration, and explores future directions for research. The exemplar studies were selected based on consensus of the study team. Team members nominated papers from highly regarded research teams published in high-impact journals with content that aligned strongly with the relevant machine learning principles reflected in this paper. Then, the team worked together to identify the specific ones with the best fit.

RESULTS

Machine Learning Overview

This section provides a high-level overview of machine learning. The Supplement has more technical details, with **Supplementary Table 1** providing commonly used machine learning terminology. While there is no universally accepted definition of machine learning, typically, a dataset is created that includes predictors, often referred to as attributes or features, along with corresponding known outcomes, often referred to as labels, creating what is referred to as a labeled dataset. This approach is called supervised learning. Then, a function (model) can be inferred (learned or trained) to map an input (a set of predictors) to the output (its corresponding label), taking into account the relevant interactions and relations among the predictors. The learning process is optimized such that the derived labels from the learned function can be as accurate as possible compared with correct labels, with good generalizability to unseen data. In suicide prediction, the attributes or features (predictors) for supervised learning would be a specific individual's characteristics, such as demographics, psychiatric diagnoses, substance abuse disorders, and emergency department utilization history. Their corresponding outcome would indicate whether the individual died by suicide (10). These labeled data are used to train a model, with the specific training process dependent on the machine learning algorithm employed (described further in section Common Supervised Learning Approaches).

Machine learning allows the data itself to drive discovery by exploiting patterns or associations in the data without making *a priori* assumptions about distributions or formulating specific hypotheses. Consequently, machine learning can synthesize

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[1] https://www.who.int/mental_health/prevention/suicide/suicideprevent/en/

[2] https://webappa.cdc.gov/sasweb/ncipc/leadcause.html

[3] https://med.stanford.edu/content/dam/sm/sm-news/documents/StanfordMedicineHealthTrendsWhitePaper2017.pdf

complex data with a large number and rich variety of variables and interactions.

Machine learning explicitly seeks to address rarity of suicide, referred to as data imbalance. While increasing the training dataset size helps address imbalance by providing more suicide cases, massive datasets with millions of cases are typically infeasible, and, even when available, they still do not completely solve data imbalance. Fortunately, imbalance mitigation strategies have been developed and are evolving. One common strategy involves under-sampling the majority class, that is, those that did not die by suicide, and over-sampling the minority class, that is, those that died by suicide, to create more balanced datasets. More sophisticated sampling methods, such as synthesizing new variants of the existing cases (11), are also popular. Ensemble methods (12) can be utilized wherein multiple models use the same minority class cases while each model works with distinct subsets of majority class cases. These trained models are then ensembled into one final classifier that combines their respective predictions into a final prediction. Further, cost-sensitive learning (13) tackles imbalance by assigning higher misclassification costs with the minority class and seeks to minimize high cost errors. Lastly, as accuracy may not be a meaningful metric when applied to imbalanced data, performance metrics that explicitly account for such imbalance, such as F1-score, can be applied with unbalanced training datasets. The **Supplementary Table 2** depicts the basic classification structure underlying most approaches, and **Supplementary Table 3** has definitions of common evaluation metrics.

Machine learning incorporates strategies for assuring robustness against overfitting (14), which is when a model is very specific to a training dataset but fails when applied to new datasets. Overfitting is more likely when the model is excessively complex, or when the number of variables or features is very large, but the data size is small. Applied to suicide prediction, overfitting might occur when too many predictive factors such as demographics, risk factors, stressors, and symptom inventories are used. Some strategies for protecting against overfitting include regularization (artificially enforcing smoothness in the model), early stopping (stopping iterations when a particular performance level is reached), or ensembling (combining predictions from multiple independent models). However, overfitting can nevertheless arise. Transfer or replication of a model trained on one dataset to other datasets derived from a similar target population is required. Only after rigorous cross-sample replication and attention to the parameters that might influence generalizability can we be confident the model is robust, valid, and ready for clinical translation.

Machine learning models can adapt over time. This means they can learn directly from data fed back into the model over time without requiring explicit human instruction. This is desirable for tasks too complex for complete manual enumeration of all precise rules or not completely understood by humans. For instance, increasingly larger combinations of newly discovered risk factors as well as the relationship between them might need to be taken into account for achieving effective suicide prediction. It would not be feasible to manually derive

the complete set of all valid logic rules to fully capture the true relationship between predictors and suicide (15)[4]. Instead, the model can be designed to adapt over time based on prediction accuracy and as new variables are introduced and new data entered into the model.

Common Supervised Learning Approaches

While many supervised learning approaches can be applied to classification and prediction, four are widely used and have been applied to suicide: penalized regressions, decision trees, random forests, and Support Vector Machines (SVMs) (9). **Supplementary Table 4** provides a summary of strengths and weaknesses of these approaches, while **Supplementary Figure 1** provides an example of a supervised learning algorithm.

Penalized regression refers to a class of iterative methods that determine optimal regression coefficients subject to certain constraints to avoid overfitting. Variants that have been explored for suicide prediction include Lasso (16) and Elastic Net (17). These variants differ primarily in the constraints applied, such as reducing the weight of the coefficients of certain features vs. completely eliminating them by setting them to zero.

A decision tree learns in a hierarchical fashion by iteratively splitting the dataset into increasingly smaller subsets based on decision criteria on a given variable. The construction of this decision tree aims to produce the most homogeneous group possible at each split (18, 19). An example of an initial split might be whether the individual has a well-known risk factor, such as bipolar disorder, and a second split might involve a second factor, such as access to a firearm. Random forest, an extension of decision trees, uses majority voting to combine decisions from multiple decision tree models that are created from different subsets of the same dataset in order to produce a final classification decision.

Another widely used supervised learning algorithm is an SVM, which belongs to the class of methods that jointly performs classification in a single decision step. SVM aims to find a decision boundary, called a hyperplane, that best divides different classes (e.g., suicide vs. not suicide) in high-dimensional space (i.e., a large number of possible predictors). The optimal hyperplane is computed using the "max-margin principle," such that data instances that are the nearest to the hyperplane, but from different classes (called the support vectors), are separated by the widest possible margin. New data examples are then mapped into that same space and predicted to belong to a class label based on the side of the hyperplane on which they land. SVMs are versatile in that they can handle sparse data and are widely applicable to numeric data.

Typically, multiple approaches are used on the same data and accuracy compared to select the best performer. Besides accuracy, interpretability of the results can be used to decide the best approach. Unlike regressions and decision trees, SVM results are not easily interpretable due to mapping of data instances into an abstract representational space and employing vectors as decision

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[4]https://cdn.preterhuman.net/texts/science_and_technology/artificial_intelligence/Introduction%20to%20Machine%20Learning%20-%20Nils%20J%20Nilsson.pdf

boundaries in this space. In situations where interpretability is important, regressions and decision trees are preferred.

Leveraging Unstructured Data Through Natural Language Processing

All machine learning approaches are applicable to structured data; they assume numeric or categorical data as input. However, much EHR data consists of unstructured narrative notes. Natural language processing (NLP) strategies have been developed to process human language by applying syntactic and semantic knowledge and extracting structured concepts that can serve as features characterizing the patient. For example, text that describes firearm ownership can be translated into binary values "yes" or "no." With clinical narratives becoming increasingly available in health system databases, NLP has become an essential tool for constructing clinically relevant structured information (20, 21). Providing early support, McCoy et al. (20) used off-the-shelf NLP technology to develop algorithms from narrative discharge summaries that better predicted suicide and accidental death after hospital discharge than traditional structured data alone.

Case Studies on Estimating Risk for Suicide

A recent meta-analysis concluded that emerging machine learning studies have led to significantly better prediction of suicide-related outcomes than earlier studies using smaller samples and classical statistical approaches (22). This literature will not be reviewed in depth, but, instead, two exemplar studies that predicted death by suicide will be used for illustration purposes.

Simon et al. used Mental Health Research Network data containing historic EHR structured data from seven civilian health systems linked with death data (16). The sample consisted of 2,960,929 individual patients ≥13 years old who contributed 19,961,059 eligible primary care or outpatient specialty mental health visits between January 1, 2009 and June 30, 2015. In the 90 days after an eligible visit, 24,133 suicide attempts and 1,240 suicide deaths were identified. The investigators developed a logistic regression model with penalized Lasso variable selection, described in section Common Supervised Learning Approaches, to predict suicide deaths and suicide attempts. Input variables (features), spanning up to 5 years before the index visit, included socio-demographic variables (e.g., age, sex, neighborhood income), current and past mental health and substance abuse diagnoses, past suicide attempts, past injury or poisoning, in-patient and emergency service use, psychotropic medications, general medical morbidity measured by Charlson Comorbidity Index (23)[5] categories, and the Patient Health Questionnaire −9 (24), a patient-reported depression severity measure. Importantly, they factored in time windows for diagnoses and acute care utilization to represent within 90 days, 1 year, and 5 years of the index visit, as well as numerous interactions between socio-demographics and health care features.

The final input pool comprised 313 variables. Suicide was rare, occurring in <1 tenth of 1% of the sample. Despite this, the model predicting suicide in 90-days after a visit had a c-statistic, synonymous with a receiver operating characteristic curve's area under the curve, of 83%-86%. Visits with risk scores above the 75th percentile identified 80% of subsequent suicide, while those above the 95th percentile identified 43% of all suicide. This accuracy was markedly greater than previously published efforts (25, 26) and was superior to several widely used medical outcome prediction tools, such as predicting rehospitalization for heart failure (27) and in-hospital mortality from sepsis (28). These historic results were likely due to several factors, including a very large dataset, enhanced ascertainment of risk factors present in EHRs, using a very large predictor pool, including interaction terms, use of temporal coding, use of robust machine learning analytic strategies, and inclusion of a patient reported measure, the Patient Health Questionnaire-9, which accounted for significant prediction variance despite being available for <20% of the sample.

A similar study completed by Kessler and colleagues (17) used EHR data from United States Veterans Health Administration. Their sample included 6,359 veterans who died by suicide during 2009–2011 and used Veterans Health Administration services in the year of their death or the prior year and a randomly selected control sample of 2,108,496 veterans who received Veterans Health Administration services but were alive at the end of the month the suicide decedent died. They began with 381 predictors spanning several domains similar to the Mental Health Research Network study, except Patient Health Questionnaire-9 scores were not available. They also incorporated time varying predictors for healthcare utilization and mental health diagnoses spanning 1, 2, 3, 6, 12, 19, and 24 months prior to the index visit. Their primary analysis used a penalized logistic regression Lasso approach to predict suicide within a 30-day window and found very promising results. Their final algorithm, which used 61 of the original 381 predictors, revealed sensitivities among individuals with the top 0.1, 1, and 5% of risk as 2.8, 11.8, and 28.2%, respectively. These sensitivities are low in absolute terms but are markedly better than historical efforts (4). Also, they were replicated when applied to an independent prospective validation sample.

Notably, Kessler's study also evaluated eight additional machine learning approaches that allow complex non-linear interactions among predictors, including those that can maximize prediction accuracy but are uninterpretable "black box" approaches, like SVM. These algorithms revealed similar sensitivities as the Lasso regression, and, one approach, a version of decision tree analysis, showed slightly stronger prediction accuracy. The authors encouraged validation with other datasets before their decision tree findings can be interpreted as reliably and meaningfully superior.

DISCUSSION

Initial efforts using machine learning to predict suicide are promising; however, the field remains in its early stages and much work remains before these approaches can be fully embraced clinically. Below, directions for future research are discussed.

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[5]https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html

Incorporating Time

Future machine learning efforts will need to address time from several perspectives. First, historical factors preceding the prediction point (the visit or date when the estimation of future probability is being made) require time boundaries, because the nearness of the feature itself may have differential associations with future event probability. A suicide attempt in the month before the prediction point may be more strongly associated with an attempt in the next 3 months than a suicide attempt 30 years ago. Second, the time horizon, or prediction window, after the prediction point is important; different features may predict short-term suicide compared to long-term suicide. Third, for features expected to fluctuate quickly, such as mood states, frequent assessment and longitudinal representation in datasets are ideal. Fourth, time, as embodied by an individual's age, likely influences model composition; suicide drivers among adolescents may be very different than drivers among the elderly. Careful attention to the variety of time-related issues are essential for building models that can adjust an individual's estimated risk based on age, modified as time passes, and trigger interventions tailored to short- vs. long-term risk.

In addition to incorporating time into model construction, future studies need to build learning models that digest new data, new predictors, suicide outcomes, and timely human feedback, leading to a continuous learning loop that improves prediction performance iteratively over time. This is a fundamental advantage of machine learning yet, to date, all published machine learning suicide studies report on static models developed using an initial database within a given time window. Building automated learning models would empower us to fully realize the value of machine learning.

Incorporating New EHR Features and Data Sources

A model is only as good as the richness of the data input, meaning classification (prediction) accuracy for future studies will benefit from new and evolving features as they become available in EHRs, such as data obtained from suicide-specific risk screening and assessments. These instruments are increasingly being adopted by health systems because of organizations such as the Joint Commission (29)[6] that are promoting new standards, which in turn are being built as EHR templates. Moreover, the use of standardized measures to guide care decisions, or measurement-based care, is becoming more common (30, 31). This means serial administration of patient reported measures, like the Patient Health Questionnaire-9, and integration of even more sophisticated measures, like computerized adaptive tests (32, 33), into EHRs are likely to improve our ability to accurately measure time-varying features, like psychiatric symptoms, escalations in substance use, and stress. Other data sources outside the EHR may be linked to improve data richness, such as small area geocode variables, judicial and penal system records, biomarkers and genomics, social media data, and mobile application data. Linking these rich data sources would mitigate

weaknesses inherent in current EHR datasets by enabling a more comprehensive and time-sensitive set of inputs, which may improve accuracy while helping adjust risk estimations over time.

Applying Novel Advances in Machine Learning

Ensemble learning, which combines predictions from a variety of approaches rather than using just one, tends to offer better prediction than single strategies (34). Future studies will need to evaluate whether the ensemble approach is worth the increased complexity and cost. Further, an advanced type of machine learning, called deep learning (35),[7] has shown promise in solving increasingly complex problems in other fields, such as recognizing objects inside of an image and understanding speech, movement, activity, sleep, and online behavior. Deep learning works by composing multi-layered non-linear computational neural network models inspired by the neural structure of the human brain. Because deep neural network models typically rely on an enormous number of labeled data instances, to fully utilize these strategies we will need to build even larger databases.

In addition to advances in computational approaches, NLP advances have created sophisticated strategies for translating text into meaningful structured data. For instance, bidirectional encoder representations from transformers (36) is a recent NLP neural language model developed by Google AI in 2018 and has demonstrated state-of-the-art results on a variety of NLP tasks. Bidirectional encoder representations from transformers contains a multi-layer neural network architecture (37)[8] that can learn optimal vector representations of each word incorporating contextual information bidirectionally. The semantic-rich representations derived from EHR narratives through bidirectional encoder representations from transformers would likely further strengthen prediction models.

Understanding Implementation

Just because suicide can be predicted successfully using a particular training dataset data does not mean these algorithms easily transfer into clinical practice. Understanding how well the algorithms translate from training data to an individual health system is essential. It is unlikely that a published algorithm can simply be "copied and pasted" into a health system. Before algorithms can be transferred to a given setting, we need to know more about factors affecting their accuracy, and, even then, a process for local validation using a health system's own data is likely necessary before algorithms can be translated into practice.

Future studies will need to evaluate the best way to visualize and communicate the results from these algorithms in such a way that they are intuitive, useful, and actionable for the clinician and the patient (38). The blending of machine learning prediction with clinician-based suicide risk assessments, what can be referred to as a "human in the loop" approach, needs exploration to develop effective decision support tools clinicians will trust and utilize. We need to better understand the relative

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[6]https://www.jointcommission.org/resources/patient-safety-topics/suicide-prevention/

[7]https://papers.nips.cc/paper/2016/file/577ef1154f3240ad5b9b413aa7346a1e-Paper.pdf

[8]https://arxiv.org/pdf/1706.03762.pdf

value of each data source for its predictive power, and to drill down to understand when information sources contradict one another, such as when a machine learning algorithm suggests a person is at high risk but the individual denies thoughts of suicide.

An essential consideration for translation into practice is EHR alert fatigue. Because prediction is driven by many long-standing factors conveying long-term risk, such as the diagnosis of major depressive disorder, an EHR alert built on an algorithm tapping into this historical data will likely persist, even after treatment has been delivered or symptoms subside. Consequently, the alerts have the potential for diminishing utility over time. In some cases, this can have serious implications for patient outcomes. For example, if a clinician becomes fatigued and ignores these alerts, he or she may miss an opportunity to intervene with a suicidal patient. This is a practical example of why building models that adjust with time, both backward by incorporating time-bounded predictors and forward by incorporating specific time horizons, are essential. Static alerts that do not reflect changes in clinical status or interventions will quickly become ignorable.

CONCLUSION

Machine learning has strong potential for improving estimation of future suicide risk and for monitoring changes in this risk over time; however, important challenges remain before this benefit can be realized clinically. Further research must address persistent methodological issues by incorporating novel methods for addressing data imbalance and overfitting and understanding factors that affect generalizability across samples and settings. Expanding the richness of the input data, leveraging newer analytic approaches, and developing automatic learning systems offer strong promise for both improving predictive ability and adjusting risk estimations over time. As important as pure predictive ability, we need to explore the best ways to represent risk to the clinician, so it is easily interpretable, actionable, and minimizes alert fatigue.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

EB was responsible for the overall manuscript preparation, including overseeing and synthesizing edits from the rest of the authors. EB, ER, FL, BW, CL, EA, SG, JS, GS, RD-M contributed materially to the conceptualization, writing, and editing of this paper. All authors contributed to the article and approved the submitted version.

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Low Level of Perfectionism as a Possible Risk Factor for Suicide in Adolescents With Attention-Deficit/Hyperactivity Disorder

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Introduction: Suicide is one of the leading causes of death among adolescents. Although it is known that both perfectionism and attention-deficit/hyperactivity disorder ('ADHD') are important risk factors for suicide, there are no studies that have investigated the relationship between suicidal behavior and perfectionism among people with ADHD.

Aim: The current study investigates the association between perfectionism and suicide in adolescents with ADHD.

Method: Subjects included 88 adolescents with ADHD and 96 non-clinical control adolescents. We used the Multidimensional Perfectionism Scale to evaluate perfectionism as well as its separate traits, and the Mini International Neuropsychologic Interview Kid to evaluate psychiatric disorders and suicidal behavior. Differences between the groups were statistically evaluated using t-tests, a Poisson regression analysis with suicide as a discrete variable, and a logistic regression analysis with suicide as a binary variable.

Results: Compared to the control group, the ADHD group showed a significantly lower level on the adaptive 'Organization' trait of perfectionism, but not on any other trait, and a significantly higher level of suicidal behavior.

Logistic regression results indicated a significant association for perfectionism in general (OR = 0.93, $p = 0.003$), and for the 'Personal Standards' trait (OR: 0.82, $p = 0.039$). Poisson regression analysis also showed a significant association with perfectionism in general (IRR = 0.90; $p < 0.001$) and with the 'Personal standards' trait model (IRR = 0.81, $p = 0.019$).

Discussion: Our results indicate that a low level of perfectionism, in particular 'Personal standards', may be a risk factor for suicidal behavior in adolescents with ADHD. We recommend that psychoeducation and therapy of adolescents with ADHD should consider focusing on adaptive perfection as a possible risk factor for suicide as well.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder ('ADHD') is one of the most diagnosed psychiatric disorder among children and adolescents (1), with a prevalence of 4–6% in children, while up to two-thirds of them have impairments in adulthood as well (2–4). The core symptoms of ADHD include inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). People with ADHD often endure stigmatization due to their symptoms including social rejection (5–7). According to Wu (8) ADHD is associated with poorer school tests, and they drop out of school more often. Faraone (9) found that children with ADHD have more often learning disabilities, are more often placed in special classes and perform poorly in classroom activities. Moreover, Kent (10) found that, even if controlled for IQ, there was a significant difference in cumulative grade point averages between adolescent males with ADHD and non-clinical adolescent males.

Both impulsivity and perfectionism (11) are transdiagnostic personality factors which previously were thought to exclude each other because impulsivity is characterized by a lack of control, while perfectionism is characterized by a rigid need for control. However, recent studies have suggested that perfectionism may play a more important role in ADHD than previously thought. It has been shown for instance that both impulsivity and perfectionism can be related to externalizing and internalizing pathology disorders and thus they do not necessarily exclude each other (12). Indeed, there have been several recent studies that have indicated a connection between perfectionism and ADHD: Strohmeier et al. (13) found that perfectionism was predominantly associated with adult ADHD and was associated with procrastination and delaying the start of a task until all conditions are fulfilled (13). Greven et al. (14) found that the severity of ADHD symptoms was associated with an increase in internalizing and externalizing problems as well as an increase in perfectionism. Arancibia et al. (15) found that so-called 'cluster C' personality traits such as perfectionism, dependency and anxiety were significantly associated with ADHD.

Importantly, there is also a growing body of research evidence that both ADHD is associated with an increased risk of suicide, which is a leading cause of death among adolescents [e.g., (1, 16)]. According to a systematic review of Balazs and Kereszteny (1), there is a positive association between ADHD and suicidal behavior both in children and adolescents. A second longitudinal review by Garas and Balazs (17) which investigated suicide risk in ADHD patients found a positive association between

ADHD and the presence of suicidal behavior at follow-up visits. Additionally, Manor et al. (18) investigated 23 subjects, who were admitted to the emergency room as a result of an attempted suicide and found that 15 did meet the criteria for an ADHD diagnosis, while only five of them were actually diagnosed with ADHD.

In addition to this, several studies have also indicated a positive relationship between perfectionism and suicidal behavior (16, 19–21) such as Hamilton and Schweitzer (19) found that perfectionism was associated with an increased 'vulnerability to suicide ideation' among university students. Limburg et al. (16) performed a meta-analysis focusing on perfectionism and psychopathology and found that perfectionism was strongly linked to depression, obsessive-compulsive disorder and anxiety disorder. Recently, Abdollahi and Carlbring (20) focused on different aspects of perfectionism regarding suicidal ideation: while 'neurotic perfectionism' was positively associated with suicidal ideation, 'adaptive perfectionism' was negatively associated with suicidal ideation. A meta-analysis, published by Smith et al. (21), found that striving for perfection was associated with an increase in suicidal ideation while the 'Organization' dimension of perfectionism was associated with a reduced level of suicide ideation. Other traits of perfectionism did not affect suicidal ideation.

Based on these recent new insights, the main aim of the present study was to explore if perfectionism may be a risk factor for suicidal behavior in adolescents with ADHD. We believe that increased knowledge in this area may help to improve suicide prevention in patients with ADHD.

MATERIALS AND METHODS

Participants and Procedure

The study was conducted with the approval of the Ethical Committee of the Medical Research Council, Hungary (ETT-TUKEB, project identification code: 50922-2/2017/EKU). Subjects were provided with written informed consents after being verbally informed on the nature of the study. After signing the informed consent, a diagnostic interview was recorded by a psychologist (see below). Afterwards, self-rated questionnaires were completed by all subjects. No compensation was provided to the participants.

Adolescents with ADHD were recruited from the Vadaskert Child Psychiatric Hospital and Outpatient Clinic, Budapest, Hungary, in Szent Rokus Hospital and Outpatient Clinic, Baja and Tolna County's Balassa Janos Hospital and Outpatient Clinic, Szekszard. Control group participants were recruited from

several high schools in Hungary. Both groups included subjects between 13 and 18 years. Further inclusion criteria for the clinical group included an ADHD diagnosis from a psychiatrist which needed to be confirmed by a structured psychiatric diagnostic interview (see below).

Exclusion criterion for both the ADHD and control groups included a medical history of intellectual disability. Further exclusion criteria for the control group included: current or previous psychiatric diagnoses or psychological treatment (see below).

Questionnaires

Mini International Neuropsychologic Interview for Children and Adolescents

Psychiatric symptoms and disorders were diagnosed using the modified version of the Mini International Neuropsychologic Interview for Children and Adolescents (MINI Kid). The modified version of the MINI Kid evaluates the presence of twenty-four psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) (APA, 2013), including ADHD and their subthreshold forms and suicidal behavior [22, 23]. The original English language MINI Kid has been shown to have adequate validity and reliability [22]. Balázs et al. [23] developed a Hungarian version of the MINI Kid, which has also been shown to have adequate test-retest reliability, specificity, and sensitivity [23]. The questions of the MINI Kid follow the DSM-5 criteria of the disorders. In its original form, the structure of the MINI Kid is branching, which means, if the core symptoms of a disorder are not present, the additional questions on the symptoms of that disorder should not be asked. However, in the current study we used the modified version of the MINI Kid, which means we excluded the 'branching logic' and in this way the MINI Kid evaluated all the possible symptoms of a disorder.

Current suicidal behavior was assessed via the following questions of the MINI Kid: "In the past month did you" "Wish you were dead?", "Want to hurt yourself?", "Think about killing yourself?", "Think of a way to kill yourself?", "Attempt suicide?" Have a method in mind to kill yourself?" Participants met the criterion for suicidal behavior after one "yes" answer and according to the points, suicidal behavior level was either "low" or "moderate" or "high" [22, 23]. The MINI Kid was administered by interviewees who were MA or PhD students in psychology or medicine. To ensure validity and inter-rater reliability, all interviewers took part in a training course on the MINI Kid before the study and were under continuous supervision by the leader of the research. As all participants were older than 13, they were interviewed according to the instructions of the Mini Kid administration procedure without parental participation [22, 23].

Multidimensional Perfectionism Scale

The level of perfectionism was evaluated with the 'Multidimensional Perfectionism Scale' ('FMPS'), a self-report scale developed by Frost et al. [24]: It contains 35 questions, which are grouped into four 'maladaptive' and two 'adaptive' traits of perfectionism [24–26].

Maladaptive traits cause a negative reaction if standards are not reached and include: 'Concern Over Mistakes' (reflecting negative reactions to errors), 'Parental Criticism' (the perception of parents being too critical), 'Parental Expectation' (the perception of high parental standards), 'Doubt About Actions' (the tendency to doubt abilities in actions). Adaptive traits do not evoke negative reactions if the goal is not reached and include: 'Personal Standards' (setting high standards for assessments), 'Organization' (the ability and importance placed on orderliness).

Response method used a 5-point liker scale (1 = strongly disagree and 5 = strongly agree). The internal consistency of the subscales ranged from 0.77 to 0.93 [26]. The total score of the FMPS is calculated by summing the scores of each trait except 'Organization' [24–26]. According to Frost et al. [24] the 'Organization' trait showed a low correlation with other total traits of the perfectionism scale, therefore it was suggested to leave this trait out when looking at the total score [24]. The FMPS scores are strongly correlated with scores of other questionnaires of perfectionism (r = 0.85 with Burns Perfectionism Scale, and r = 0.59 with the Perfectionism Scale from the Eating Disorder Scale) [24].

Demographic Questionnaire

A structured parent-rated questionnaire was developed specifically for this study to gather information about the demographic data of the participants, including the combined education level of the parents, family history of psychological or psychiatric treatment, economic activity of the father/mother (e.g. active worker, unemployed, retired, full-time parent, deceased), as well as the structure of the family. The questionnaire consisted of closed questions and each answer belonged to a point.

Statistical Analysis

Comparison of Levels of Perfectionism and Suicidal Behavior

Statistical analyses were performed using Stata 14 [27]. Differences in FMPS scores between the ADHD and control group were evaluated using t-tests. The distribution of the suicide scale of the MINI Kid significantly violated normality assumptions [28] and was therefore evaluated using a non-parametric Mann-Whitney test and a Spearman correlation test. Because multiple comparisons were performed, the p-value for each variable was calculated using a Holm-Bonferroni correction method (adjusted p-value). Effect sizes were calculated with Cohen's d for the parametric test (t-test), a rank correlation r-value for the non-parametric Mann-Whitney test [29] and the Cramer's V for comparisons between two nominal variables. For all descriptive statistics, the reliability was above .70 and thus acceptable [30]. The descriptive statistics of the variables can be found in **Table 1**.

Association Between Perfectionism and Suicidal Behavior in ADHD

Two types of regression models were used to analyze suicidal behavior as we believe they both provide important information on the phenomenon. In the first clinical approach, suicidal

TABLE 1 | The descriptive statistics of the variables.

Variable	ADHD					Non-clinical controls				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Age	88	14.6	1.77	13	18	96	14.8	1.53	13	18
Parental education	88	3.05	1.78	0	6	96	4.09	1.13	2	6
Concern over mistakes (perfectionism)	88	20.8	7.17	9	42	96	20.9	7.29	9	39
Personal standards (perfectionism)	88	18.6	6.32	7	35	96	20.2	6.15	8	34
Parental expectations (perfectionism)	88	12.2	4.52	5	25	96	12.0	4.23	5	20
Parental criticism (perfectionism)	88	8.77	3.89	0	18	96	8.12	3.47	4	20
Doubt about actions (perfectionism)	88	10.9	3.61	4	20	96	10.1	3.60	4	18
Organization (perfectionism)	88	21.7	5.19	6	30	96	24.0	4.70	11	30
General scale (Perfectionism)	88	71.3	20.0	35	137	96	71.2	19.1	32	121
Suicidal symptom scale	86	0.30	1.17	0	7	96	0.01	0.10	0	1

ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation.

behavior is included as a binary variable representing the presence of the symptom and evaluated using a logistic regression approach. For this approach we calculated the Odds Ratio ('OR') as a relative measure of association. The OR is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group.

For the second approach, suicidal behavior was evaluated as a continuous discrete variable and evaluated using a Poisson regression. For this approach, the Incidence Rate Ratio ('IRR') was calculated as a measure of association.

Within this analysis, over dispersion was evaluated using the alpha statistic. If standard deviations were not equal (indicated by an alpha significantly greater than zero), a negative binomial regression was used instead of a Poisson regression (31).

For both approaches, we evaluated perfectionism either as a unidimensional or multidimensional concept. The unidimensional approach includes only one total score of perfection, based on all traits except 'Organization'. For the multidimensional approach we included all traits of perfection (except 'Organization') as separate variables.

The other explanatory variable included in each regression analyses was a combined ADHD diagnosis. The two ADHD variables ('Predominantly Inattentive', 'Predominantly Hyperactive/Impulsive') were combined into one variable because of their high dependence [$\rho_{(182)} = 0.69, p < 0.001$].

Control variables for all regression analyses included age and the education level of the parents. Gender was not included as a control variable because the ADHD group was too severely skewed toward male subjects (92% male). The best model fits were decided by using the Akaike information criterion ('AIC') index. If the control variables did not provide a better fit for the models, then they were not included in the regression analysis.

RESULTS

Sample

In the present study the ADHD group included 88 adolescents (mean age: 14.58; SD: 1.77) and the control group 96 adolescents (mean: 14.77; SD: 1.53). There was no significant difference in age between the groups. In regard to gender, there was a significant difference between the clinical and control group: in the control group 46% of the participants were girls whereas in the clinical group only 8% of the participants were girls [$\chi 2_{(1)} = 39.32; p < 0.0001, V = 0.46$].

Table 2 presents the comparison of ADHD and control groups regarding information about the demographic data of the participants.

Comparison of Perfectionism Between the ADHD and Control Group

The comparison of the ADHD and control group regarding each perfectionism scale can be found in **Table 3**. There was one subscale showing a significant difference between the groups, namely 'Organization': The ADHD group scored significantly lower on this trait than the control group [$t_{(183)} = 3.153 p = 0.002$]; effect size medium [$d = 0.47$; clinical group: $M = 21.73$; sd $= 5.18$, control group: $M = 24.02$; sd: $= 4.7$, standard deviations were homogeneous ($F = 0.946; p = 0.332$)]

Comparison of Suicidal Behavior Between the ADHD and Control Group

Table 3 presents the comparison of ADHD and control groups regarding suicidal behavior and perfectionism. The distribution of the suicide scale (symptom frequency) was significantly skewed due to the rarity of the symptoms, therefore a non-parametric Mann-Whitney analysis was applied, as mentioned

TABLE 2 | Comparison of ADHD and control groups regarding information about the demographic data of the participants.

		ADHD n = 88	Nonclinical controls n = 96
Combined education level of the parent scoring: 1 = High School; 2 = College; 3 and above = University		3.05 (SD=1.78)	4.09 (SD=1.13)
Family history of psychological or psychiatric treatment n (%)	Yes	50 (59.52%)	45(47.87%)
	No	34 (40.48%)	49 (52.13%)
Father's economic activity n (%)	Active worker	57 (80.28%)	81 (84.38%)
	Unemployed	6 (8.45%)	2 (2.08%)
	Retired	3 (4.23%)	3 (3.13%)
	Full-time parent	1 (1.41%)	6 (6.25%)
	Deceased	4 (5.63%)	4 (4.17%)
Mother's economic activity n (%)	Active worker	47 (62.67%)	75 (78.95%)
	Unemployed	10 (13.33%)	4 (4.21%)
	Retired	2 (2.67%)	1 (1.05%)
	Childcare	1 (1.33%)	7 (7.37%)
	Full-time parent	14 (18.67%)	7 (7.37%)
	Dependent	1 (1.33%)	0 (0.00%)
	Deceased	0 (0.00%)	1 (1.05%)
The structure of the family n (%)	Original full family	41 (50.62%)	72 (75.79%)
	Incomplete family (mother only)	19 (23.46%)	11 (11.58%)
	Incomplete family (father only)	0 (0.00%)	1 (1.05%)
	Complete family with foster mother	5 (6.17%)	2 (2.11%)
	Complete family with foster father	13 (16.05%)	9 (9.47%)
	Family with other relative	3 (3.70%)	0 (0.00%)

ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation. No data available of the 88 ADHD participants to the question: 'Family history of psychological or psychiatric treatment': n = 4 'Father's economic activity': n = 17, 'Mother's economic activity': n = 13, 'The structure of the family': n = 7. No data available of the 96 Nonclinical controls: 'Family history of psychological or psychiatric treatment': n = 2, 'Father's economic activity': n = 0, 'Mother's economic activity': n = 1, 'The structure of the family': n = 1.

in the methods section. Statistical evaluation of the suicide scale revealed a significantly higher presence of suicidal behavior in the ADHD group, but the effect size was low [$z_{(182)} = -2.975$, $p = 0.003$, $r = 0.22$].

Negative Binominal Regression

Negative binominal regression analysis used suicidal behavior as a discrete variable. According to the AIC index, the model without demographic variables showed the best fit.

For the simple model, the IRR for the variable ADHD was 1.57 ($p - 0.012$), indicating that if the combined ADHD scale increased by one unit, the incident rate for suicidal behavior increases with 57 %. The IRR for 'Total Perfectionism' was 0.90, ($p < 0.001$), which indicates that if the perfectionism scale increases by one point, it would reduce the incident rate of suicide behavior scale with 10%. The detailed results of the simple model regression can be found in **Table 4**.

TABLE 3 | Comparison of ADHD and controls regarding suicidal behavior and perfectionism.

Variable	Significance test ADHD—control	Adjusted p value
Concern over mistakes	$t_{(183)} = 0.095$	1.00
Personal standards	$t_{(183)} = 1.68$	0.76
Parental expectations	$t_{(183)} = -0.26$	1.00
Parental criticism	$t_{(183)} = -1.18$	1.00
Doubt about actions	$t_{(183)} = -1.38$	1.00
Organization*	d: 0.47 $t_{(183)} = 3.15$	0.016
Perfectionism (general)	$t_{(183)} = 0.04$	1.00
Suicidal behavior	$R = 0.22$ $z(181) = -2.98$	0.016

Adjusted p value: calculated for each variable, using a Holm-Bonferroni correction method.

The extended model revealed a significant association for 'Personal standards' (IRR = 0.81, $p = 0.019$), indicating that for each unit increase in the Likert-scale for 'Personal Standards', the percent change in the incident rate of suicidal behavior was 19%.

Logistic Regression Analysis Results

The logistic regression approach used suicide as a binary variable. According to the AIC indicator, the fit of the model without demographic variables showed the best fit.

The simple model indicated a significant association for 'total perfectionism' (OR = 0.93, $p = 0.003$), indicating that an increase in one unit on the perfectionism score reduced the chance of suicidal behavior by 7%. The presence of ADHD increased the chance of suicidal behavior by 48% (OR = 1.48, $p = 0.012$). **Table 5** shows the detailed results for the simple model.

With the extended model including five perfectionism traits, the factor 'Personal Standards' was significantly associated with suicide behavior [OR: 0.82 ($p = 0.039$)]. This result indicates that an increase of one unit in 'Personal Standards' reduced the chance of suicidal behavior by approximately 8%.

DISCUSSION

According to our knowledge this is the first study which investigates if perfectionism is a risk factor for suicidal behavior in adolescents with ADHD. The main finding of the current study is that the level of suicidal behavior was negatively associated with adaptive perfectionism.

Our study also indicated that adolescents with ADHD show a significantly higher level of suicidality than the control group. This result is in line with previous studies which have also indicated a significantly increased level of suicidality in adolescents with ADHD (1, 11, 32, 33).

We found a significant *negative* association between adaptive perfectionism and suicidal behavior among adolescents with ADHD. This result is in line with several previous findings in clinical populations with other psychiatric disorders [e.g., (34–36)]. Only the adaptive 'Personal Standards' trait was found

TABLE 4 | Negative binominal regression analysis with discrete suicide variable.

Suicide scale	IRR	st. err.	z-value	p-value	95% conf. int.
Perfectionism (general)**	0.90	0.025	−3.75	<0.001	0.85–0.95
ADHD (combined)*	1.57	0.28	2.50	0.012	1.10–2.24
Other statistical values					
Mean dependent var	0.15	SD dependent var		0.82	
Pseudo r-squared	0.18	Number of obs		182	
Chi-square	21.1	Prob > chi2		<0.001	
Akaike crit. (AIC)	104.5	Bayesian crit.		117.3	

ADHD, attention-deficit/hyperactivity disorder; IRR, incidence rate ratio; st.err, standards error; 95 conf.int: confidence interval.

TABLE 5 | Logistic regression results with binary suicide variable.

Dummy	OR	st.err.	z-value	p-value	95% conf. int.
Perfectionism (general)**	0.93	0.023	−3.02	0.003	0.88–0.97
ADHD* (combined)	1.48	0.23	2.50	0.012	1.09–2.00
Other statistical values					
Mean dependent var	0.060	SD dependent var		0.24	
Pseudo r-squared	0.203	Number of obs		182	
Chi-square	16.9	Prob > chi2		<0.001	
Akaike crit. (AIC)	72.2	Bayesian crit.		81.8	

**p <0.01, *p < 0.05. ADHD, attention-deficit/hyperactivity disorder; OR, odds ratio; st. err, standards error; 95% conf.int: confidence interval.

to be significant in the perfectionism model by having a negative association with suicidal behavior among adolescents with ADHD. Moreover 'Personal Standards' may indeed be a protective factor for suicide in an ADHD population. These results have drawn the attention of clinicians to the importance of improving adaptive perfectionism in patients with ADHD. The study of Abdollahi et al. (37) provides compelling evidence for the importance of 'cognitive behavioral therapy' ('CBT') in the reduction of maladaptive perfectionism in patients with social anxiety disorder ('SAD'). Further studies that focus on the efficacy of CBT in increasing the level of adaptive perfectionism in patients with ADHD, could help improve prevention of suicide in this population. As our study is the first to investigate the role of perfectionism as a possible risk factor for suicide in adolescents with ADHD, our results need to be replicated by future studies.

Besides our main findings, our results also indicated that within the subscales of perfectionism, adolescents with ADHD only scored lower than nonclinical controls on the adaptive 'Organization' trait. Over the past 30 years, a large body of research has examined the role of perfectionism in a variety of psychiatric disorders, including anxiety disorders, depression, eating disorders, suicide risk, social phobia (38–41) as well as ADHD (13–15). While Frost et al. (24) stated that perfectionism is linked to a higher level of psychopathology, there have been studies that have contradicted this statement (38–41). Our result is in line with previous studies: Weyandt and DuPaul (42) found that adolescents with ADHD have poorer organizational skills and a recent study by Christian et, al. (12), using latent profile analysis to identify subgroups in a population of 1,353 undergraduate students, found that the dimensions 'impulsivity'

and 'perfectionism' can co-occur within the same person. Stoeber and Otto (36) already raised concerns whether 'Organization' is part of the perfectionism construct (24) and previously considered 'Organization' to be associated with perfectionism, but not a defining trait. Thus, it is not impossible that adolescents with ADHD have low organizational skills in combination with a normal level of perfectionism.

Based on these results the psychoeducation and therapy of adolescents with ADHD should focus on their organizational skills as well. Our results underline the importance of Buitelaar et al. (33) review on the treatment strategies for children and adolescents with ADHD, which suggests that these strategies should include time management, planning, and organizational skills. Bul et al. (43) invented a gaming approach specifically for children and adolescents for ADHD focused on the improvement of time management, organizational and planning skills. Langberg et al. (44) found that teachers' and parents' ratings of material management was the best predictor of cumulative grade. They suggested that organization is critical when adolescents with ADHD are completing their homework. Wiener et al. (33) found that if teachers had knowledge about an ADHD diagnosis, it increased the understanding of the organizational problems.

Our results should be interpreted in the light of the following limitations: First, it is a cross-sectional study, we were not able to assess any causational relationships. Second, we used self-rating scales for the assessment of perfectionism. It is always a chance by the self-rated scales of not marking the most relevant answer by rushing through the questions or making themselves seems better. Third, there was a gender difference between the

ADHD and control groups, however it is important to note that this difference does reflect the natural occurrence of ADHD, as ADHD is more common among boys than girls (45). Fourth, there are no published norms of the FMPS, but several normative information can be found in the various articles published using the scale (24, 25, 45–52).

In conclusion, our study is the first to report that perfectionism, in particular 'Personal standards', was associated with an increase in suicidal behavior in adolescents with ADHD. This result suggests that a low level of adaptive perfectionism may be a risk factor for suicidal behavior in adolescents with ADHD. Our findings could have important clinical implications, as this new knowledge could help improve prevention of suicide in this group of patients. Based on these results we recommend that psychoeducation and therapy of adolescents with ADHD should consider focusing on organizational skills as well as adaptive perfection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was conducted with the approval of the Ethical Committee of the Medical Research Council, Hungary (ETT-TUKEB, project identification code: 50922-2/2017/EKU). Each subject as well as their parents provided written informed consents after being verbally informed on the nature of the study.

AUTHOR CONTRIBUTIONS

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Identifying Distinguishable Clinical Profiles Between Single Suicide Attempters and Re-Attempters

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More than 800,000 individuals die from suicide each year in the world, which has a devastating impact on families and society. Ten to twenty times more attempt suicide. Previous studies showed that suicide attempters represent a heterogeneous group regarding demographic characteristics, individual characteristics of a suicidal attempt, and the assumed clinical factors, e.g., hopelessness or impulsivity, thus differently contributing to the likelihood of suicidal behavior. Therefore, in the present study, we aim to give a comprehensive clinical description of patients with repeated suicide attempts compared to single attempters. We explored putative differences between groups in clinical variables and personality traits, sociodemographic information, and specific suicide attempt-related information. A sample of patients with a recent suicide attempt ($n = 252$), defined according to DSM-5 criteria for a suicidal behavior disorder (SBD), was recruited in four psychiatric hospitals in Thuringia, Germany. We used a structured clinical interview to assess the psychiatric diagnosis, sociodemographic data, and to collect information regarding the characteristics of the suicide attempt. Several clinical questionnaires were used to measure the suicide intent and suicidal ideations, depression severity, hopelessness, impulsivity, aggression, anger expression, and the presence of childhood trauma. Univariate and multivariate statistical methods were applied to evaluate the postulated risk factors and, to distinguish groups based on these measures. The performed statistical analyses indicated that suicide attempters represent a relatively heterogeneous group, nevertheless associated with specific clinical profiles. We demonstrated that the re-attempters had more severe psychopathology with significantly higher levels of self-reported depression, suicidal ideation as well as hopelessness. Furthermore, re-attempters had more often first-degree relatives with suicidal behavior and emotional abuse during childhood. They also exhibited a higher degree of specific personality traits, i.e., more "urgency" as a reaction to negative emotions, higher excitability, higher self-aggressiveness, and trait anger. The multivariate discriminant analysis significantly discriminated the re-attempters from single

attempters by higher levels of self-aggressiveness and suicidal ideation. The findings might contribute to a better understanding of the complex mechanisms leading to suicidal behavior, which might improve the early identification and specific treatment of subjects at risk for repeated suicidal behavior.

INTRODUCTION

More than 800,000 individuals die from suicide each year in the world; thus every 40 s a person commits suicide (1). This has a devastating impact on families and society. The psychological, social, and financial impacts on the family and community are immeasurable.

Despite an exponential increase in the number of publications in the field of suicidology in recent years (2), prediction of future suicidal behavior (SB) and treatment of individuals after a suicide attempt (SA) remain a significant challenge. For instance, the suicide rate in the first 3 months after psychiatric hospital discharge is 100 times higher than the global suicide rate, particularly among patients admitted with SB, indicating the strong need for better prediction and treatment (3).

Many previous studies focused on specific clinical and personality factors that might enhance the likelihood of suicidal behavior. For instance, these studies found an association between suicide attempts and the presence of psychiatric disorders (4–6), greater hopelessness (6, 7), higher level of impulsivity and aggression (8, 9) and the presence of childhood trauma (10–12).

However, a recent meta-analysis markedly revealed that 50 years of research had improved our knowledge about SB and suicidal ideations (SI). However, it has had a limited impact on increasing our knowledge about suicide/SA prediction (13). Most of the assumed clinical risk factors for SB, as was long believed, are predictive for the emergence of suicidal ideations (13). For instance, the predictive role of mental disorders, like Major Depressive Disorder (MDD), has been considered as one of the most significant risk factors for a long time. However, this association primarily exists because mental disorders facilitate the development of SI but do not distinguish suicide attempters from ideators (14–16). Thus, the only clinically relevant predictor for future SB to date is the history of previous suicide attempts (13, 17–19).

Several reasons partially explain this slow progress. One of the reasons can be found in the complex and multifactorial pathophysiological mechanisms leading to SB that make its prediction and prevention still challenging (20–22). For instance, the exclusive presence of specific psychosocial factors, like the experience of acute stressful conditions (e.g., interpersonal conflicts), did not explain the development of SB or still suicidal ideation. Instead, there is strong consensus on the notion that a combination of several risk factors is required to exhibit SI and additional factors to transit from suicidal ideation to acts (19). To address these complex multifactorial mechanisms, stress-diathesis-models e.g., J. John Mann and Mina M. Rizk (23) and

ideation-to-action models, e.g. Joiner (24) and Van Orden et al. (25) were proposed.

Furthermore, the different and often idiosyncratic definitions of SB and self-harm, used in previous studies and thus leading to several phenotypes along the suicide continuum may have contributed to a huge variability regarding risk factors associated with SB and make it difficult to summarize, integrate, and compare previous findings (26, 27). Only recently, the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) proposed criteria for "suicidal behavior disorder" (SBD) to establish a common language for researchers and clinicians as well as to set the basis for improved identification and definition (28).

In addition, previous studies, as well as clinical experience, clearly recognize that suicide attempters cannot be seen as a homogeneous group because of the significant variability in clinical factors, sociodemographic aspects, personality profiles, as well as regarding specific characteristics of the suicide attempt (29).

Therefore, a better understanding of SB and thus more knowledge about specific markers at the individual level are urgently needed to improve our ability to predict future SA and suicide as well as to implement effective suicide prevention and intervention strategies.

Thus, we aimed in our study to explore different patterns of risk factors based on previous findings and theories in an integrative way, specifically focusing on the group of patients with the highest risk for a future suicide attempt or suicide, i.e., patients with past suicide attempt(s).

Previous studies showed significant differences in sociodemographic and psychopathological profiles between single suicide attempters vs. re-attempters. Regarding sociodemographic factors, the repeated attempters were shown to have younger age, being often females (30), unemployed and living alone as well as having lower educational status (31). In addition, it was also demonstrated that re-attempters had in general more severe psychopathology that included higher levels in affective, anxiety, psychotic, PTSD symptoms and higher frequency of comorbid, alcohol, and substance abuse disorders (31, 32).

Other clinical factors related to re-attempters compared to single-attempters included family history of suicidal behavior, presence of childhood trauma and/or emotional abuse, higher scores in hopelessness and motor impulsivity, lifetime history of aggressive behavior, poorer interpersonal functioning (e.g., deficits in conflict resolution skills) and a greater number of stressful life events (33, 34).

To sum up, suicide attempters are recognized as a high-risk group, underscoring the importance of identifying specific

characteristics, e.g., clinical or personality markers, that might improve the accurate detection of future suicide re-attempters. On this basis, prevention strategies like targeted psychotherapeutic or psychosocial interventions could be optimized. Therefore, in the present study, we aim to give a comprehensive clinical description of patients with repeated suicide attempts compared to single attempters. To achieve this goal, we explored putative differences between groups in clinical variables and personality traits, sociodemographic information, and specific suicide attempt-related information. Based on previous studies, we expected to find significant differences in these variables between the high-risk subgroups of single- vs. re-attempters.

MATERIALS AND METHODS

Subjects

A sample of adult inpatients ($n = 252$) with a current suicide attempt (SA) was recruited from 2018 to 2020 in four different cooperating sites in Thuringia, Germany (Departments of Psychiatry and Psychotherapy of the University Hospital Jena, of the Thüringen-Kliniken "Georgius Agricola" Saalfeld, of the Asklepios Fachklinikum Stadtroda and the Helios Fachkliniken Hildburghausen), as part of an ongoing suicide prevention project ("Network for suicide prevention in Thuringia"), founded by the federal ministry of health (BMG). We only included subjects who fulfilled the DSM-5 (35) criteria for the current suicidal behavior disorder (SBD). In the DSM-5, "suicide attempt" is explicitly defined as "a self-initiated sequence of behaviors by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death." Since this definition strongly emphasizes the intent to die, we have systematically assessed it using the Suicide Intent Scale, SIS (36) in our study. The current diagnosis of SBD was thus clearly differentiated from the "Non-suicidal Self-Injury" (NSSV), another condition for further study in DSM-5. We also used a more conservative time criterion than setting down in DSM-5, i.e., not more than 12 months since the recent attempt. According to DSM-5, exclusion criteria were acute psychosis, acute intoxication, withdrawal symptoms, diagnosed intelligence impairment, language barriers, lack of insight, and dementia diseases. Based on these criteria, we excluded 40 participants so that the final sample included $n = 212$ participants. **Table 1** presents further information about sample characteristics. The local ethics committees of the Friedrich-Schiller University, Jena and of State Chamber of Physicians of Thuringia, Germany approved the study. Informed written consent was obtained from all participants before their participation. Patients were contacted and interviewed by a trained psychologist with a Master degree (M.L., S.J., L.B., and A.S.). Subsequently, questionnaires were explained and given to the patients to fill out in the following days.

Clinical Assessment Tools

The data collection included structured interviews and a comprehensive battery of questionnaires to measure clinical symptoms and personality traits. The presence of psychiatric diseases was assessed by trained psychologists using the Mini International Neuropsychiatric Interview, M.I.N.I. (37), a short structured diagnostic interview for DSM-IV Axis I disorders. We also collected systematic information about the sociodemographic characteristics, the number of suicide attempts, familial history of suicidal behavior among the first-degree degree relatives, number of past psychiatric/psychotherapeutic treatments, medication status, and the circumstances and trigger of the recent suicide attempt. Suicidal ideations during the past week were assessed using the German version of the Beck Scale for Suicide Ideation, BSS (38). Depressive symptoms were evaluated by the Montgomery-Åsberg Depression Rating Scale, MADRS (39), and *via* self-report using the Revised Becks Depression Inventory, BDI-2 (40). Hopelessness was measured with the revised version of the validated German Hopelessness Scale (41), based on Beck's cognitive theory of depression (42), and which explores pessimism concerning the future. Impulsivity was assessed by a German version of the Impulsive Behavior Scale, UPPS (43), exploring four dimensions of impulsivity: lack of premeditation, urgency, sensation seeking, and lack of perseverance. To evaluate aggressive traits, two questionnaires were used. The first one, a short version of the validated and widely used German Questionnaire for Assessing Factors of Aggression, K-FAF (44), was applied to measure readiness for aggressive behavior, including spontaneous aggressiveness, reactive aggressiveness, excitability, self-aggressiveness, and aggression inhibition. The second questionnaire, the State-Trait Aggression Inventory, STAXI-2 (45), was used to explore the intensity of anger as an emotional state and the disposition to experience angry feelings as a personality trait. Finally, we assessed childhood trauma using the Childhood Trauma Scale, CTQ (46), exploring physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect during infancy.

Statistical Analysis

We used SPSS Version 21.0 (https://www.ibm.com/de-de/analytics/spss-statistics-software) for the statistical analyses. To investigate differences in categorical variables, i.e., in sociodemographic factors, motives, and triggers of the current suicide attempt, the non-parametric χ^2-test was used. In addition, Mann-Whitney U-test was utilized for measures with the non-Gaussian distribution. To explore the assumed differences in clinical risk factors (e.g., suicidal ideation, hopelessness, depression) Student's *t*-tests for continuous variables were calculated based on the data of clinical questionnaires.

The whole sample of patients was compared using *t*-tests (https://www.medcalc.org/calc/comparison_of_means.php) regarding personality traits to the norm samples as specified in the questionnaire's related manuals, i.e., K-FAF (47) and STAXI-2 (45) or in the corresponding publication, i.e., UPPS (43). A Bonferroni correction was applied for controlling Type I error due to multiple comparisons. In addition, we used a logistic regression to explain single attempts vs. re-attempts by the binarized motives/triggers of the current suicide attempt and sociodemographic factors. We further used the discriminant

TABLE 1 | Sociodemographic characteristics of single- and re-attempters' groups.

Characteristics	Single attempters (n = 99)	Re-attempters (n = 113)	Test statistic	df	p
Gender (% male)	64 (64.6%)	48 (42.5%)	$\chi^2 = 10.018$	1	0.002**[b]
Age (years) (Mean ± SD)	49.16 ± 19.3	39.2 ± 17.5	$t = 3.94$	210	<0.0001**[c]
Suicide intent scale (Mean ± SD)	12.13 ± 5.18	12.45 ± 4.21	$t = -0.49$	205	0.62[c]
Number of past suicide attempts (Mean ± SD)	–	2.79 ± 3.0			
Time between the last suicide attempt and the interview in months (Mean ± SD)	0.42 ± 1.29	0.74 ± 1.52	$t = -1.63$	210	0.104[c]
Education					
Special needs school	1 (1.0%)	2 (1.8%)			
8 years school	18 (18.2%)	28 (24.8%)			
10 years school	54 (54.5%)	54 (47.8%)			
12 years school	11 (11.1%)	18 (15.9%)			
University/college	12 (12.1%)	10 (8.8%)			
Family status			$\chi^2 = 16.539$	4	0.002**[b]
Unmarried	34 (34.3%)	69 (61.1%)			
Divorced	13 (13.1%)	8 (7.1%)			
Widowed	9 (9.1%)	5 (4.4%)			
Married, but living apart	8 (8.1%)	10 (8.8%)			
Married	34 (34.3%)	21 (18.6%)			
Employed (%)[a]	48 (48.5%)	55 (48.7%)	$\chi^2 = 0.048$	1	0.827[b]
Living alone (%)	36 (36.4%)	43 (38.1%)	$\chi^2 = 0.161$	1	0.688[b]
Number of children (Mean ± SD)	1.41 ± 1.32	0.88 ± 1.15	$Z = -3.35$		0.001**[d]
1st degree relatives with suicidal behavior (%)	9 (9.1%)	23 (20.4%)	$\chi^2 = 5.223$	1	0.022*[b]
Means of suicide attempt (% non-violent)	67 (67.7%)	72 (63.7%)	$\chi^2 = 0.367$	1	0.565[b]
Previous psychiatric/ psychotherapeutic treatment (%)	46 (46.5%)	100 (88.5%)	$\chi^2 = 142.521$	1	<0.0001**[b]
Psychiatric disorder (DSM-IV)					
MDD	65 (65.7%)	65 (57.5%)			
BPD	3 (3.0%)	19 (16.8%)			
Substance abuse	7 (7.1%)	10 (8.8%)			
BD	6 (6.1%)	8 (7.1%)			
AD	11 (11.1%)	2 (1.8%)			
ASD/PTSD	4 (4.0%)	2 (1.8%)			
Phobic disorder	–	3 (2.7%)			
OCD	1 (1.0%)	1 (0.9%)			
Other PD	1 (1.0%)	1 (0.9%)			
Autism	–	1 (0.9%)			
Somatoform disorder	1 (1.0%)	–			
Pathological gambling	–	1 (0.9%)			
Psychotropic medication					
SSRI	25 (25.3%)	30 (26.5%)			
SSNRI	21 (21.2%)	27 (23.9%)			
SNDI	–	4 (3.5%)			
SNRI	–	2 (1.8%)			
SARI	–	2 (1.8%)			
NaSSA	35 (35.4%)	29 (25.7%)			
AAP	26 (26.3%)	50 (44.2%)			
TAP	4 (4.0%)	13 (11.5%)			
TCA	2 (2.0%)	11 (9.7%)			
BZD	13 (13.1%)	10 (8.8%)			
LiS	4 (4.0%)	8 (7.1%)			
AED	3 (3.0%)	12 (10.6%)			

(Continued)

TABLE 1 | Continued

Characteristics	Single attempters (n = 99)	Re-attempters (n = 113)	Test statistic	df	p
APD	–	2 (1.8%)			
DA	1 (1.0%)	–			
MA	1 (1.0%)	–			
Motives for suicide attempt					
Interpersonal conflicts	59 (59.6%)	71 (62.8%)	$\chi^2 = 0.233$	1	0.629[b]
Acute stressful events	30 (30.3%)	50 (44.2%)	$\chi^2 = 4.367$	1	0.037*[b]
Persistent stressful circumstances and experience of overstrain	16 (16.2%)	18 (15.9%)	$\chi^2 = 0.002$	1	0.963[b]
Expectation of severe somatic or mental disorder	14 (14.1%)	2 (1.8%)	$\chi^2 = 11.575$	1	0.001**[b]
Psychiatric symptoms	16 (16.2%)	31 (27.4%)	$\chi^2 = 3.886$	1	0.049*[b]
Somatic symptoms	17 (17.2%)	9 (8.0%)	$\chi^2 = 4.157$	1	0.041*[b]
Burdensomeness	20 (20.2%)	33 (29.2%)	$\chi^2 = 2.280$	1	0.131[b]
Disconnectedness	18 (18.2%)	32 (28.3%)	$\chi^2 = 3.009$	1	0.083[b]
Hopelessness	57 (57.6%)	69 (61.1%)	$\chi^2 = 0.266$	1	0.606[b]
Fear of the future	14 (14.1%)	9 (8.0%)	$\chi^2 = 2.082$	1	0.149[b]

$*p < 0.05$, $**p < 0.01$.
[a] Being employed include fulltime or part-time employment, guarded employed, volunteering work, federal volunteer service and being in training or retraining, students, and pupils.
[b] χ^2-test.
[c] T-test with (assumed) equal variances.
[d] Mann-Whitney-U-Test.
MDD, major depressive disorder; BPD, borderline personality disorder; SUD, substance use disorder; BD, bipolar disorder; AD, adjustment disorder; ASD/PTSD, acute stress disorder/post-traumatic stress disorder; PD, phobic disorder; OCD, obsessive-compulsive disorder; PD, personality disorder; ASD, autism spectrum disorder; SoD, somatoform disorder; PG, pathological gambling; SSRI, selective serotonin reuptake inhibitors; SSNRI, selective serotonin-norepinephrine reuptake inhibitors; SNDI, serotonin and norepinephrine disinhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; SARI, serotonin antagonist and reuptake inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressant; AAP, atypical antipsychotics; TAP, typical antipsychotics; TCA, tricyclic antipsychotics; BZD, benzodiazepine; LiS, lithium salt; AED, antiepileptic drugs; APD, antiparkinson drugs; DA, dopamine-agonist; MA, melatonin-agonist.

analysis, as a multivariate model, to differentiate the single- and the re-attempters based on the assessed clinical and personality questionnaires. This method was used to find a linear combination of variables that separates both studied groups of suicide attempters. The resulting combination can be used as a linear classifier.

RESULTS

Single- vs. Re-attempters
Sociodemographic Data
We found significant differences in the sociodemographic characteristics between single attempters and re-attempters. The latter patients were significantly younger, included more females, were often unmarried, had significantly fewer children and had significantly more first-degree relatives with a familial history of suicidal behavior (see **Table 1**). Furthermore, the re-attempters were significantly more often in psychiatric/psychotherapeutic treatments before the recent suicide attempt compared to the single attempters.

Clinical Data and Personality Traits
We did not observe any significant differences between both groups regarding the intent to die as assessed by SIS (see **Table 1**). However, several significant differences were found in clinical questionnaires, as depicted in **Table 2**. The re-attempters had

significantly higher scores in suicidal ideation (BSS) as well as in self-reported depression severity (BDI-2) and hopelessness (H-R-scale). Interestingly, no significant difference could be found in the clinician-based depression severity (MADRS).

Nearly 50% of suicide attempters reported emotional abuse in the whole sample, and nearly 60% reported emotional and physical neglect during their childhood. As shown in **Table 2**, the re-attempters had significantly higher scores only for the emotional abuse scale in the CTQ compared to single attempters.

Regarding the investigated personality traits, we observed in the whole sample of suicide attempters significantly higher impulsivity (UPPS) scores for the trait "urgency" ($M = 31.5$, $SD = 6.3$) compared to the reference sample (43) and significantly lower scores for "sensation seeking" ($M = 27.1$, $SD = 7.8$) at the Bonferroni adjusted alpha level of 0.05, but not for two other impulsivity traits. Furthermore, compared to single attempters, the re-attempters exhibited higher scores in three of four UPPS subscales. However, the p-values did not survive the Bonferroni correction (see **Table 2** and **Figure 1**).

In addition, compared to the norm sample (47) significantly elevated aggression scores ($p < 0.05$, Bonferroni corrected) were found in the whole sample for the total aggression score ($M = 57.0$, $SD = 28.2$) and for all subscales of the K-FAF ("spontaneous aggressiveness": $M = 12.4$, $SD = 9.6$; "reactive aggressiveness": $M = 23.7$, $SD = 10.8$; "excitability": $M = 21.1$, $SD = 11.6$; self-aggressiveness: $M = 27.7$, SD

TABLE 2 | Clinical characteristics and personality traits of single- and re-attempters' groups.

	Single attempters (n = 99)	Re-attempters (n = 113)	Test statistic	df	p
General psychopathology					
Montgomery-Åsberg Depression Rating Scale (MADRS)	19.26 ± 10.94	22.39 ± 10.02	t = −2.04	183	0.043*
Beck Depression Inventory (BDI 2)	18.42 ± 13.49	27.80 ± 12.87	t = −4.30	144	<0.0001** [b]
Hopelessness Scale (H-R-Skala)	62.11 ± 20.78	76.92 ± 20.15	t = −4.56	157	<0.0001** [b]
Beck Scale for Suicide Ideation (BSS)	3.30 ± 7.05	10.74 ± 10.58	t = −5.1	153	<0.0001** [b]
Aggression, impulsivity, and childhood trauma					
Impulsive Behavior Scale (UPPS)					
Urgency	30.10 ± 5.68	32.83 ± 6.65	t = −2.71	151	0.007**
Premeditation	21.85 ± 4.92	23.69 ± 5.39	t = −2.19	150	0.030*
Perseverance	20.23 ± 5.27	22.26 ± 5.68	t = −2.28	150	0.024*
Sensation seeking	26.57 ± 7.61	27.57 ± 8.01	t = −0.79	151	0.432
Short Questionnaire for Assessing Factors of Aggression (K-FAF)					
Spontaneous aggressiveness	10.66 ± 8.75	13.82 ± 10.14	t = −1.89	129	0.062
Reactive aggressiveness	21.88 ± 9.52	25.11 ± 11.62	t = −1.71	128	0.090
Excitability	17.71 ± 10.39	23.85 ± 11.94	t = −3.10	129	0.002** [b]
Self-aggressiveness	22.92 ± 10.12	31.53 ± 9.42	t = −5.04	129	<0.0001** [b]
Aggression inhibition	19.98 ± 6.09	18.85 ± 6.31	t = −1.04	129	0.300
Total score[a]	50.25 ± 24.63	62.68 ± 29.78	t = −2.56	128	0.012*
State-Trait Anger Expression Inventory (STAXI-2)					
Trait Anger	20.18 ± 6.12	24.04 ± 7.00	t = −3.33	129	0.001** [b]
Expression out	12.90 ± 4.92	14.51 ± 5.03	t = −1.84	129	0.068
Expression in	20.63 ± 5.49	22.31 ± 5.90	t = −1.73	129	0.087
Anger control	30.50 ± 6.62	28.31 ± 6.68	t = 1.88	129	0.063
Childhood Trauma Questionnaire (CTQ)					
Emotional abuse	9.12 ± 5.13	12.10 ± 5.13	t = −3.38	154	0.001** [b]
Physical abuse	6.86 ± 3.74	8.42 ± 4.76	t = −2.26	155	0.025*
Sexual abuse	6.14 ± 4.22	7.86 ± 5.24	t = −1.73	152	0.027*
Physical neglect	8.47 ± 4.98	9.79 ± 5.43	t = −1.31	156	0.038*
Emotional neglect	11.0 ± 3.79	12.58 ± 4.08	t = −1.58	155	0.061

*$p < 0.05$, **$p < 0.01$.
[a] Comprise the subscales spontaneous aggression, reactive aggression, and excitability.
[b] Remains significant after a Bonferroni correction.

= 10.6) except "aggression inhibition." Compared to single attempters, the re-attempters scored significantly higher in K-FAF subscales "excitability," "self-aggressiveness" (see **Table 2** and **Figure 1**).

Regarding the State-Trait Aggression Inventory (STAXI-2), the whole sample of patients showed significantly higher scores in all subscales ("trait anger": $M = 22.3$, $SD = 6.9$; "expression out": $M = 13.8$, $SD = 5.0$; "expression in": $M = 21.5$, $SD = 5.6$), except "anger control" ($p < 0.05$, Bonferroni corrected). But the re-attempters scored significantly higher than single attempters only in "trait anger" (see **Table 2** and **Figure 1**).

Triggering Factors of the Current Suicide Attempt

Interpersonal conflicts (61%) and other acute stressful events (38%), as well as hopelessness (59%), were reported most frequently as motives and triggering factors of the current suicide attempt. Around 25% of patients also indicated two

interpersonal constructs of Joiner's ideation-to-action model (25), i.e., perceived burdensomeness and disconnectedness, as central motives for their suicide attempt. However, comparing single attempters vs. re-attempters, no significant group differences were found regarding these triggering factors. Furthermore, the re-attempters indicated significantly more often acute stressful events and the presence of psychiatric symptoms. In contrast, single attempters indicated significantly more often the expectation of a severe somatic and/or mental disorder and the presence of somatic symptoms as triggering factors for the last suicide attempt (see **Table 1**). The logistic regression with sociodemographic and motives/triggering factors conferred the results of single χ^2-tests revealing, that suicide re-attempts were significantly predicted by acute stressful events ($\beta = 0.67$, $p = 0.039$), younger age ($\beta = −0.03$, $p = 0.002$) and female gender ($\beta = −0.8$, $p = 0.009$), and single-attempts by the expectation of a severe somatic and mental disorder ($\beta = −2.270$, $p = 0.008$).

FIGURE 1 | Standardized values (*T*-scores) computed from the corresponding norm samples are separately depicted for the single attempters and the re-attempters for the subscales of the German questionnaire to measure aggressiveness factors (K-FAF), of the State-Trait Anger Expression Inventory (STAXI-2), and of the Impulsive Behavior Scale (UPPS).
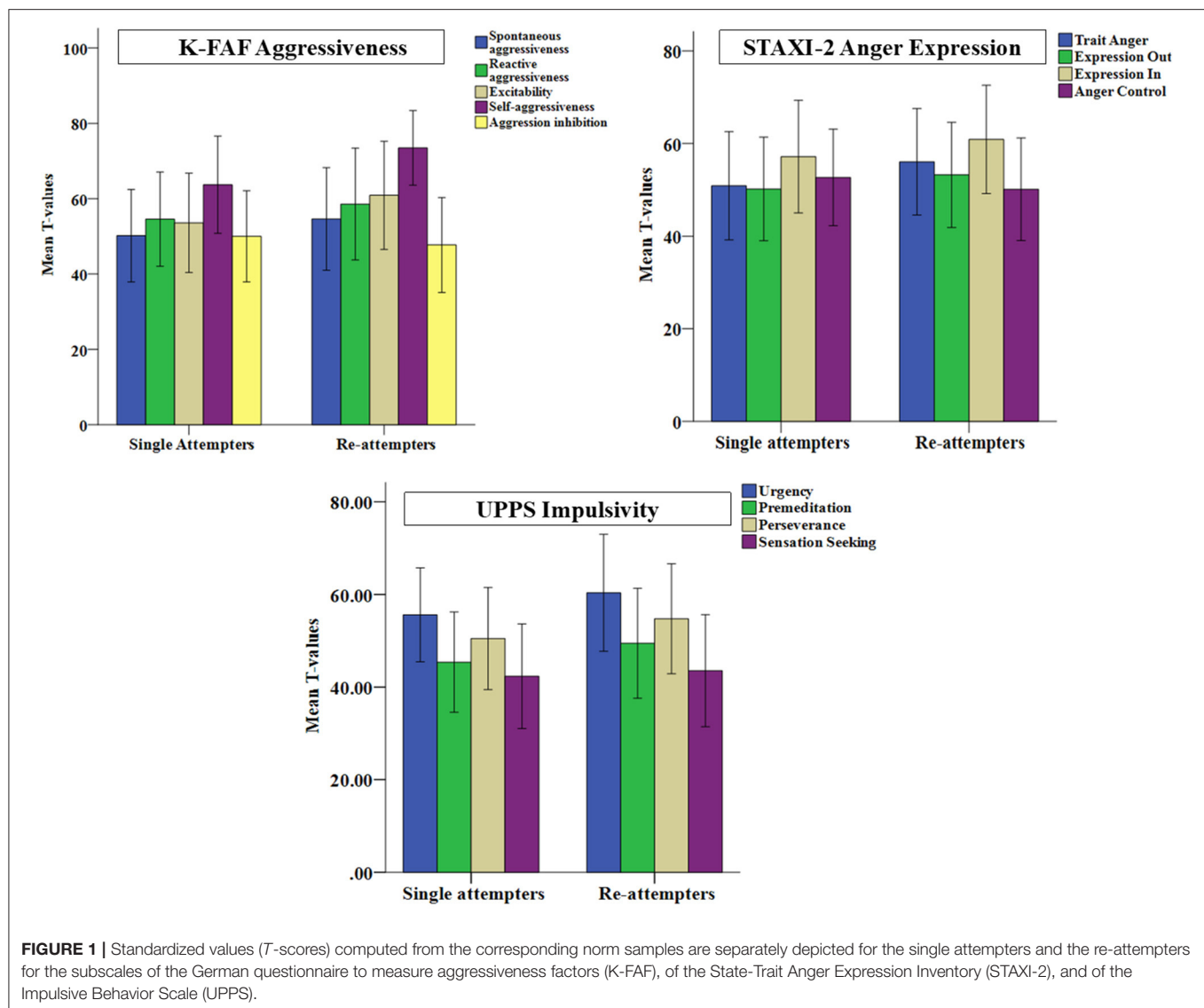
Most Discriminating Clinical and Personality Factors

Finally, using step-wise discriminant analysis, the variables, self-aggressiveness and suicidal ideation, were identified as the two factors, which significantly discriminated between the single- and the re-attempters groups (in the first step with "K-FAF self-aggression" W$\curlywedge$ = 0.83, F = 18.75, and $p <$ 0.0001, in the second step with "BSS total score" W$\curlywedge$ = 0.78, F = 12.49, and $p <$ 0.0001). Wilks' Lambda test was used to indicate which variable significantly contributes to the discriminant function. The closer Wilks' lambda is to 0, the more the variable contributes to the discriminant function. The standardized canonical discriminant function coefficients were for self-aggression 0.65 and for suicide ideation 0.55. According to the structure matrix, the correlations of K-FAF subscale "self-aggressiveness" and BSS total score with the discriminant function were 0.86 and 0.80, respectively. We also assessed how well the discriminant function works. 67.0% of the cases were correctly classified in the present study (see **Figure 2**).

Reaction Toward Survival After a Suicide Attempt

Using Mann–Whitney *U*-test, we compared single attempters and the re-attempters regarding their reaction toward survival after a suicide attempt at the time of the interview measured on a 3-point scale (negative = −1, indifferent = 0, and positive = 1). Patients in both groups mostly showed a positive reaction toward their survival. However, single attempters (M = 0.69, SD = 0.59) reported significantly more often positive reactions (Z = −3.2, p = 0.001) than the re-attempters (M = 0.39, SD = 0.74).

DISCUSSION

The large diversity in risk factors and theoretical models does not significantly contribute to a better-than-chance prediction of future suicidal behavior (13, 48). As a result, suicide risk assessment remains vague, leading to uncertainties in therapists, nurses, and, thus, in some cases to inappropriate treatment

FIGURE 2 | Histograms of the first canonical discriminant function scores are separately depicted for single- and re-attempters. The standardized canonical discriminant function coefficients were for K-FAF self-aggression 0.65 and for BSS suicide ideation 0.55.
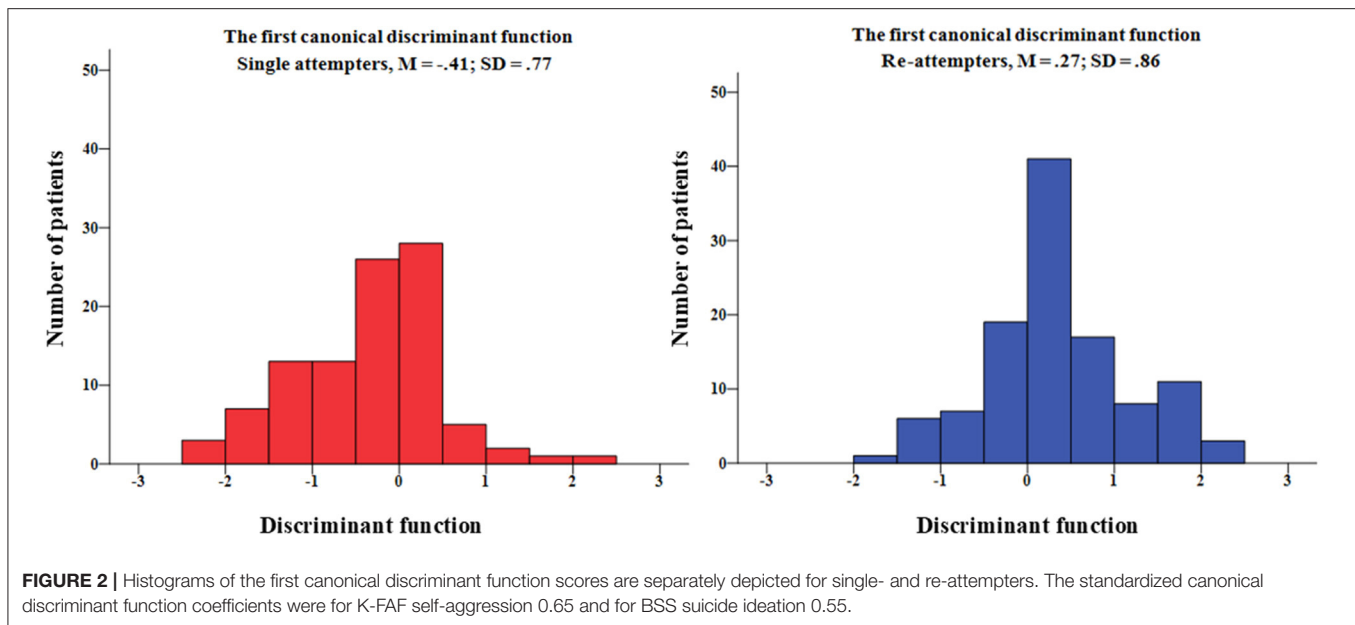
strategies with negative consequences for patients. In addition, because of the heterogeneity of suicide attempters, differing clinical profiles should be considered in risk assessment and subsequent treatment.

Thus, we focused on the differences between single- and re-attempters in sociodemographic, clinical, and personality measures in the present study. We investigated a sample of suicide attempters using a comprehensive battery of structured interview, clinical, and personality questionnaires. In agreement with previous studies, suicide re-attempters differed significantly from single attempters in several sociodemographic characteristics. They were significantly younger, often female, unmarried, had fewer children and had more first-degree relatives with suicidal behavior than single attempters. They also reported more previous psychiatric/psychotherapeutic treatments, which, given a more severe psychopathological profile, is reasonable (49). Thus, present findings confirmed the previously assumed risk factors for a suicide re-attempt [e.g., (31, 32)]. Furthermore, we extended these previous findings by providing additional information about specific facets of impulsivity, aggressiveness, anger processing, and clinical characteristics.

We demonstrated that the suicide re-attempters had more severe psychopathology with significantly higher levels of self-reported depression, suicidal ideation as well as hopelessness. Furthermore, emotional abuse during childhood and specific personality traits, i.e., more urgency as a reaction to negative emotions, higher excitability, more self-aggressiveness, and higher scores in trait anger, were found in the suicide re-attempters. Finally, the discriminant analysis discriminated the re-attempters from single attempters by higher levels of self-aggressiveness and suicidal ideation in the re-attempters group. These are new promising findings with a high potential for optimizing risk assessment and treatment.

Interestingly, suicidal ideation remained high after the suicide attempt, especially in the re-attempters group. This finding seems surprising, as a cathartic relieving effect after the suicidal act was observed in some clinical patients. Matsuishi et al. (50) investigated in a study with 88 suicide attempters the severity of suicidal ideation immediately before and after the suicide attempt. They found significantly decreased suicidal ideation after the suicide attempt that varied among different ages (only significant decrease in patients under 60 years old) and psychiatric disorders, conferring the catharsis-hypothesis that suicide appears to be an ultimate form of catharsis (51, 52). In the present study suicidal ideation remained relatively high in the re-attempters compared to single attempters indicating a less cathartic effect. Accordingly, Joiner and Rudd (53) found out that re-attempters experienced a longer duration of suicidal crises in response to negative life events. The presence of higher suicidal ideation and lower relieving effect of a suicide attempt observed in the present study points into the direction of a prolonged suicidal crisis in the re-attempters than single attempters.

The other most discriminating factor was the degree of self-aggressiveness that was much higher in the re-attempters group than single attempters. The items in this K-FAF subscale address self-reproaches, resentments, and mistrust, but also depressive mood (including suicidal ideation). These factors might enhance the probability of suicidal behavior as an extreme type of self-aggressive behavior.

The General Aggression Model (54) provides an excellent theoretical basis to integrate and interpret present results. According to this model (54), three critical stages are consisting of (1) person and situation inputs, followed by (2) a specific internal state including cognition, arousal, affect, and brain activity and (3) appraisal and decision-making processes that could lead to impulsive/aggressive vs. thoughtful actions. Feedback loops can influence future cycles of aggression in

terms of learning processes and, thus, enhance the probability of repeating the (self-)aggressive behavior. Accordingly, the repetition of suicide attempts could establish self-aggressive behavior as an automatic (Pavlovian) response (55) to the critical person (e.g., trait anger as an internal state) and situation related factor, e.g., social stress/rejection. In the present study re-attempters experienced significantly more frequently acute stressful events as triggering factors than single attempters, which was also reported by other studies (33, 34). The appraisal of internal states and subsequent decision-making processes (3) are biased by the suicidal mode (56) that is characterized by self-aggressive thoughts (e.g., "I am worthless."), dysphoria (e.g., anger, sadness, and shame) and physiological arousal, leading to suicidal behavior. In a previous study, self-aggressiveness was related to deficits in emotion regulation in terms of higher impulsivity, low self-directedness, more potent inhibition of aggression, and a tendency to inwardly directed anger (8).

Moreover, we found higher diathesis in suicide re-attempters, i.e., higher vulnerability for suicidal behavior (23). These patients had potentially higher genetic predisposition in terms of significantly more first-degree relatives with suicidal behavior than single attempters and reported more frequently traumatic childhood experiences, which might be associated with specific epigenetic changes (57). Furthermore, the above-discussed personality traits, i.e., aggression, anger, pessimism/hopelessness are known to enhance the vulnerability for suicidal behavior (58). Previous studies showed a significant association between certain aspects of childhood trauma (sexual and emotional abuse, physical neglect) and suicide attempt (10). The epigenetic changes induced by childhood trauma affect gene expression related to HPA axis functioning (59), leading to an abnormal HPA axis activity to stress (60). Furthermore, the experience of childhood trauma was shown to increase impulsivity, diminishing the brain's capacity to inhibit negative actions and control emotions (61). A significant association between childhood trauma and aggressive traits was also observed in several studies (62). Thus, our results indicate, that besides the above-discussed learning processes (as a copy strategy) that could enhance the probability of repeating the (self-)aggressive behavior, the diathesis for suicidal behavior seems to be significantly elevated in the re-attempters compared to the single attempters. This diathesis might lead to a more frequent experience of stress and extremely negative emotions finally leading to suicidal re-attempts or suicide, because of deficits in emotion regulation and of specific favoring personality traits.

Finally, the present findings might also have relevance for designing psychopharmacological, psychotherapeutic and psychosocial interventions. Due to the apparently different risk profiles of single attempters and the re-attempters, it is conceivable to design different intervention approaches for single attempters vs. re-attempters, specifically targeting the more severe psychopathology, deficits in emotion regulation, and problem-solving abilities, higher self-aggressiveness and higher suicidal ideation in re-attempters. As observed in our recent systematic review about psychotherapeutic interventions to prevent suicide re-attempts (63), previous studies applying

PT interventions included a varying proportion of multiple5 attempters. However, they did not systematically investigate differences in the PT outcomes between single attempters and re-attempters.

This study must be considered in light of its strengths but also limitations. Data were collected in a cross-sectional design, i.e., few weeks after the suicide attempt. Thus, we cannot interpret our results in a predictive way and do not know about the dynamics/stability of the measured constructs. Furthermore, there might be a selection bias because of our exclusion criteria (acute psychosis, acute intoxication or withdrawal symptoms, diagnosed intelligence impairment, language barriers, lack of insight, and dementia diseases), reducing the generalizability of our results. Additionally, since participation was voluntary, our sample was potentially biased by patients that were more open to talking about their suicide attempt. On the other side, patients that were not willing to talk about their suicide attempt might be a group at higher risk regarding future attempts, potentially showing a more negative reaction toward their survival. Furthermore, we had no prospective information on whether some of the included single attempters will attempt suicide again (33). Finally, the re-attempters might also represent a heterogeneous group, e.g., depending on the number of attempts and the time passed between the attempts. The diathesis might be much more established in re-attempters with a high number of attempts, but also the postulated predominance of automatic (Pavlovian) self-destructive processes (55), which should be considered in tailored treatment strategies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by Friedrich-Schiller University, Jena and State Chamber of Physicians of Thuringia, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GW, TS, K-JB, UP, UK, and MW contributed to conception, design and conducting of the study. ML, LB, SJ, AS, and JB organized the database and performed clinical assessments. GW, ML, and JB performed the statistical analysis. ML and GW wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Attentional Bias Deficits in Adolescent Suicide Attempters During an Emotional Stroop Task: An ERP Study

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There is increasing evidence that, in adolescence, attentional bias plays a critical role in the vulnerability for suicidal behaviour. No studies to date have investigated the neurophysiological correlates of attentional bias in adolescent suicidality. The present study uses event-related potentials (ERPs) to investigate such processing in inpatient adolescents admitted for an acute suicide crisis using an Emotional Stroop Task (EST). In this task, participants are asked to name the colour of words varying in emotional valence (positive, negative, neutral, suicide-related). Suicidal individuals are hypothesised to be more preoccupied by the context of the suicide-related stimuli, which may interfere with their ability to perform the colour naming task. Seventeen adolescents with acute suicidal behaviour and 17 age- and gender-matched healthy controls performed an EST while ERPs were recorded. Suicide attempters showed increased reaction times to suicide-related words compared to other emotion categories, while the controls did not. The amplitude of the early posterior negativity (EPN) was not significantly different across groups or emotional valence. A double peak P3 (early-P3 and late-P3) was observed in both groups. Both the early- and late-P3 were significantly reduced in amplitude in the suicide attempter group compared to the control group, regardless of emotional valence. The late-P3 latency was also significantly delayed in the suicide attempters compared to controls. The behavioural findings support the attentional bias theories of suicide attempters and extend these findings to adolescents. Furthermore, large early- and late-P3 provide evidence that cognitive strategies employed by two groups did markedly differ.

Keywords: suicidality, adolescence, attentional bias, event-related potentials, Emotional Stroop Task

INTRODUCTION

Suicide is the second leading cause of death among 10- to 24-year-olds worldwide (1). Among this age group, there are also approximately 25 non-fatal suicide attempts for every completed suicide (1). In adolescence, suicidal behaviour is associated with cognitive impairments that are known to have debilitating impacts on psychosocial functioning (2). There is increasing evidence that cognitive impairments play a critical role in the vulnerability for suicidal behaviour

(3, 4). Along this line, a cognitive model of suicide suggests that individuals at risk for suicidal behaviour exhibit an attentional bias specific to suicide-related stimuli (5). According to this model, these individuals give preferential attention to suicide-related information. This may increase the risk for future suicide attempts by focusing on negative thoughts and prolonging distress. The attentional bias hypothesis has not, however, been tested extensively. In addition, this hypothesis was developed to explain suicidal behaviour in adults; attempted suicide may be a different phenomenon in adolescents than in adults. This may be particularly true considering that adolescence is a critical time for the maturation of cognitive and emotional processes (6).

The Emotional Stroop Task

Traditionally, the Stroop task (7) has been used to investigate what is termed, attentional control, the ability to control attentional resources towards goal-directed behaviour. In the traditional Stroop task, the participant is presented with two types of stimuli. In congruent trials, colour names are printed in the same colour ink (the word "red" printed in red ink) while in incongruent trials, colour names are printed in different coloured ink (the word "red" printed in green ink). When participants are asked to name the colour of the word, reaction times (RT) become prolonged and accuracy of responding decreases on incongruent trials. This is referred to as Stroop interference. The general explanation for this effect is that participants automatically read the task-irrelevant words even though the task does not require this, and in so doing, compromise the processing of the words colour. There are generally two processes thought to be involved in the Stroop task. The first process, reading words, is considered to be largely automatic. This is due to extensive prior learning, resulting in attentional resources being automatically allocated towards the word's semantic content. The second process, colour naming, is considered to be a controlled process, in which attentional resources must be effortly directed towards the stimulus colour. It is generally thought interference occurs when these two processes compete for the allocation of attentional resources [for a review see (8), but see (9, 10) for alternative perspectives].

The Emotional Stroop Task (EST) has been used to investigate attentional bias towards the processing of emotional stimuli rather than colour words (11). In the EST, words having different emotional valence (e.g., neutral vs. negative) are displayed in different ink colours. The participant's task is typically to respond to the ink colour while ignoring the semantic meaning of the words. Similar to the traditional Stroop, the processing of the words semantic meaning (i.e., their emotional context) is thought to result in interference because of the competing automatic and controlled processes (12–14). Evidence of interference of the emotional valence of the words is apparent in a deterioration in performance on the colour-naming task. Accuracy of detection decreases, and RT increases to the emotional compared to neutral words. Clinical studies have used the EST to investigate attentional bias towards stimuli directly related to the nature of the participant's psychopathology. For instance, studies have shown that RTs to colour-naming are generally slower for words related to spiders compared to neutral words in individuals with

spider phobia (15). Such findings indicate that the semantic meaning of the word is processed even though such processing is irrelevant to the colour naming task. By contrast, in controls behavioural signs of interference have generally not been observed (16–22).

The EST and Suicide

In studies with suicidal samples, suicide-related words are included among the emotional and neutral words. Suicidal adults show prolonged RTs and a decrease in accuracy of detection of the suicide-related words compared to non-suicidal attempters. The suicide-attempters thus show a bias towards the suicide-related words (23–26). Furthermore, this effect has been shown to be largest for those with more recent suicide attempts. The effect is also a strong predictor of subsequent attempts within a 6-month period (26). Not all studies, however, report these effects. Chung and Jeglic (27) and Richard-Devantoy et al. (3) did not observe longer RTs to suicide-related words compared to other emotional valences (negative, positive, neutral). To date, relatively few studies have employed the EST in the study of suicidal adolescents. Stewart et al. (28) examined performance on an EST task in adolescent suicide ideators and suicide attempters using positive, negative, neutral, and suicide-specific words. They indicated that suicide attempters showed greater interference than suicide ideators for all emotional stimuli, regardless of emotional valence (e.g., positive, negative, suicide-specific). They suggested that this may be due to inefficient regulation of attention to emotional stimuli in general, and that this may serve as a risk marker for the transition from ideation to attempt.

The EST and Event-Related Potentials

A problem with the strict reliance on behavioural measures in the EST is that the extent of processing that led to the response selection can only be inferred on the basis of performance (i.e., accuracy of responding and RT). Event-related potentials (ERPs), on the other hand, provide an exquisite means to monitor the extent and time course of such processing prior to, at the time of, and following the actual response. ERPs reflect changes in the electrical activity of the brain (EEG) that are elicited by external sensory input or internal psychology events. ERPs consist of a series of negative- and positive-going components thought to reflect different stages of processing.

Different ERP components are elicited during the EST task. An early posterior negativity (EPN), occurring at about 200–300 ms following stimulus onset, is maximal at parieto-occipital electrode sites. The EPN is claimed to be associated with the early stages of attentional processing during tasks involving emotional information (29, 30). Previous studies have generally shown that its amplitude is larger for emotionally valenced words (e.g., positive and negative) compared to neutral words (31–33), although there are some exceptions (34–36). The EPN has been shown to be task-independent; it is not dependent on the nature of the task, depth of processing, or categorisation of emotional content (29, 30, 37–39). This suggests that the EPN indexes early, implicit processing of semantic emotional content.

Another component shown to be influenced in the EST is a late positivity, the P3. The P3 is a parietally maximum, positive-going component, occurring from 300 to 600 ms following stimulus onset. The P3 has been observed in a wide variety of studies involving processes related to stimulus evaluation and categorisation [for reviews, see (40–43)] in tasks requiring attentional control, decision-making, and memory updating. Its amplitude is affected by a variety of factors such as attentiveness, equivocation/uncertainty, processing demands, stimulus salience, and task difficulty, while its latency is primarily affected by the time course of stimulus evaluation and classification (40, 44–47).

Studies using the traditional Stroop task have found that the amplitude of P3 elicited by incongruent stimuli is attenuated compared to the P3 elicited by congruent stimuli (48–51). This has been explained by greater difficulty in responding to the colour of the word as a result of the semantic conflict generated by the incongruent stimuli. The latency of the P3 has generally not been found to be later for incongruent stimuli (49–57). This suggests that the delay in RT to incongruent stimuli is not a result of the time to classify the stimuli, but rather a result of a delay in response initiation and execution. Thus, while the decision has already been made (stimulus classification), the actual behavioural response is delayed, perhaps due to uncertainty of the response or conflict with additional processing of the sematic content of the word.

P3 findings in the context of the EST have been mixed. Franken et al. (31), Li et al. (58), and Stewart et al. (59) observed larger P3 amplitudes for negative words compared to neutral words, when participants were asked to indicate the word colour. Thomas et al. (60) observed a larger P3 for threat words in a task involving naming the word emotion, but when participants had to indicate the colour of the words, the P3 amplitude differences between both threat and neutral words decreased. When Zurrón et al. (50) and Sass et al. (61) asked participants to ignore the word content and detect the colour, neither behavioural performance nor P3 amplitude differences were found between positive, negative, and neutral stimuli. Zurron et al. (50) did, however, observe that RTs were slower and the P3 amplitude was smaller overall for the positive, negative, and neutral words than for the non-words. This suggests that participants did process the lexical validity of the word. The presumably automatic processing of words to be lexically valid affected performance and P3 amplitude.

Some traditional Stroop and EST studies have also reported the presence of additional positive ERP components occurring after the P3. An early study by Johnson and Donchin (62) suggest that the P3 may be followed by an additional positivity, which closely resembled the earlier P3, and that this double P3 may be elicited by a single event, in their case a time estimation task in which subjects were instructed to respond to a stimulus after 1 s. The functional significance of this additional positivity remains unclear. Some researchers have suggested that in more complex tasks, stimulus evaluation and response selection may involve multiple serial decisions, associated with multiple P3s. The execution of a behavioural response may thus occur well after the initial P3 component (63–65), whereas in simpler tasks,

stimulus evaluation and response selection may be processed in parallel. Similarly, Falkenstein et al. (66, 67) also showed that in "multiple choice" paradigms the P3 was followed by a later positivity, the latency of which increased with the complexity of the task demands. This late positivity was absent in simple tasks and appeared exclusively when the participants had to choose among various possible responses after stimulus evaluation. While the latency of the earlier P3 did not vary with increasing task difficulty, the later positivity was significantly delayed in the case of difficult response selection (67). Other researchers have suggested that the additional positivity reflects subsequent processing following the initial stimulus categorisation, which may occur in parallel with response execution (49). In Stroop tasks, this additional positivity occurs at about 450–550 ms, while the initial P3 occurs at about 300–400 ms (49, 50, 57, 68, 69). In their EST, Zurron et al. (50) observed an early and a late positivity, at about 350 and 500 ms, respectively, but neither of these were affected by the emotional valence of the words, suggesting that the components are not modulated by semantic interference processes. This additional positivity may be similar to a positivity labelled as the late positive potential (LPP) component in other EST studies (31, 70, 71).

Only a limited number of studies have examined the P3 component in association with suicidal behaviour in adults (72–76) and adolescents (77). These studies have generally used simple "oddball" target detection tasks in which the participant is asked to detect a rare (or odd) target stimulus representing a change from the more frequently occurring standard stimulus. A history of suicide attempts is generally associated with a somewhat reduced P3 amplitude, but differences are not always significant.

The Present Study

The present study is the first to record ERPs during the EST in cases of suicidality. This task is, of course, much more complex than the usual oddball detection task. The EST also includes words that have high personal relevance for suicidal individuals. The present study is also the first to examine the ERP correlates of attentional bias in relation to adolescent suicidality. Most previous studies have examined behavioural measures in individuals with non-acute suicidal ideation or those with a lifetime history of previous suicide attempts. Furthermore, very few studies have examined acute suicide risk with an inpatient population. It should be noted that several features might distinguish individuals with acute suicidal behaviour from suicide ideators (78, 79). In the present study, all inpatients had attempted suicide within 1 month of the study session. The EST consisted of positive, negative, neutral, and suicide-related words presented in different colours. Participants were asked to detect the colour of the words while ignoring their meaning. Based on most previous EST studies with suicidal samples, it is hypothesised that the inpatient adolescents would exhibit greater interference, indexed by poorer behavioural performance and reduced P3 amplitude, to the suicide-related stimuli, compared to controls. On the other hand, Stewart et al. (28) indicated that suicide attempters showed greater interference for all emotional stimuli, regardless of emotional valence. It is thus possible that

the interference effect on both performance measures and the P3 amplitude will generalise across all emotional stimuli.

MATERIALS AND METHODS

Participants

Participants were 17 adolescent psychiatric inpatients (11 females) admitted to the Children's Hospital of Eastern Ontario for an acute risk of suicide and 17 age- and gender-matched healthy controls. Adolescents ranged in age from 13 to 17 years (mean = 15.64, SD = 0.99 years). None of the participants had any reported history of hearing or neurological disorders. Prior to the study, written informed consent was obtained from all participants, and from legal guardians of those 15 years of age and younger. Participants received an honorarium for their participation. The study was approved by both the University of Ottawa's Health Sciences and Science Research Ethics Board and the Children's Hospital of Eastern Ontario's Research Ethics Board. The study was conducted according to the Canadian Tri-Council guidelines (Medical, Natural, and Social Sciences) on ethical conduct involving human participants. The demographic and clinical characteristics of both groups are listed in **Table 1**.

Medication

A requirement was that potential inpatient participants were not being treated using benzodiazepines prior to the start of the study. Fifteen of the patients were treated with medication, including antidepressants [i.e., selective serotonin reuptake inhibitors (SSRIs)] and/or atypical antipsychotics (see **Table 1**).

TABLE 1 | Demographic and clinical characteristics of the control and patient groups (SD in parentheses).

	Control group (n = 17)	Patient group (n = 17)
Age: mean (SD)	15.65 (0.99)	15.65 (0.99)
Age range	13–17 years	13–17 years
Gender (f/m)	11/6	11/6
Number of suicide attempts: mean (SD)	0 (0)	2.70 (1.36)
Medications (n)	0	15
Antidepressants: SSRI	0	11
Antidepressants: SARI	0	7
Antidepressants: SNRI	0	1
Atypical antipsychotics	0	3
Sleep aids	0	3
RCADS: mean (SD)		
Total internalising	28.58 (13.99)	75.94 (24.29)***
Total anxiety	23.06 (12.62)	54.58 (21.14)***
Generalised anxiety	4.47 (2.70)	10.11 (3.62)***
Social phobia	10.64 (5.75)	18.35 (7.13)***
Separation anxiety	1.82 (2.21)	7.00 (3.43)***
Obsessive-compulsive disorder	2.53 (2.42)	5.52 (3.92)**
Panic disorder	3.47 (2.50)	14.53 (7.91)***
Depression	5.53 (2.40)	21.35 (3.87)***

**p < 0.01; ***p < 0.001.*

Psychological Assessment

The severity of depression symptoms was assessed using the Revised Children's Anxiety and Depression Scale (RCADS) (80). It assesses 6 subscales: (1) Separation Anxiety Disorder, (2) Social Phobia, (3) Obsessive Compulsive Disorder, (4) Panic Disorder, (5) Generalised Anxiety Disorder, (6) and Major Depressive Disorder. It also provides two total scores, (1) an overall index of anxiety levels, (2) and a total level of internalising symptoms.

The presence and severity of suicidal symptoms were assessed using the Self-Injurious Thoughts and Behaviours Interview (SITBI) (81). The SITBI is a structured interview that assesses the presence, frequency, and characteristics of a wide range of self-injurious thoughts and behaviours, including non-suicidal self-injury (NSSI), suicidal ideation, and suicide attempts.

Neurophysiological Recording

EEG and electrooculography (EOG) activity were recorded using Grass gold-cup electrodes, filled with electrolytic paste, and affixed to the skin by surgical tape and to the scalp by gauze. Brain Products BrainAmp amplifiers and Recorder software were used for the recording of the physiological signals. The EEG was recorded from 13 electrodes across frontal, central, parietal, and occipital sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, M1, M2) according to the 10/20 system of electrode placement. Vertical EOG was recorded from electrodes placed at the supra-orbital and infra-orbital ridges of the left eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. The nose served as a reference for all channels, including the EOG channels. Inter-electrode impedances were kept below 5 kΩ. The high-frequency filter was set at 75 Hz and the time constant was set at 2 s. The physiological data were digitised continuously at a 500 Hz sampling rate.

Procedure and Stimuli

Participants were seated ∼70 cm in front of a 17-inch (43 cm) computer monitor in a dimly lit room performing an EST while ERPs were recorded. A series of single words were presented in the centre of the monitor. Neutral (e.g., *museum, paper, engine*), suicide-related (e.g., *suicide, dead, funeral*), negative (e.g., *alone, rejected, stupid*), and positive (e.g., *happy, success, pleasure*) words occurred equally often. Half the words were printed in red and half in blue. The order of presentation of the words was randomised. The words were chosen from the Affective Norms for English Words (82). The words did not differ in length, concreteness, or frequency of use in the English language. Trials began with a white screen with a fixation cross "+" in the middle (1 s), followed by the coloured word. The word remained on until the subject responded at which time the next trial, beginning with the fixation cross, was initiated. Participants were instructed to indicate the colour of each word by pressing a corresponding red or blue key on a keyboard as quickly and as accurately as possible. A practise session consisting of 8 trials was run to ensure participants followed the instructions. The test session was subsequently presented, consisting of a total of 120 trials (30 trials for each of the four emotional valence categories). The entire test session was repeated a second time to ensure adequate trials

for ERP averaging. The colour of the words was counterbalanced during the second session to avoid practise effects.

ERP Analysis

The data were reconstructed using Brain Products' Analyzer2 software. The continuous EEG data was band-pass filtered between 0.5 and 20 Hz (24 dB/octave slope). A vertical EOG channel was computed by subtracting activity recorded at supra-orbital and infra-orbital ridges of the left eye. A horizontal EOG channel was computed by subtracting activity recorded at the outer canthus of each eye. Independent Component Analysis (83, 84) was used to identify eye movement and blink artefacts that were statistically independent of the EEG activity. These were then partialled out from the EEG trace. The continuous data were subsequently reconstructed into discrete single trial 1,000 ms segments, beginning 100 ms before stimulus onset. The pre-stimulus period following some stimuli were not stable and varied between the two groups therefore a -50 to 50 ms para-stimulus baseline correction was applied to all stimuli for both participant groups. Segments in which EEG activity exceeded ± 100 µV relative to the baseline were excluded from further analyses. No more than 5% of total trials were rejected from further analyses per participant. There was no variation in the rejection of trials across stimuli or groups. The single trials were then sorted and averaged separately for correct responses of each emotional valence (i.e., button pressed within 100–1,000 ms of word onset) at each electrode site.

Quantification and Statistical Analyses

All ERPs were initially identified using the grand averaged data (the average of all participants' averages) separately for patients and controls. The EPN was observed in both groups across all four categories. The later P3 had a distinct double peak, with the early component occurring around 300 ms and the later around 450–500 ms. All ERP component amplitudes where measured relative to the mean zero-voltage para-stimulus baseline. They were quantified for each individual participant using the mean of all the data points within ± 25 ms of the peak amplitude that was identified in the grand average. ERP component latencies were analysed using peak latency measures. They were identified as the maximal peak in the latency windows of 150–280 ms for the EPN, 250–400 for the early-P3, and 400–600 ms for the late-P3. All ERPs were initially identified at Pz where they tend to be maximum in amplitude.

Electrode sites were grouped into regions of interest (ROIs) based on where the ERP components have been quantified in previous studies. Specifically, ROIs included a central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, O2) cluster. The EPN is maximal at parieto-occipital sites and was thus quantified at the parietal and occipital clusters while the early- and late-P3 are largest at centro-parietal sites and therefore quantified at the central and parietal clusters.

The amplitude and latency of the ERP components were tested separately using mixed-model analysis of variance (ANOVA) procedures with group (patients, controls) as a between-subject factor and emotional valence (negative, neutral, positive, suicide-specific) as a within-subject factor. For ERP amplitudes, separate

ANOVAs were run on the parietal and occipital clusters for the EPN, and the central and parietal clusters for the early- and late-P3. For ERP latencies, ANOVAs were run at the parietal ROI, for all ERP components, where they tend to be maximum in amplitude. Significant main effects and interactions were followed up with Fisher's least significant difference (LSD) *post-hoc* testing. For all statistical analyses, a Geisser-Greenhouse correction was used when appropriate (85). Behavioural performance data were analysed separately for accuracy and RT using an ANOVA with group (patients, controls) as a between-subject factor and emotional valence (negative, neutral, positive, suicide-specific) as a within-subject factor. In addition, correlations were conducted on the individual participants' ERP amplitudes and latencies compared to the scores on the 6 subscales and 2 total scores of the RCADS. Correlations were conducted separately for patients and controls and were computed at Pz for all ERP components.

To account for the possible confounding effects of medications on the ERP components and behavioural findings in the patient group, patients were divided into two groups and ANOVAs were conducted between these groups separately for the amplitude and latency of the ERP components as well as accuracy and RTs. As there were only two patients not on any medication during the time of recording, patients were instead divided into a "low" medication group which comprised of 8 participants who were either on no medications or a maximum of one medication, and a "high" medication group which comprised of 9 participants who were on two or more medications [see (86)]. For each ANOVA, emotional valence (negative, neutral, positive, suicide-specific) served as a within-subject factor, while medication group (low, high) served as a between-subject factor. Additionally, correlations were conducted on the individual patients' number of medications (ranging from 0 to 3) and the ERP component amplitudes and latencies at Pz.

RESULTS

Psychological Assessment

Compared to the healthy controls, the suicidal patients had significantly higher scores across all subdomains of the RCADS ($p < 0.01$ in all cases). None of the control group participants exhibited any signs of NSSI, suicidal ideation, or suicidal behaviour.

Behavioural Results

Accuracy of responding and RT data are presented in **Figure 1**. Overall, accuracy of responding was high and not significantly different across groups, $F_{(1, 32)} = 0.75$, $p = 0.39$, $\eta_p^2 = 0.02$. Similarly, there was no significant effect of emotional valence on accuracy, $F_{(3, 96)} = 0.96$, $p = 0.41$, $\eta_p^2 = 0.02$. The group x emotional valence interaction was also not significant, $F_{(3, 96)} = 0.41$, $p = 0.75$, $\eta_p^2 = 0.01$.

There was a significant group x emotional valence interaction for RT, $F_{(3, 96)} = 3.36$, $p = 0.02$, $\eta_p^2 = 0.10$. Fisher's LSD revealed that for patients, RTs were significantly longer for suicide-related words than for neutral ($p = 0.02$), positive ($p = 0.006$), and negative ($p = 0.03$) words. On the other hand, RT for the controls

FIGURE 1 | Pirate plots of accuracy of responding and reaction times (RT). The thick, solid horizontal lines reflect the mean. The light-coloured box around the mean reflects the 95% confidence intervals. The larger colour shaded area reflects the smoothed frequency distribution. The dark, solid points within the shaded area reflect the individual participant data points.

did not significantly differ across the emotional valences ($p > 0.05$ in all cases). There were no significant main effects for group, $F_{(1, 32)} = 0.17$, $p = 0.68$, $\eta_p^2 = 0.005$, or emotional valence, $F_{(3, 96)} = 0.98$, $p = 0.40$, $\eta_p^2 = 0.03$.

In regards to the effects of medication, neither accuracy of responding nor RTs were significantly different between the low and high medication patient groups, $F_{(1, 15)} = 4.21$, $p = 0.06$, $\eta_p^2 = 0.22$ and $F_{(1, 15)} = 0.72$, $p = 0.41$, $\eta_p^2 = 0.05$, respectively. Additionally, there were no significant interactions involving emotional valence and medication group for either accuracy or RT ($F < 1$ in all cases).

ERP Amplitudes

Figure 2 presents the grand average ERPs to all emotional valences in both patients and controls. **Figure 3** presents the amplitude and latency values of the various ERP components in both patients and controls.

EPN

The EPN was apparent in the ERP waveform across all emotional valences at about 200 ms. For the parietal ROI, there was no difference in the amplitude of the EPN across groups, $F_{(1, 32)} = 0.38$, $p = 0.54$, $\eta_p^2 = 0.01$, or emotional valence, $F_{(3, 96)} = 0.04$, $p = 0.98$, $\eta_p^2 = 0.001$. The group x emotional valence interaction was also not significant, $F_{(3, 96)} = 1.93$, $p = 0.13$, $\eta_p^2 = 0.05$.

For the occipital ROI, there was no difference in the amplitude of the EPN across groups, $F_{(1, 32)} = 0.02$, $p = 0.87$, $\eta_p^2 = 0.0007$, or emotional valence, $F_{(3, 96)} = 0.23$, $p = 0.87$, $\eta_p^2 = 0.007$. The group x emotional valence interaction was also not significant, $F_{(3, 96)} = 0.77$, $p = 0.51$, $\eta_p^2 = 0.02$.

The analysis of medication effects in patients revealed no significant difference in the amplitude of the EPN across low or

high medication groups and there was no significant emotional valence x medication group interaction for either the parietal or occipital ROIs ($F < 1$ in all cases).

Early-P3

A distinct double peaked P3 was apparent in both groups across all word categories, with an initial early P3 at about 300 ms and a later P3 at about 450–500 ms. At the central ROI, the overall amplitude of the early-P3 was significantly reduced in patients compared to controls, $F_{(1, 32)} = 13.70$, $p = 0.0008$, $\eta_p^2 = 0.30$. There was also a significant effect of emotional valence, $F_{(3, 96)} = 3.05$, $p = 0.03$, $\eta_p^2 = 0.08$. *Post-hoc* testing revealed that the early-P3 was larger to the negative words compared to positive words ($p = 0.003$). There were no other significant differences across other emotional valences ($p > 0.05$ in all cases). The group x emotional valence interaction was not significant, $F_{(3, 96)} = 0.14$, $p = 0.93$, $\eta_p^2 = 0.004$.

Results were similar at the parietal ROI. The overall amplitude of the early-P3 was again significantly reduced in patients compared to controls, $F_{(1, 32)} = 12.09$, $p = 0.001$, $\eta_p^2 = 0.27$. There was also a significant effect of emotional valence, $F_{(3, 96)} = 3.09$, $p = 0.03$, $\eta_p^2 = 0.08$. *Post-hoc* testing revealed that the early-P3 was larger to the negative words compared to positive words ($p = 0.003$). There were no other significant differences across other emotional valences ($p > 0.05$ in all cases). The group x emotional valence interaction was not significant, $F_{(3, 96)} = 0.07$, $p = 0.97$, $\eta_p^2 = 0.002$.

The analysis of medication effects in patients revealed no significant difference in the amplitude of the early-P3 across low or high medication groups and there was no significant emotional valence x medication group interaction for either the central or parietal ROIs ($F < 1$ in all cases).
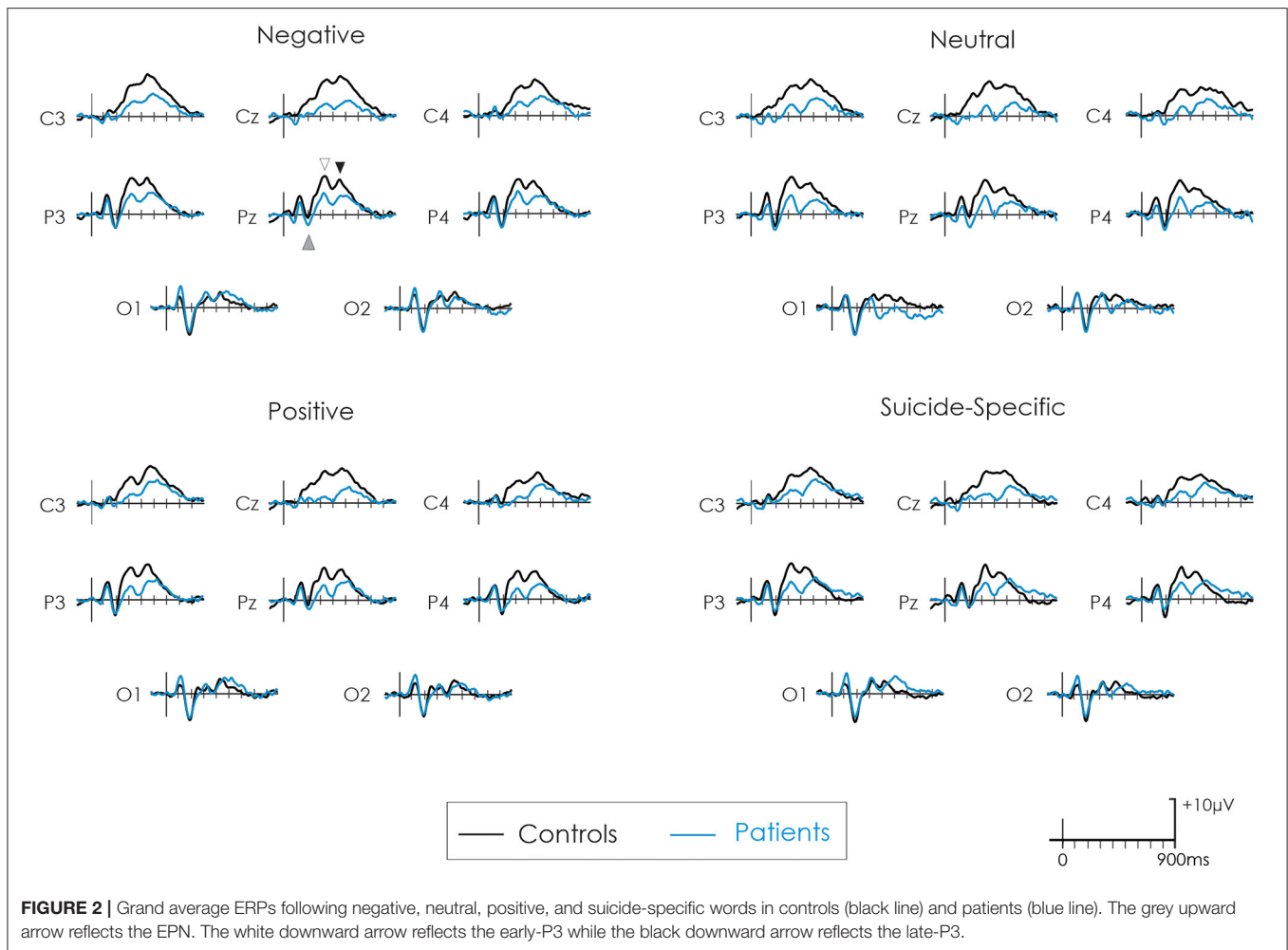
FIGURE 2 | Grand average ERPs following negative, neutral, positive, and suicide-specific words in controls (black line) and patients (blue line). The grey upward arrow reflects the EPN. The white downward arrow reflects the early-P3 while the black downward arrow reflects the late-P3.

Late-P3

At the central ROI, the overall amplitude of the late-P3 was significantly reduced in patients compared to controls, $F_{(1, 32)}$ = 5.50, p = 0.02, η_p^2 = 0.15. There was no significant effect of emotional valence, $F_{(3, 96)}$ = 0.75, p = 0.52, η_p^2 = 0.02. The group x emotional valence interaction was also not significant, $F_{(3, 96)}$ = 2.09, p = 0.11, η_p^2 = 0.06.

At the parietal ROI, the main effect of group just failed to reach significance, $F_{(1, 32)}$ = 3.20, p = 0.08, η_p^2 = 0.09. There was no significant effect of emotional valence, $F_{(3, 96)}$ = 1.72, p = 0.17, η_p^2 = 0.05, or a group x emotional valence interaction, $F_{(3, 96)}$ = 0.42, p = 0.73, η_p^2 = 0.01.

The analysis of medication effects in patients revealed no significant difference in the amplitude of the late-P3 across low or high medication groups and there was no significant emotional valence x medication group interaction for either the central or parietal ROIs ($F < 1$ in all cases).

ERP Latencies

The EPN latency was not significantly different across groups, $F_{(1, 32)}$ = 0.02, p = 0.87, η_p^2 = 0.0007, or emotional valence

$F_{(3, 96)}$ = 0.59, p = 0.62, η_p^2 = 0.02. The group x emotional valence interaction was also not significant, $F_{(3, 96)}$ = 1.27, p = 0.28, η_p^2 = 0.04. The early-P3 latency was also not significantly different across groups, $F_{(1, 32)}$ = 0.01, p = 0.94, η_p^2 = 0.0002, or emotional valence, $F_{(3, 96)}$ = 0.70, p = 0.55, η_p^2 = 0.02. The group x emotional valence interaction was also not significant, $F_{(3, 96)}$ = 0.67, p = 0.57, η_p^2 = 0.02. The late-P3 latency was significantly longer in patients compared to controls, $F_{(1, 32)}$ = 14.45, p = 0.0006, η_p^2 = 0.31. There were no differences in its latency across emotional valence, $F_{(3, 96)}$ = 1.46, p = 0.23, η_p^2 = 0.04. The group x emotional valence interaction was not significant, $F_{(3, 96)}$ = 1.23, p = 0.30, η_p^2 = 0.04.

The analyses of medication effects in patients on ERP latencies revealed no significant main effect of medication group or medication group x emotional valence interaction for the latency of the EPN or early-P3 ($F < 1$ in all cases). There was a significant medication group x emotional valence interaction for the late-P3 latency, $F_{(1, 15)}$ = 2.94, p = 0.04, η_p^2 = 0.16. Fisher's LSD revealed that the late-P3 was significantly earlier for the high medication group (mean = 496 ms, SD = 435 ms) following neutral words compared to the low medication group (mean = 536 ms SD =
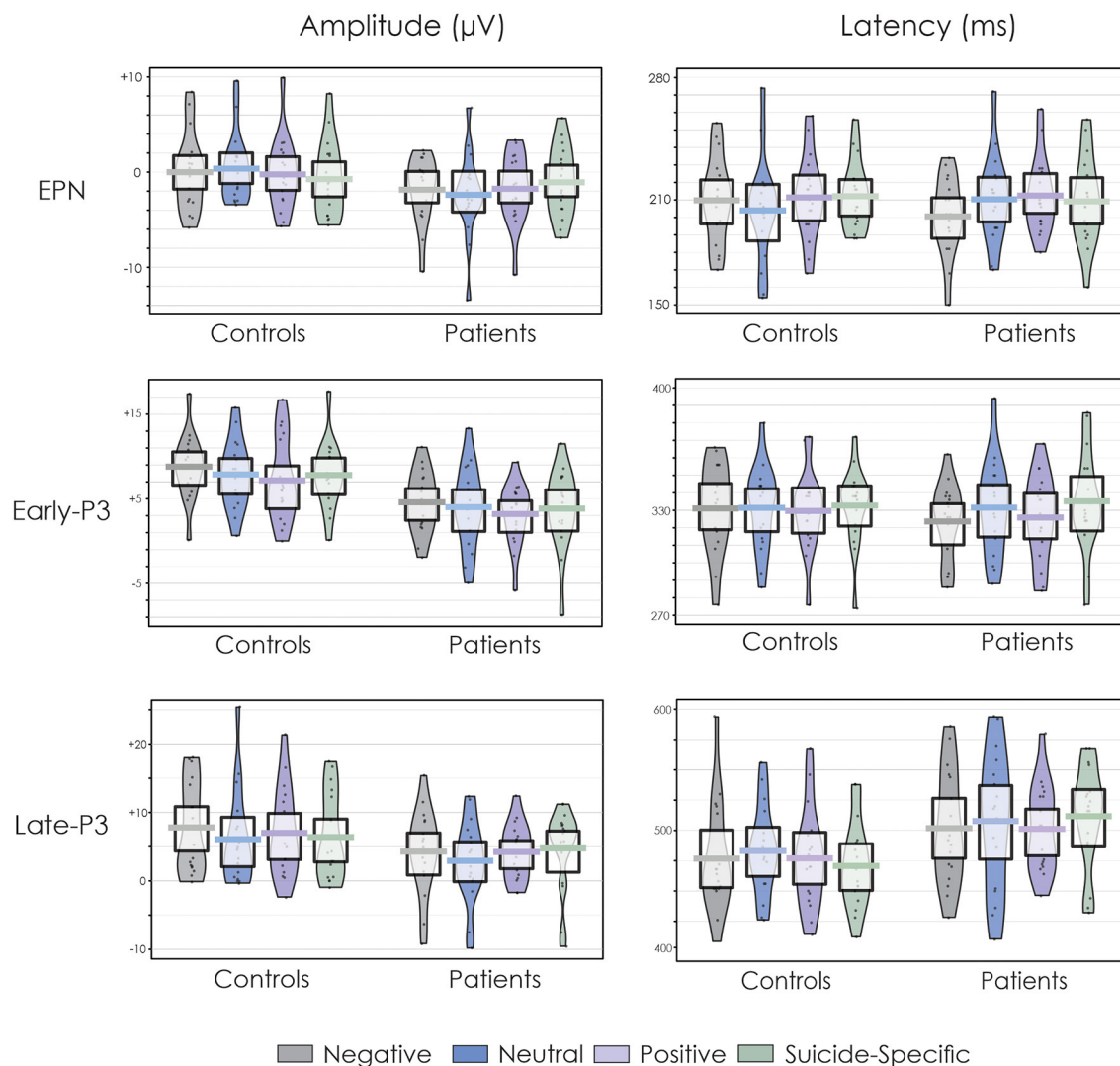
FIGURE 3 | Pirate plots of the EPN, early-P3, and late-P3 amplitude and latency at the Pz electrode site. The thick, solid horizontal lines reflect the mean. The light-coloured box around the mean reflects the 95% confidence intervals. The larger colour shaded area reflects the smoothed frequency distribution. The dark, solid points within the shaded area reflect the individual participant data points.

440 ms) ($p = 0.03$). There were no significant differences between groups for the negative, positive, or suicide-specific words ($p > 0.05$ in all cases).

Correlations

There were no significant correlations for the EPN and late-P3 and the scores on the RCADS for either group. **Table 2** presents the correlations between the early-P3 and the RCADS for both groups. Correlations for the other ERP components are not presented as they were small and not significant. For controls, the early-P3 latency to suicide-specific stimuli was positively correlated with Separation Anxiety and Major Depression. Thus, those with higher scores on the Separation Anxiety and Major Depression scales tended to have longer early-P3 latency following presentation of suicide-specific stimuli. The patients

exhibited numerous significant positive correlations for both early-P3 amplitude and latency. In general, for the significant correlations, as scores of the various subscales increased, the amplitude and latency of the early-P3 also tended to increase.

Additionally, no significant correlations were found between the number of medications patients were administered and the amplitude and latency of the ERP components when measured at Pz ($p > 0.05$ in all cases).

DISCUSSION

Behavioural Findings

The present study examined attentional bias using an EST in adolescent suicide attempers. Participants were presented with neutral, positive, negative, or suicide-specific words. They

TABLE 2 | Correlations between the early-P3 amplitude and latency at the Pz electrode site and the sub scores on the RCADS.

	Amplitude				Latency			
Controls	**Negative**	**Neutral**	**Positive**	**Suicide**	**Negative**	**Neutral**	**Positive**	**Suicide**
Social phobia	0.10	0.08	0.33	0.38	−0.20	−0.38	0.04	0.08
Panic disorder	−0.07	−0.28	0.09	−0.02	0.05	−0.13	0.42	0.34
Separation anxiety	−0.14	−0.34	0.11	−0.06	0.10	−0.13	0.43	**0.53***
Generalised anxiety	0.07	−0.15	0.14	0.35	−0.28	−0.38	0.22	0.29
OCD	−0.04	−0.20	0.01	0.17	−0.22	−0.38	0.18	0.19
Major depression	−0.10	−0.37	0.03	−0.18	0.20	−0.12	0.46	**0.54***
Total internalising	0.01	−0.19	0.21	0.23	−0.12	−0.35	0.31	0.36
Total anxiety	0.03	−0.14	0.23	0.29	−0.17	−0.37	0.26	0.30
Patients								
Social phobia	**0.64****	0.44	**0.61****	**0.55***	**0.66****	0.35	**0.58***	0.17
Panic disorder	0.21	0.37	0.36	0.42	0.34	**0.65****	−0.02	−0.21
Separation anxiety	0.15	0.29	0.16	0.22	0.22	**0.62****	−0.01	−0.33
Generalised anxiety	0.43	0.39	0.42	0.43	**0.63****	0.46	0.22	−0.25
OCD	0.23	**0.48***	0.30	0.43	0.29	**0.57***	0.06	−0.18
Major depression	0.20	0.36	0.22	0.41	0.21	0.48	0.03	−0.09
Total internalising	0.39	0.45	0.43	**0.49***	**0.50***	**0.57***	0.23	−0.14
Total anxiety	0.38	0.43	0.45	0.46	**0.52***	**0.57***	0.24	−0.15

*p < 0.05; **p < 0.01.
Correlations were run separately for controls and suicide attempters.
Bold values reflect statistical significant correlations.

were asked to make a decision about the colour of the words while ignoring the task-irrelevant semantic content. Accuracy of responding to the colour of the word was not affected by the emotional valence of stimuli for either group. This was not the case for the speed of responding. RTs were significantly slower in the suicide attempter group but only for suicide-related words. The control group did not exhibit such RT differences. Suicide-related words thus appear to interfere with the colour naming task in the suicidal group. This finding is similar to previous EST studies in adult suicide samples indicating an attentional bias towards suicide-specific stimuli (23–26). The present study also extends these findings to an adolescent sample. Furthermore, the control group in the present study did not exhibit performance differences across the emotional words, which is in line with previous EST studies (16–22, 60, 87, 88). From a behavioural perspective, the present findings offer support for the Wenzel and Beck (5) cognitive model of suicide in which an active suicide schema preferentially draws the patient's attention to suicide-related stimuli at the expense of completing the relevant task assigned to the participant (colour naming).

ERP Findings

There was no significant difference in the amplitude or latency of the EPN between groups or across emotional valence suggesting that the early stages of attention processing in the context of the EST are not affected in adolescent suicidality. While no previous studies to date have examined the EPN in suicidality, previous studies with healthy controls have observed that it is modulated by the emotional content of stimuli (31–33, 89), suggesting that the words emotional significance amplifies early stages of

semantic analysis. Research on the effects of emotional written words on ERPs during childhood and adolescences is scarce. The vast majority of previous studies have focused on emotional facial expressions or pictorial scenes, with inconsistent findings (90–95). The discrepancies between the present results and previous studies may be attributable to differences in methodological design. Further research is needed to replicate and confirm these findings. The EPN reflects an early stage of automatic word semantic processing. It also possible that in adolescents, early recognition of the emotional content may be less automatic in younger participants and requires additional processing as reflected by the later positivities.

A distinct double peaked positivity was subsequently also observed in both groups. Both the early- and late-P3 were significantly reduced in the suicide attempter group. This is in contrast to the behavioural results. The P3 results indicate that processing of all word categories is very different across the suicidal and control groups, suggesting that different cognitive strategies may have been used by the suicidal group for the colour-naming task.

It is possible that the early-P3 reflects the initial colour categorisation process. The attentional bias hypothesis would predict that the patients might focus attention more on the irrelevant semantic content of the words rather than focusing attention on the relevant feature (i.e., its colour). Because fewer resources are devoted to colour naming, its categorisation would be carried out with more difficulty, resulting in a smaller amplitude early-P3. Johnson and Donchin (62) have suggested that the presence of an additional later P3 reflects additional processing during the course of arriving at subsequent

decisions following the initial stimulus categorisation process. This additional processing may occur in parallel with response execution (49). In this regard, the late-P3 may reflect additional, but needless, processing of the word content, even when no semantic processing is required for the task. A problem with this interpretation, however, is that presumably the semantic content of the words would have been much more relevant to the patients. As such, it would have been expected that the late-P3 would have been larger in the patient group, not smaller.

Other researchers have offered an alternate explanation for the occurrence of a double P3. In complex tasks, stimulus evaluation and response selection may involve multiple decisions and may be separated in time (50, 57, 65, 69, 96–99). The execution of a behavioural response may thus occur after the initial P3, resulting in the occurrence of a subsequent P3 component. This interpretation assumes that the early-P3 reflects the colour evaluation and categorisation process. It is reduced in patients due to their attentional bias towards the semantic content of the word rather than its colour. The late-P3 may then be related to the response selection process, with RTs (500–550 ms) coinciding with the latency of the late-P3 (450–500 ms). Thus, because the patient's attention was focused on the semantic content of the words, the actual initiation and execution of the response may have been made with more equivocation in the patients, also resulting in a reduced late-P3. Johnson (41) indicates that equivocation about a decision will be associated with a reduced amplitude P3. In line with this interpretation, when Tavakoli et al. (77) employed a simpler oddball reaction time task with suicidal adolescents, only a single peak P3 was observed, presumably because stimulus evaluation and response selection occurred simultaneously.

Furthermore, the late-P3 was also significantly delayed in the suicide attempters. Falkenstein et al. (66, 67) indicated that the latency of the late positivity increased with the complexity of the task demands in tasks with multiple choices. The delayed late-P3 latency provides further support for the response selection interpretation of the late-P3. The suicide attempters may have carried out additional processing of words delaying response selection. Although the interpretation of the group differences during the EST remains somewhat speculative, the very large early- and late-P3 differences leaves little doubt that cognitive strategies employed by the two groups did markedly differ.

Lastly, the group differences in the early- and late-P3 across all emotional valences do not support the behavioural findings in which RT was only modulated by suicide-specific stimuli in the suicidal group. This suggests that ERPs may be a more sensitive method than behavioural measures in capturing attentional bias in adolescents with suicidal behaviour. Previous studies using both clinical and non-clinical samples have also demonstrated that ERPs are more sensitive than behavioural measure for investigating attentional bias (60, 100–104).

Limitations

The extent to which comorbid depression and/or anxiety could influence these results has been disputed. Future studies should examine the differential effects of comorbid psychopathologies on these results. Nevertheless, depression and anxiety are highly common in adolescents with suicidal behaviour and as such, the results obtained from the present study are more likely representative of a suicidal population than results from a pure suicidal group with no other comorbidities.

Medication is another possible confounding factor. Ideally, a non-medicated sample of patients should also be studied. This may not, however, be ethically or morally justifiable in those seeking emergency intervention for acute risk of suicide and deemed to require pharmacological treatment. Most of our patient sample was treated with antidepressants and/or atypical antipsychotics. It is possible that these medications may influence the ERP findings. Research on the effects of antidepressant and antipsychotic medication on ERPs is mixed, with some studies suggesting no changes in later cognitive ERPs following medication (105) while other have shown modulations of ERPs following medication (106). The specific ERP components studied and the experimental design can likely account for the consistencies in results. Further extensive research is necessary to determine the specific effects of antidepressant and antipsychotic medications on the different ERP components. In the present study, in order to determine whether the number of medications patients were administered affected both behavioural performance as well as the amplitude and latency of the ERP components, low (0–1 medications) and high (2+ medications) medication groups within the patients were compared. Results revealed that accuracy and RT, amplitude of the EPN, early-P3 and late-P3, and latency of the EPN and early-P3 were not affected by the amount of medication taken. Furthermore, correlations between the number of medications in patients and the amplitude and latency of the ERP components were not significant. Therefore, the major significant findings of this study regarding significantly attenuated P3 amplitudes in patients do not appear to be associated with the number of medications, although these effects cannot be ruled out until further research is conducted.

There was a medication group x emotional valence interaction for the late-P3, suggesting that patients who are on 2 or more medications have an earlier peaking late-P3 amplitude only for neutral words compared to patients who are on fewer medications. It is possible that the use of multiple medications in patients increases information processing speed when patients are faced with neutral as opposed to emotional information. Some researchers have shown that after treatment for major depression with Sertraline, an SSRI, the P3 latency of patients were normalised (104). Furthermore, others have found that antipsychotic medication, especially of the atypical class, could partially improve P3 latencies (107–109). In the present study, the healthy controls had a mean late-P3 latency of 482 ms (SD = 423 ms) for the neural words (**Figure 3**) while the high medication group had a mean latency of 496 ms (SD = 435 ms) and the low medication group had a mean latency of 536 ms (SD = 430 ms). It is, therefore, possible that in suicidal adolescents, a combination of two or more medications which include both

SSRI and atypical antipsychotics can normalise the latency of the late-P3.

Conclusion

Research shows that one-third of adolescents with suicidal ideation will transition to a suicide attempt within 1 year (81). This is the first study to assess attentional bias to emotional stimuli using ERPs in adolescents with acute suicidal behaviour. The present findings have notable clinical implications. Traditional risk assessments primarily rely on clinical assessments or self-report measures. Furthermore, current research on suicidality and cognitive functioning is largely based on performance measures. A problem with strict reliance on performance measures is that they do not provide a measure of how information was processed. The ERP data provide strong evidence that the word stimuli were processed very differently in the suicidal and control groups. It is possible that the recording of ERPs during the EST task may serve as a biomarker for the efficacity of different forms of treatment.

The present results also support the existing research on the cognitive model of suicide and further demonstrate that such findings can be extended to an adolescent sample. Identifying cognitive functions modulated by suicidal behaviour is an important step in identifying potential factors driving the development of suicidality. The large P3 differences between groups in the present study may serve as an objective marker of suicide risk among adolescents. Although the present findings suggest that the group differences in P3 amplitude are not associated with the number of medications in patients, these effects cannot be ruled out altogether. Further research is needed to replicate these findings in a non-medicated group and to investigate the various subsamples of suicidality (e.g., ideation vs. attempt, number of attempts, lethality of attempt). This could aid in improving the clinical detection and risk profile of high-risk adolescents to ultimately reduce the alarmingly high suicide rates.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by both the University of Ottawa's Health Sciences and Science Research Ethics Board and the Children's Hospital of Eastern Ontario's Research Ethics Board. The study was conducted according to the Canadian Tri-Council guidelines (Medical, Natural, and Social Sciences) on ethical conduct involving human participants. Written informed consent to participate in this study was provided by the participant, as well as the participants' legal guardian/next of kin when the participant was below 16 years of age.

AUTHOR CONTRIBUTIONS

PT, EJ, AB, and KC contributed to the rationale and the design of the study and read and approved the final manuscript. The manuscript was written by PT. AB carried out the psychiatric assessment and evaluation of the patient population. PT and EJ assisted with the collection and analysis of the EEG data. All authors contributed to the article and approved the submitted version.

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The 4-Level Approach: Prevention of Suicidal Behaviour Through Community-Based Intervention

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Due to the many different factors contributing to diagnostic and therapeutic deficits concerning depression and the risk of suicidal behaviour, community-based interventions combining different measures are considered the most efficient way to address these important areas of public health. The network of the European Alliance Against Depression has implemented in more than 120 regions within and outside of Europe community-based 4-level-interventions that combine activities at four levels: (i) primary care, (ii) general public, (iii) community facilitators and gatekeepers (e.g., police, journalists, caregivers, pharmacists, and teachers), and (iv) patients, individuals at high risk and their relatives. This review will discuss lessons learned from these broad implementation activities. These include targeting depression and suicidal behaviour within one approach; being simultaneously active on the four different levels; promoting bottom-up initiatives; and avoiding any cooperation with the pharmaceutical industry for reasons of credibility.

Keywords: suicide prevention, depression, 4-level approach, multilevel intervention, community-based intervention

INTRODUCTION

Given the variety of contributing factors and the complexity of suicidal behaviour, multifaceted community-based interventions combining different suicide preventive measures [e.g., (1–3)] are amongst the most promising approaches to prevent suicidal behaviour (attempted and completed suicides) (4, 5), as no single intervention for suicide prevention is at a clear advantage (6). The EAAD (European Alliance Against Depression e.V.) 4-level-intervention concept (7) combines in a coherent manner several interventions, for which at least some evidence of suicide preventive effects exists (6). These encompass education of primary care and mental health professionals, gatekeeper trainings, digital interventions for depression, guidelines for media, a public awareness campaign, and a reduction of access to lethal means. In addition, the 4-level approach combines the two, partly overlapping aims of improving care for people with depression and preventing suicidal behaviour. The advantages of these dual aims will be discussed below. Intervention activities are implemented simultaneously at four levels in the community (see **Figure 1**).

Evidence for the efficacy of this 4-level intervention concept regarding the prevention of suicidal behaviour (attempted and completed suicides as primary outcome) is summarised in **Table 1**.
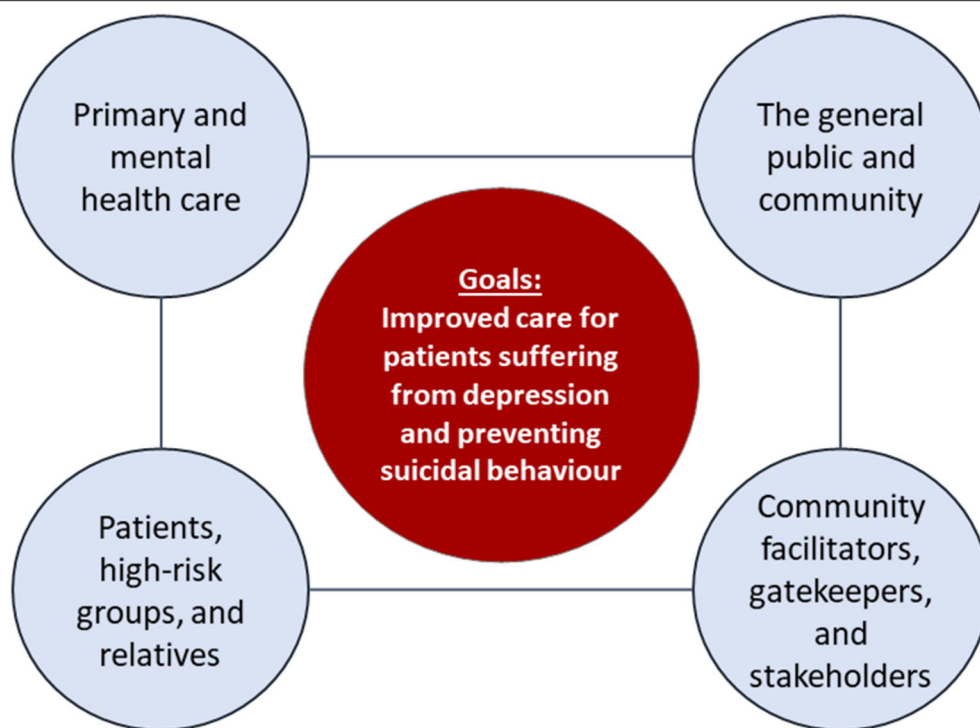
FIGURE 1 | The 4-level intervention concept (reproduced with courtesy of the European Alliance Against Depression e.V.). *Level 1—Interventions for primary and mental health care professionals:* training sessions and practise support for General Practitioners (GPs) and mental health care professionals regarding the diagnosis and treatment of depression and managing suicidality, including iFightDepression®, an e-learning guided web-based intervention tool for their patients. For more details on the iFightDepression®-tool please refer to Oehler et al. (8). *Level 2—Interventions for the general public and community:* a professional public relations campaign, addressing the general public with the key messages "Depression can affect anyone," "Depression is a real disease," and "Depression can be treated." Generally, regional suicide preventive activities are started by an opening ceremony in a public place, together with a famous spokesperson. *Level 3—Interventions for community facilitators, gatekeepers, and stakeholders:* training sessions concerning the topics depression and suicide risk for community facilitators and gatekeepers such as geriatric care givers, priests, pharmacists, police, and journalists. These trainings involve role-plays on topics such as how to explore suicide risk and mental ill-health. Cooperation with journalists is based on a media guide with the aim to reduce copycat suicides (Werther effect). *Level 4—Interventions for patients, high-risk groups, and relatives:* support for patients and their relatives by providing information on depression and the iFightDepression® tool, supporting other self-help activities and providing an emergency card for people after an attempted suicide. An important aspect of suicide prevention, reducing access to lethal means, is considered in different levels (e.g., smaller package size of lethal drugs, identification and securing "hot spots" for suicide in the community). For more details please see Hegerl et al. (9).

Based on a priori defined primary outcome, and a baseline and a control region, clear support for preventive effects on suicidal acts and the sustainability of these effects was provided by the model project, Nuremberg Alliance against Depression (NAD) [(1, 14), see **Table 1**]. The large international controlled intervention study, OSPI-Europe [Optimising Suicide Prevention Programmes and their Implementation in Europe, (15)], replicated the preventive effects of the 4-level intervention concept in one region in Portugal, but did not find statistically significant effects in regions in Germany, Ireland, and Hungary (9). Reasons for these mixed results are discussed by Hegerl et al. (9). When considering completed suicides, evidence for the anti-suicidal efficacy of the 4-level intervention concept has been provided by studies from Germany and Hungary (see **Table 1**). Reliable data for effect sizes of single intervention elements that are applied within the 4-level intervention concept are difficult to obtain, as synergistic effects are generated by simultaneous activities on all four levels (12, 16). A variety of partly

unforeseeable factors [e.g., national election interfering with the PR-campaign, flooding catastrophe in an intervention region interfering with the implementation, differences in intervention intensity; for discussion see (13)] have introduced a considerable variance to observed effect sizes for the 4-level intervention as a whole (9).

LESSONS LEARNED

Since 2008, the 4-level intervention concept has been implemented in more than 120 regions in Germany and a further 15 countries in Europe, plus Australia, and North and South America. Extensive practical experience in the implementation of these community-based interventions in different countries and thus health care systems, has been accumulated. In addition, systematic process evaluation and implementation research was conducted within the OSPI-Europe project addressing efficiency, capacity building processes and

TABLE 1 | Evidence supporting the 4-level intervention concept (controlled studies only).

Study	Intervention region and period	Primary outcomes	Results
Hegerl et al. (1)	Nuremberg, Germany (ca. 500,000 inhabitants) 2001–2002	Number of suicidal acts (attempted + completed suicides) compared to both a baseline year (2000) and a control region (Wuerzburg, 270,000 inhabitants).	A significant reduction in the number of suicidal acts (−21.7%) was found in Nuremberg compared to both a baseline year (2000) and the control region. Compared to rates in the baseline year 2000, reductions of suicidal acts was sustainable in the follow-up year (2003, −32.4%).
Hübner-Liebermann et al. (10)	Regensburg, Germany (ca. 150,0000 inhabitants) 2003–2007	Suicides rates during the 5 years of 4-level interventions were compared to those in the preceding 5 years, as well as to changes in two control regions and the nation-wide overall suicide rate.	A significant decrease of suicide rates was observed compared to the baseline and two control regions, and to the national trend.
Székely et al. (11)	Szolnok, Hungary (ca. 70,000 inhabitants) 2004–2006	Suicide rates during the 2 years of 4-level intervention and one follow-up year were compared to the rates in a control region (Szeged, ca. 160,000 inhabitants) and to national suicide rates.	The decrease of annual suicide rates in Szolnok after the onset of the intervention was significantly stronger than the one observed in the control region ($p = 0.0015$) and the whole country ($p = 0.017$).
OSPI-Europe ("*Optimising Suicide Prevention Programmes and their Implementation in Europe*") Main outcome paper: Hegerl et al. (9) Process analysis: Harris et al. (12, 13)	1. Amadora (Portugal, ca. 170,000 inhabitants) 2. Leipzig (Germany, ca. 500,000 inhabitants) 3. Limerick (Ireland, ca. 190,000 inhabitants) 4. Miskolc (Hungary, ca. 170,000 inhabitants) 2008–2011	Number of suicidal acts (attempted + completed suicides) compared to a 1-year baseline in the intervention regions and the respective control regions (Almada, Portugal, ca. 165,000 inhabitants; Magdeburg, Germany, ca. 230,000 inhabitants; Galway, Ireland, ca. 240,000 inhabitants; Szeged, Hungary, ca. 170,000 inhabitants).	Significant intervention effects compared to baseline and corresponding changes in the control region were observed in Portugal. No such effects were found in Germany, Ireland, and Hungary. Major intervening factors identified by systematic process analysis performed within the OSPI project are discussed (e.g., flooding and elections in Hungary, celebrity suicide of Robert Enke in Germany, negative societal impact of the economic recession in Ireland). Better recognition of suicidal acts due to the awareness campaign might have introduced a bias in the official numbers of suicidal acts in the intervention regions.

synergistic effects that unfold through the interplay between the four single intervention levels (12, 13). In the following, six lessons learned from both the practical experience and the process analyses will be summarised:

Combine the Targets of Improving Care for Depression and Suicide Prevention

The 4-level intervention concept combines the following two, partly overlapping aims: (i) to improve care for people with depression and (ii) to prevent suicidal acts. At a first glance, this approach may appear unfamiliar, as it is generally different research groups working on suicide prevention to those dealing with depression. However, combining these aims makes sense for several reasons:

➢ Depression as a very prevalent and severe disorder is the mental disorder associated with by far, the largest burden of disease in the population (17). Depression is also a key causal factor concerning suicidal behaviour (18). Of course, other mental disorders such as schizophrenia, drug and alcohol addictions, bipolar affective disorders, eating disorders or personality disorders are also associated with an increased suicide risk. However, to address all these disorders with sufficient intensity might be very challenging, as their manifestation, prevention and treatment options or treatment gaps differ considerably and therefore require specific interventions.

➢ Depression affects directly or indirectly more than 50% of the population and a public relations campaign on depression is likely to have a greater resonance in the community than a pure suicide prevention campaign.

➢ Campaigns focusing solely on suicide may on the one side be beneficial by destigmatizing suicide and improving help-seeking of those at risk, but on the other side may even increase suicide rates *via* a variety of possible mechanisms. For instance, destigmatization and normalisation of suicidal behaviour may reduce the threshold concerning suicide. Also, uncontrollable secondary reporting about the topic suicide, in social media for example (e.g., discussion of lethal methods), may have unwanted effects by increasing the cognitive availability of certain suicidal methods (19), by elevating suicide capability and knowledge of lethal means due to increased internet searches (20) or by inducing the Werther effect [copycat suicides (21–23)]. Whilst talking about suicide responsibly is not likely to increase the risk of suicide and active exploration by health professionals is strongly recommended; the question concerning the benefit-risk ratio of large anti-suicide public relation campaigns addressing the general public is difficult to answer, as outlined above. Great importance has to be placed on how such a campaign is designed (communication style, approach, and platforms). By combining the aims of improving care for depression and suicide prevention, the focus of campaigns can be shifted to depression when addressing the general public, and more

to suicide prevention when addressing general practitioners, mental health professionals, and community facilitators.

➢ Depression and suicide prevention are substantial, yet overlapping public health concerns, both with a huge room for improvement. Combining and addressing them within one intervention concept is highly cost effective. A study modelling prospectively the value of the implementation of the 4-level intervention concept demonstrated its cost-effectiveness at the population level and resulted in cost-savings due to averted suicide deaths and a reduction in life years lost (24).

Be Simultaneously Active at All Four Intervention Levels

Combining different interventions has not only added, but also created synergistic effects (12). For instance, the public health campaign within the EAAD 4-level intervention starts with a public launch ceremony in the respective community. This facilitates the uptake and visibility of trainings available for general practitioners, community facilitators and journalists, and leads to increased media reporting. For those affected by depression or other mental disorders, the public campaign may increase knowledge about the symptoms of depression, treatment options and reduce the perceived depression stigma, thus improving help seeking behaviour and lessening the isolation which contributes to despair and suicide risk (25). It also helps general practitioners to confront a patient presenting mainly somatic symptoms with a possible mental disorder. In addition, catalytic effects can be triggered: the community-based intervention within the 4-level approach has been observed to stimulate additional activities that add value to, but are nevertheless external to, planned activities. An example is improvement of intersectoral cooperation between mental health professionals in the community [see (12)]. It is important to become simultaneously active with sufficient intensity on all four intervention levels to create a critical mass of activities as well as synergistic and catalytic effects.

Keep the Balance Right Between a Bottom-Up and Top-Down Approach

A strong bottom-up approach, inherent to the EAAD 4-level-intervention concept, proved to be helpful for successful implementation and to create an ownership feeling at the community level (1). Therefore, it is important to go out into the community and organise meetings for example, not in the leading academic institution, but preferably in a known, shared public space. This bottom-up approach also improves sustainability, whereas interventions financed top-down risk being perceived as a time-limited project associated with a lower level of ownership from the community. However, in countries with less developed social capital and civic engagement, a more pronounced top-down element might be helpful and necessary for successful implementation.

Although the bottom-up approach is encouraged, as it develops a strong sense of community ownership, being cognisant of national policy, legislation and actions related to mental health can be beneficial. Understanding this context can provide opportunities, for example to engage in a national narrative around suicide prevention to the benefit of local awareness or to leverage funding opportunities created by a national mental health strategy (5).

Work Independently of the Pharmaceutical Industry

Antidepressants and other pharmacotherapies play an important role in the treatment of psychiatric disorders associated with a high suicide risk. Lithium has been shown to have specific anti-suicidal effects in unipolar depression (26). Therefore, promoting guideline-oriented psychopharmacological treatment is an important topic in the training of health professionals. However, for credibility reasons and to avoid conflict of interests, the pharmaceutical industry should not be involved in the funding and execution of the 4-level intervention activities.

Start Locally: Develop a Model Project and Then Transfer to Further Regions in That Country

Experience from Germany and other countries shows that when the intervention materials have been developed and the 4-level intervention concept has been implemented in a model project [in Germany it was the Nuremberg Alliance against Depression, (1, 14)], other regions might be interested to also implement this intervention. As the local alliances are the ones that carry out activities on each of the 4 levels, it makes sense to create a learning network of all implementing regions/partners with the aim to exchange experiences, support each other with advice and to further improve or complement the intervention material catalogue. Regions intending to implement an alliance and those with newly established alliances benefit from the experience of the partners in the EAAD network and the support of a national coordinator. More than 85 regions have started their own regional 4-level interventions in Germany (27) and in order to promote the exchange of experiences, the partners from the different regions are invited by the national coordinator three times per year to a meeting. Typical topics discussed at these meetings are how best to design the organisational and operational structure of the alliance and how to integrate its activities within the local community and service environment, how to professionalise fundraising (e.g., How do I identify and approach a potential sponsor? Which institutions typically support a local alliance in other regions?), how to organise a press conference, or how to optimise the impact of PR-campaigns with limited resources.

Depending on the resources available, the evaluation of a project applying the 4-level intervention concept comprises the documentation of intervention activities, the primary outcomes (suicidal behaviour), and a variety of intermediate outcomes, such as evaluations of trainings of general practitioners and community facilitators (28–30), changes in stigma and knowledge in the general population (25, 31), and changes in media coverage (32).

Keep Your Borders

The intervention region should be clearly defined by postal codes and the start of the intervention should always be marked by a prominent opening ceremony. Sometimes, there

can be a tendency or desire to extend the campaign from depression to mental health in general. As stated above, it has been crucial to focus on depression rather than all mental illnesses as it allows the interventions to be sufficiently specific, ensuring they are seen, remembered, and effective. We therefore advise against expanding the intervention concept to include other mental disorders (e.g., anxiety disorders) or non-clinical aspects such as well-being and lifestyle (e.g., stress and burnout). The same applies to debates about the geographical size of intervention regions. Envisioning alliances on a bigger geographical level (e.g., federal states) might be tempting. However, a more regional approach is helpful for creating a feeling of ownership and for identifying local stakeholders that become part of "their alliance against depression." In order to be clearly perceived and identifiable, it is genuinely important that the community-based 4-level intervention keeps its borders in terms of geographical reach, time and content.

OUTLOOK

Combining the targets *Depression* and *Suicide* in the 4-level intervention concept has proven to have major advantages and allows a shift in focus between the two aspects depending on the target group.

The 4-level intervention concept developed by the EAAD is the most broadly implemented and evaluated community-based program targeting both depression and suicide worldwide. It has been recognised by numerous awards and in 2019, was voted by European Union Member States as best practise in

mental health at the European Commission's Joint Research Centre. A comprehensive catalogue of intervention and evaluation materials has been established and optimised over the last 20 years. Among the intervention materials is the iFightDepression® tool, a guided, web-based intervention for mild to moderate depression and dysthymia (8). This self-management tool is based on the principles of Cognitive Behavioural Therapy (CBT) and is available in 12 languages, including an Arabic version. Core 4-level intervention materials have been translated to more than ten different languages for implementation in EAAD member countries, a number that will be expanded during the European Union funded project "EAAD-Best" (European Union Health Programmes Fund, 2021-2023). This new project is focused on implementing the 4-level intervention concept in five Eastern and Southern European countries (Bulgaria, Estonia, Greece, Italy, and Poland) that are yet to have a national suicide strategy, and on expanding interventions to new regions in three EAAD-member countries (Hungary, Ireland, and Spain). Experience to date shows that all intervention materials can be easily adapted to different cultures and health care systems. The European Alliance Against Depression (www.eaad.net) provides support for all regions in and outside of Europe that intend to start their own 4-level intervention programmes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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29. Coppens E, Van Audenhove C, Iddi S, Arensman E, Gottlebe K, Koburger N, et al. Effectiveness of community facilitator training in improving knowledge, attitudes, and confidence in relation to depression and suicidal behavior: Results of the OSPI-Europe intervention in four European countries. *J Affect Disord.* (2014) 165:142–50. doi: 10.1016/j.jad.2014.04.052

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Mental Pain Surrounding Suicidal Behaviour: A Review of What Has Been Described and Clinical Recommendations for Help

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Objective: To conduct a comprehensive review of scientific publications related to mental pain and suicide risk in order to deepen relevant aspects to guide clinical interventions.

Method: Using a text analysis tool, we collected the terms most frequently linked with that situation in published results of research using various tools to evaluate mental pain or psychache.

Discussion: We propose clinical interventions for the clinical conditions most commonly associated with mental pain.

Keywords: suicide prevention, suicidal mental pain, suicide intervention, suicide clinical assessment, suicidal states and traits

INTRODUCTION

For decades, suicide and its associated behaviours (SB) have been considered as priority problems in the health policies of many countries and the world (78). Despite this, we do not have adequate strategies to significantly reduce its incidence. This is explained by the complex nature of this behaviour, in which sociocultural, familial, biological, and psychological aspects concur. This is what many studies conducted in different countries over several decades consistently teach (1).

Today, despite our solid knowledge of the different variables associated with this behaviour, it has not been possible to generate interventions that allow us to anticipate SB (2). This is a limitation that includes the estimation of immediate and future behaviour. Given this, many authors have raised the need to study this behaviour using methods other than traditional ones (3, 4), in what some have described as a "paradigm shift." An example of the limitations that traditional SB risk indicators face in order to anticipate these behaviours can be seen in studies that have explored the clinical utility of SB severity ranking scales. The available evidence does not support the clinical use of these scales (5, 6). Furthermore, there is considerable agreement regarding the uselessness and eventual risk of the use of scales and other clinical instruments in order to rank suicide risk in risk subjects (7–9).

SB is infrequent even in those patients whose clinical condition is frequently associated with risk factors. An example of this is the case of having a previous history of suicide attempts. While a prior suicide attempt is one of the best predictors of suicide risk, most of those who attempt suicide will die from another cause. This shows the importance of state variables in the risk of SB.

When comparing depressive patients with and without SB, we can recognise a set of variables that, when presented simultaneously, could configure a risk state for SB (10). But we can also describe what the psychic experience that precedes the suicidal behaviour is like in order to identify a particular clinical condition in those who might have SB. The latter is what Shneidman proposed when underlining the crucial role that a specific psychic state has as the antecedent of all SB: "in most cases, suicide stems from psychological pain, and the psychache itself arises from frustrated psychological needs" (11). For this important author, all SB was preceded by a state that he defined as "psychache" (12). This term describes a state of intense disturbance that has also been defined as "mental pain" (MP), "psychological pain," and "psychic pain" by different authors (13). For many, this state represents a way of responding to adversity and suffering that seems inevitable, and that is what would incline someone to end his/her life.

The role of psychache as a mediator between circumstances, risk factors, and suicidal behaviour has led several authors to recognise the central role that psychache plays in SB (14). Several scales have been developed to recognise and identify its severity (13, 15, 16). One of the most recent proposals is the incorporation of this dimension as part of the patient-reported outcomes (PRO) in treatment outcome studies (15). But there are two difficulties in this: firstly, the capacity in those who experience this state to understand it as MP, and secondly, the difficulty for clinicians to interpret the different aspects of the mental examination under the concept of MP.

Indeed, a particular problem of SB is the knowledge that the patient has of his/her own state. It is quite possible that psychache's own deep emotional distress and disturbance prevents many subjects from being able to understand their behaviour and decisions. For some, the latter forces patients to consider the possibility of suicidal behaviour, even if they do not express it explicitly (17). If this is the case, then those who evaluate patients with severe psychiatric problems should assess the general condition of the patient without restricting themselves exclusively to what the patient says when assessing the risk of SB. This clinical problem would allow us to understand those cases of subjects who consulted for a short time before committing suicide without manifesting ideation or death plans when being evaluated. In the latter cases, it is often thought that the subjects concealed their will, and although in many cases this could have been the case, it is possible that many of them were unaware of the state of risk in which they were.

Today we have several scales to assess the severity of MP and psychache that have been used in samples of very diverse groups of patients at risk of suicide (adolescents, students, the elderly, migrants, patients with a history of high-risk suicide attempts). As some point out, "mental pain provides the clinical threshold that is essential for determining the amount of distress that is worthy of clinical attention, in conjunction with diagnostic criteria. It may be a better specification of the criteria on 'clinically significant distress' that frequently recurs in DSM IV" (13). On the other hand, this state would be a factor associated with suicide independent of the diagnosis. MP can be established

progressively during the different stages of suicidal behaviour—ideation, attempt, and suicide—as a continuous phenomenon. The association of other factors with the state of MP could increase or decrease its intensity. Although these scales help to assess the severity of MP, it is not enough to recognise its existence and severity, since it is necessary to know for each subject what factors explain this state in her/him. The latter is what a good clinical interview should achieve by identifying what facts and factors promote this state in each individual subject (13). Research on suicidal behaviour has always tried to find what might prevent it. For some, the task should be broader, since the research should also be directed to identify aspects that could be a target for intervention: "Existing suicide prediction models which attempt to pinpoint the patients at highest suicide risk, do not tell us which suicide-focused treatments are right for which patient. This is the key clinical question critics of suicide risk screening have in mind when they say in-depth clinical assessments should focus on need for treatment rather than risk of suicide" (7). By establishing the determining factors of MP for each patient, we could then define interventions to mitigate the impact of this state according to highly individual needs.

The aim of this study is to contribute to the accuracy of the understanding of MP in suicide risk through a qualitative review of 73 studies that present findings about the state and experience associated with MP in suicide risk. This information will help clinicians to guide the clinical interview to assess those areas of psychic life typically associated with MP. For this purpose, we have selected studies conducted to evaluate MP or Psychache following the same criteria used by the authors of a recent major review (14). Our findings seek to translate the information from many studies carried out in diverse populations into the clinic.

MP is a transdiagnostic construct which has been recognised as one of the most important proximal predictors of suicidal risk well beyond depression (14, 18, 19). "MP is also understood as "psychache" (20) and defined as an acute state of intense psychological pain associated with negative cognitive and emotional aspects of the self—i.e., thoughts of self-disappointment or inadequacies and feelings of guilt, anguish, fear, panic, angst, loneliness, and helplessness often accompanied by a sense of disconnection, loss, or incompleteness of the self (13, 21, 22).

Aspects that stand out in suicidal MPs are certain experiences of connectedness and impulsivity. On the one hand, connectedness would be associated with: feeling socially excluded; loneliness-even when apparently accompanied by others; not having mutual and satisfactory interpersonal relationships; perception of being a burden to others. This is linked [according to the Interpersonal Theory of Suicide proposed by Joiner (23)] to an acquired capacity to commit suicide. Impulsivity, on the other hand, MP would be related to the experience of out-of-control expressions of aggression, trait anger, risk-taking behaviours in the face of intolerable and impossible to communicate experiences in requesting help (24).

With regard to the above, a development of clinical interventions aimed at addressing connectedness and the

management of reactive impulsivity would be especially beneficial for clinical interventions. This would be particularly useful in critical services such as psychiatric emergencies and in the case of pathologies usually associated with suicidal risk, such as depressive disorders, dependencies, psychotic disorders, eating disorders and personality dysfunctionalities (25, 26).

MP is viewed as stemming from the discrepancy between the ideal and the actual perception of oneself, accompanied by the awareness of one's role in the experience of emotional pain (13). This suffering would be found around a perception of the gap between what we want and what we can have. Along with the realisation of the existence of this gap, there is a certain impossibility of tolerating this gap. MP sufferers accept that the gap exists and are unable to intuit alternatives to find solutions besides death.

We agree with the literature demonstrating that the moment bordering on suicidal ideation and attempt is affected by a particular emotional transitory state and a personality style characterised by traits that lead to the activation of suicidal risk.

A psychological state is a construct defined as characteristic patterns of thinking, feeling, and behaving in a concrete situation at a specific moment in time; it is a transitory experience that can be affected by external events and by internal movements of the self. State variables such as depression, hopelessness, and anxiety have been shown to have a significant relationship with suicide risk (27).

Other factors include stable or enduring differences between individuals. Such long-term tendencies, sometimes referred to as traits, could be a wistful temperament, genetic predisposition, personality style (27), or characteristic patterns or tendencies of thinking, feeling, and behaving that generalise across similar situations, differ systematically between individuals, and remain rather stable across time (28). Self-destructiveness, poor impulse control, and antisocial behaviour are among the main suicide risk factors observed in suicidal patients with personality dysfunctions (29).

Our purpose through this comprehensive study is to pinpoint those factors most commonly associated with suicide risk, as shown by studies examining MP and suicide. Using this information, we propose clinical interventions that would allow us to reduce the state of MP.

MATERIALS AND METHODS

We carried out a comprehensive review of scientific publications that studied the concept of mental pain, offering a high-quality data synthesis of the studies, according to the following search criteria:

a) Systematic reviews and original research from 1996 to 2021 that were published in international scientific journals in the English language, describing mental pain and psychache in relation to suicidal ideation, suicide attempts, suicidal behaviour, and high-lethality suicide attempts.
b) Among the exclusion criteria, we considered meta-analyses, letters to the editor, single-case studies, general reviews, conference presentations, books, and abstracts.

c) The search was directed to the following platforms: Web of Science, PubMed, Scopus, Google Scholar, PsycLit, and ProQuest.
d) The search keywords were psychological suffering OR psychache OR emotional pain OR psychic pain OR psychological pain OR mental pain OR self-harm AND suicid*.

This inquiry yielded 73 studies. The details are shown in **Table 1**. The heterogeneity of the resulting scientific articles in terms of methods and sample types made it impossible to gather criteria for quantitative analysis. Given the above, we performed a qualitative analysis in three successive steps:

1) Qualitative review of concepts associated with mental pain and psychache in suicidal crisis, based on the results and discussion sections of the reviewed articles.
2) For first-word filtering, the text mining package (tm) library for R was used.
3) The concepts that stood out for their repetition were selected, for which we used a free program available online which organises texts according to their content and frequency of appearance—Text Analyzer (https://www.online-utility. org/text/analyzer.jsp). Points, spaces, prepositions, and conjunctions were filtered.

In the next step of the analysis, the groupings obtained were assembled under concepts of abstraction, as shown below:

a) The diagnostic variables.
b) The psychological experience variables.
c) The trait variables.

Grouping by similarity allowed us to guide the clinical reflection of these maladaptive ways of being with oneself and with others in order to select pertinent psychotherapeutic interventions for these conditions that are associated with suicidal risk. We discuss the clinical recommendations in the final section.

To visualise the words that emerged in the analysis, they were organised in proportion to the number of times they appeared in the revised texts. We extracted those words that appeared at least 10 times and presented them in word clouds. This criterion had the simple function of ensuring that the words were visible in the graph, as words with lower frequencies would be too small to be clearly seen.

For the diagramming, we used the free online program EdWordle, a tool that organises word clouds based on Wordle using concepts or groupings of words. The result graphically shows what is presented in a text according to the weight of the words as a whole (http://www.edwordle.net/).

The layout can be seen in **Figures 1**, **2** "Groupings of concepts of state in mental pain (diagnosis and psychological experience, respectively)" and in **Figure 3** "Groupings of concepts of traits in mental pain."

Finally, in the discussion, we propose strategies to use these findings in such a way that they serve as a response to difficult circumstances, interpersonal adversities, and psychological suffering that seems inevitable and is intolerable. This can be oriented toward aspects such as

TABLE 1 | Detail of papers in comprehensive review of scientific publications that studied the concept of mental pain.

	Reviewed papers	Year	Type of study	Sample
1	Barak A, Miron O. Writing characteristics of suicidal people on the internet: a psychological investigation of emerging social environments. Suicide Life Threat Behav (2005) 35(5):507–24. doi: 10.1521/suli.2005.35.5.507	2005	Quantitative	3 samples: 65, 80, 63 sujects
2	Becker, G., Orbach, I., Mikulincer, M., Iohan, M., Gilboa-Schechtman, E., & Grossman-Giron, A. (2019). Reexamining the mental pain–suicidality link in adolescence: The role of tolerance for mental pain. Suicide and Life Threating Behavior, 49(4), 1072–1084. https://doi.org/10.1111/sltb.12506	2019	Quantitative	Study 1: 183 nonclinical sample Study 2: 139 clinical sample Study 3:24 psychiatric patients with suicidality, 24 non-suicidal psychiatric patients, 24 adolescents non-clinical,
3	Bolger, E. (1999). Grounded theory analysis of emotional pain. Psychotherapy Research, 9(3), 342–362. https://doi.org/10.1080/10503309912331332801	1999	Qualitative	7 adults
4	Cáceda, R., Durand, D., Cortes, E., Prendes-Alvarez, S., Moskovciak, T., Harvey, P. D., & Nemeroff, C. B. (2014). Impulsive Choice and Psychological Pain in Acutely Suicidal Depressed Patients. Psychosomatic Medicine, 76(6), 445–451. doi: 10.1097/psy.0000000000000075 (2014) 44(1):77–88. doi: 10.111/sltb.12056	2014	Quantitative	82 adults 18–65.
5	Campos R, Holden R, Santos S. (2018). Exposure to suicide in the family: Suicide risk and psychache in individuals who have lost a family member by suicide. J. Clin. Psychol. 2018;74:407–417. doi: 10.1002/jclp.22518	2018	Quantitative	225 subjects, 53 patients, and 172 controls
6	Campos RC, Holden RR, Laranjeira P, Troister T, Oliveira AR, Costa F, et al. Self-report depressive symptoms do not directly predict suicidality in nonclinical individuals: contributions toward a more psychosocial approach to suicide risk. Death Stud (2016) 40(6):335–49. doi: 10.1080/07481187.2016.1150920	2016	Quantitative	961 subjects for 3 different samples
7	Campos RC, Holden RR. Testing models relating rejection, depression, interpersonal needs, and psychache to suicide risk in nonclinical individuals. J Clin Psychol (2015) 71(10):994–1003. doi: 10.1002/jclp.22196	2015	Quantitative	203 adults (100 males, 103 women)
8	Coohey C, Easton S, Kong J, Bockenstedt JKW. Sources of psychological pain and suicidal thoughts among homeless adults. Suicide Life Threat Behav (2015) 45(3):271–80. doi: 10.1111/sltb.12126	2015	Quantitative	457 subjects
9	DeLisle M, Holden RR. Differentiating between depression, hopelessness, and psychache in university undergraduates. Meas Eval Couns Dev (2009) 42(1):46–63. doi: 10.1177/0748175609333562	2009	Quantitative	587 students undergraduated
10	Demirkol, M.E., Tamam, L., Naml, Z., Eriş Davul, Ö., 2019. Validity and reliability study of the Turkish version of the tolerance for mental pain scale-10. Psychiat. Clin. Psych.	2019	Quantitative	121, 62 with SB
11	Esther L. Meerwijk and Sandra J. Weiss, Tolerance for Psychological Pain and Capability for Suicide: Contributions to Suicidal Ideation and Behavior, Psychiatry Research, https://doi.org/10.1016/j.psychres.2018.02.005	2018	Quantitative	219 facebook users
12	Farshid Shamsaei, Safura Yaghmaei & Mohammad Haghighi (2020) Exploring the lived experiences of the suicideattempt survivors: a phenomenological approach, International Journal of Qualitative Studies on Health and Well-being, 15:1, 1745478. doi: 10.1080/17482631.2020.1745478	2020	Qualitative	16 subjects, in depth interviews
13	Fertuck, E. A., Karan, E., & Stanley, B. (2016). The specificity of mental pain in borderline personality disorder compared to depressive disorders and healthy controls. Borderline Personality Disorder and Emotion Dysregulation, 3(2), 1–8. https://doi.org/10.1186/s40479-016-0036-2.	2016	Quantitative	79 patients and 31 controls
14	Flamenbaum R, Holden RR. Psychache as a mediator in the relationship between perfectionism and suicidality. J Couns Psychol (2007) 54(1):51–61. doi: 10.1037/0022-0167.54.1.51	2007	Quantitative	264 undergraduate students
15	Fleming, M. (2006). Distinction between mental pain and psychic suffering as separate entities in the patient's experience. International Forum of Psychoanalysis, 15(4), 195–200. https://doi.org/10.1080/08037060500522754.	2006	Qualitative	Theory review
16	Gould MS, Kalafat J, HarrisMunfakh JL, Kleinman M. An evaluation of crisis hotline outcomes part 2: suicidal callers. Suicide Life Threat Behav (2007) 37(3):338–52. doi: 10.1521/suli.2007.37.3.338	2007	Quantitative	1.085 patients with SB evaluated, and 380 (35.0%) followed up.

(Continued)

TABLE 1 | Continued

	Reviewed papers	Year	Type of study	Sample
17	Grossman-Giron, A., Becker, G., Kivity, Y., Shalev, S., & Tzur Bitan, D. (2020). Mental pain intensity and tolerance as predictors of psychotherapy process and outcome. Journal of Clinical Psychology. https://doi.org/10.1002/jclp.23085	2020	Quantitative	53 Patients
18	Guimarães, R., Fleming, M., & Cardoso, M. F. (2014). Validation of the Orbach & Mikulincer Mental Pain Scale (OMMP) on a drug addicted population. Social Psychiatry and Psychiatric Epidemiology, 49(3), 405–415. https://doi.org/10.1007/s00127-013-0751-6.	2014	Quantitative	403 patients
19	Gvion Y, Levi-Belz Y. (2018). Serious Suicide attempts: Systematic Review of Psychological Risk Factors. Frontiers in Psychiatry doi: 10.3389/fpsyt.2018.00056	2018	Systematic review	39 studies
20	Gvion, Y., Horesh, N., Levi-Belz, Y., Fischel, T., Treves, I., Weiser, M., et al. (2014). Aggression-impulsivity, mental pain, and communication difficulties in medically serious and medically non-serious suicide attempters. Comprehensive Psychiatry, 55(1), 40–50. https://doi.org/10.1016/j.comppsych.2013.09.003.	2014	Quantitative	196 subjects
21	Gviona Y, Horesh N, Levi-Belz Y, Apter A. A proposed model of the development of suicidal ideations. Compr Psychiatry (2015) 56:93–102. doi: 10.1016/j.comppsych.2014.09.019	2015	Quantitative	196 subjects.
22	Holden RR, Mehta K, Cunningham EJ, McLeod LD. Development and preliminary validation of a scale of psychache. Can J Behav Sci (2001) 33:224–32. doi: 10.1037/h0087144	2001	Quantitative	Study 1: 294 age average promedio de edad 19,1 (sd: 1,6) 102 subjects: Study 2: 211 women (19,4 sd = 2,4)
23	Horesh N, Levi Y, Apter A. Medically serious versus non serious suicide attempts: relationships of lethality and intent to clinical and interpersonal characteristics. J Affect Disord (2012) 136:286–93. doi: 10.1016/j.jad.2011.11.035	2012	Quantitative	102 subjects:
24	Huanhuan L, Weizhen X, Xinwei L, Rog F, Chuan S, Xiangyu Y, et al. Clarifyng the role of psychological pain in the risks of suicidal ideation and suicidal acts among patients with major depressive episodes. Suicide Life Threat Behav (2014) 44(1):77–88. doi: 10.111/sltb.12056	2014	Quantitative	111 patients
27	Ismael Conejero, Emilie Olié, Raffaella Calati, Déborah Ducasse, Philippe Courtet (2018). Psychological Pain, Depression, and Suicide: recent evidence and Future Directions. Current Psychiatry Reports (2018) 20: 33	2018	Theory review	Theory review
25	Jollant F, Near J, Turecki G, Richard-Devantoy S. (2016). Spectroscopy markers of suicidal risk and mental pain in depressed patients. Progress in Neuropsychopharmacology & Biological Psychiatry doi: 10.1016/j.pnpbp.2016.10.005	2016	Quantitative	25 pacients and 33 controls.
26	Lambert C, Troister T, Ramadan Z, Montemarano V, Fekken C, Holden R. (2020). Psychache Predicts Suicide Attempter Status Change in Students Starting University. Suicide and Life-Threatening Behavior 50 (3) June 2020 © 2020 The American Association of Suicidology doi: 10.1111/sltb.12624	2020	Quantitative	516 university students follow up, 10 weeks
27	Landi, G., Furlani, A., Boccolini, G., Mikulincer, M., Grandi, S., & Tossani, E. (2020). Tolerance for Mental Pain Scale (TMPS): Italian validation and evaluation of its protective role in depression and suicidal ideation. Psychiatry Research, 291, 113263.	2020	Quantitative	204 participantes entre 18 y 68
28	Leenars AA, Lester D. A note on Shneidman's psychological pain assessment scale. Omega: J Death Dying (2005) 50(4):301–7. doi: 10.2190/WH9X-80M3-NJ54-5GCU	2005	Quantitative	127 subjects: 37 males 90 female (22,9 sd 6,4)
29	Lester D. Psychache, depression, and personality. Psychol Rep (2000) 87:940. doi: 10.2466/PR0.87.7.940-940	2000	Quantitative	51 students
30	Levi Y, Horesh N, Fischel T, Treves I, Or E, Apter A. Mental pain and its communication in medically serious suicide attempts: an "impossible situation". J Affect Disord (2008) 111:244–50. doi: 10.1016/j.jad.2008.02.022	2008	Quantitative	102 patients with SB, 71 controls
31	Levi-Belz Y, Gvion Y, Grisaru S & Apter A. (2018) When the Pain Becomes Unbearable: Case-Control Study of Mental Pain Characteristics Among Medically Serious Suicide Attempters, Archives of Suicide Research, 22:3, 380–393. doi: 10.1080/13811118.2017.1355288	2018	Quantitative	241 participants (142 men, 99 women) 20–85 years old

(Continued)

TABLE 1 | Continued

	Reviewed papers	Year	Type of study	Sample
32	Levi-Belz Y, Gvion Y, Horesh N, Apter A. Attachment patterns in medically serious suicide attempts: the mediating role of self-disclosure and loneliness. Suicide Life Threat Behav (2013) 43(5):511–22. doi: 10.1111/sltb	2013	Quantitative	102 subjects
33	Levinger, S., Somer, E., & Holden, R. R. (2015). The importance of mental pain and physical dissociation in youth suicidality. Journal of Trauma & Dissociation, 16(3), 322–339. https://doi.org/10.1080/15299732.2014.989644	2015	Quantitative	123 subjects
34	Li, S., Yaseen, Z. S., Kim, H. J., Briggs, J., Duffy, M., Frechette-Hagan, A., Cohen, L. J., & Galynker, I. I. (2018). Entrapment as a mediator of suicide crises. BMC psychiatry, 18(1), 4. https://doi.org/10.1186/s12888-018-1587-0	2018	Quantitative	200 subjects 18–65 years old
35	Yang, L., Liu, X., Chen, W., & Li, L. (2019). A Test of the Three-Step Theory of Suicide among Chinese People: A Study Based on the Ideation-to-Action Framework. Archives of suicide research: official journal of the International Academy for Suicide Research, 23(4), 648–661. https://doi.org/10.1080/13811118.2018.1497563	2019	Quantitative	1,097 subject non-clinical 594 women, three public universities in China
36	Mee S, Bunney BG, Bunney WE, Hetrick W, Potkin SG, Reist C. Assessment of psychological pain in major depressive episodes. J Psychiatr Res (2011) 45:1504–10. doi: 10.1016/j.jpsychires.2011.06.011	2011	Quantitative	73 subjects, 96 control (non-psyquiatrics)
37	Mee, S., Bunney, B. G., Reist, C., Potkin, S. G., & Bunney, W. E. (2006). Psychological pain: A review of evidence. Journal of Psychiatric Research, 40(8), 680–690. https://doi.org/10.1016/j.jpsychires. 2006.03.003.	2006	Review	
38	Meerwijk, E. L., & Weiss, S. J. (2011). Toward a unifying definition of psychological pain. Journal of Loss and Trauma, 16(5), 402–412. https://doi.org/10.1080/15325024.2011.572044.	2011	Revisión Sistemática	6 studies
39	Meerwijk, E. L., Chesla, C. A., & Weiss, S. J. (2014). Psychological pain and reduced resting state heart rate variability in adults with a history of depression. Psychophysiology, 51(3), 247–256. https://doi.org/10.1111/psyp.12175.	2014	Quantitative	35 depresive adults
40	Meerwijk, E. L., Mikulincer, M., & Weiss, S. J. (2019). Psychometric evaluation of the tolerance for mental pain scale in United States adults. Psychiatry Research, 273, 746–752. https://doi.org/10.1016/j.psychres.2019.01.101.	2019	Quantitative	225 Facebook users
41	Meerwijk, E.L., Ford, J.M., Weiss, S.J., 2013. Suicidal crises because of diminishing tolerance to psychological pain. Brain Imag. Behav. 7, 245–247. https://doi.org/10.1007/s11682-012-9179-y.	2013	Teoric reviex	Teoric review
42	Mills J, Green K, Reddon J. An evaluation of the psychache scale on an offender population. Suicide Life Threat Behav (2005) 35(5):570–80. doi: 10.1521/suli.2005.35.5.570.	2005	Quantitative	136 men imprisoned by the law
43	Montemarano V, Troister T, Lambert C, Holden R. (2018). A four-year longitudinal study examining psychache and suicide ideation in elevated-risk undergraduates: A test of Shneidman's model of suicidal behavior. J. Clin. Psychol. 2018;74:1820–1832. doi: 10.1002/jclp.22639.	2018	Quantitative	82 high suicidal university students
44	Ohana, I., Golander, H., & Barak, Y. (2014). Balancing psychache and resilience in aging holocaust survivors. International Psychogeriatrics, 26, 929–934.	2014	Quantitative	214 participants; 101 women, 113 men
45	Olié E, Guillaume S, Jaussent I, Courtet P, Jollant F. Higher psychological pain during a major depressive episode may be a factor of vulnerability to suicidal ideation and act. J Affect Disord (2010) 120:226–30. doi: 10.1016/j.jad.2009.03.013.	2010	Quantitative	210 inpatients hospitalised with major depression diagnosis
46	Orbach, I., Mikulincer, M., Gilboa-Schechtman, E., & Sirota, P. (2003). Mental pain and its relationship to suicidality and life meaning. Suicide and Life-Threatening Behavior, 33(3), 231–241. https://doi.org/10.1521/suli.33.3.219.23219.	2003	Quantitative	Study 1: 32 adults 14 men y 18 women Study 2: 98 israel students 79 women 23 men

(Continued)

TABLE 1 | Continued

	Reviewed papers	Year	Type of study	Sample
47	Orbach, I., Mikulincer, M., Sirota, P., & Gilboa-Schechtman, E. (2003). Mental pain: a multidimensional operationalization and definition. Suicide and Life-threatening Behavior, 33(3), 219–230. doi: 10.1521/suli.33.3.219.23219.	2003	Mixed	Study 2: 255 israel students (194 women 61 men) Study 3: 100 students
48	Pachkowski M, May A, Tsai M, Klonsky, D. (2019). A Brief Measure of Unbearable Psychache. Suicide and Life-Threatening Behavior 49 (6) December 2019 1721© 2019 The American Association of Suicidology doi: 10.1111/sltb.12556		Quantitative	Study 1: 1.006 adults (53% men) Study 2: 190 psychiatryc adults (47% men)
49	Patterson A, Holden R. (2012) Psychache and Suicide Ideation among MenWho AreHomeless: ATest of Shneidman's Model Suicide and Life-Threatening Behavior 42(2) April 2012 147 2012 The American Association of Suicidology doi: 10.1111/j.1943-278X.2011.00078.x	2012	Quantitative	97 men
50	Pereira E, Kroner D, Holden RR, Flamenbaum R. Testing Shneidman's model of suicidality in incarcerated offenders and in undergraduates. Pers Individ Dif (2010) 49:912–7. doi: 10.1016/j.paid.2010.07.029	2010	Quantitative	73 imprisoned men, 80 students men; 80 students women
51	Pompili M, Lester D, Leenars A, Tatarelli R, Girardi P. Psychache and suicide: a preliminary investigation. Suicide Life Threat Behav (2008) 38(1):116–21. doi: 10.1521/suli.2008.38.1.116	2008	Quantitative	88 inpatients (35 men y 53 women)
52	Pompili, M. (2018). The increase of suicide rates: the need for a paradigm shift. thelancet.com Vol 392 August 11, 2018	2018	Revission	Theory revission
53	Reisch T, Seifritz E, Esposito F, Wiest R, Valach L, Michel K. An fMRI study on mental pain and suicidal behavior. J Affect Disord (2010) 126(1):321–5. doi: 10.1016/j.jad.2010.03.005	2010	Mixed	Recent (past month) suicide attempters
54	Rizv. ia S, Iskrica A, Calatic R, & Courtetc P. (2017) Psychological and physical pain as predictors of suicide risk: evidence from clinical and neuroimaging findings. 0951-7367 Copyright 2017 Wolters Kluwer Health, Inc. All rights reserved. www.co-psychiatry.com	2017	Systematic revisión	Systematic revission
55	RuthTrakhtenbrot, YariGvion, YossiLevi-Belz, NettaHoresh, TsviFischel, MarkWeiser, IlanTreves, Alan Apter (2016) Predictive value of psychological characteristics and suicide history on medical lethality of suicide attempts: afollow-upstudy of hospitalized patients. Journal ofAffectiveDisorders199(2016)73–80. http://dx.doi.org/10.1016/j.jad.2016.03.054_0165-0327/ & 2016Elsevier	2016	Quantitative	153 psyquiatric patients
56	Segal-Engelchin, D., Kfir-Levin, N., Neustaedter, S. B., & Mirsky, J. (2015). Mental pain among female suicide attempt survivors in Israel: An exploratory qualitative study. International Journal of Mental Health and Addiction, 13(4), 423–434. https://doi.org/10.1007/s11469-015-9545-2	2015	Qualitative	4 women suicide attempters (21–58 years old)
57	Shelef L, Fruchter E, Hassidim A, Zalsman G. Emotional regulation of mental pain as moderator of suicidal ideation in military settings. Eur Psychiatry (2015) 30:765–9. doi: 10.1016/j.eurpsy.2014.12.004	2015	Quantitative	168 soldiers (100 men: 59,5%) 18–21 years old
58	Schuck, A., Calati, R., Barzilay, S., Bloch-Elkouby, S., Galynker, I (2018). Suicide Crisis Syndrome: A review of supporting evidence for a new suicide-specific diagnosis. Behav Sci Law. 2019;37:223–239. wileyonlinelibrary.com/journal/SBl doi: 10.1002/SBl.2397	2018	Revisión	Bibliographic revission
59	Skevington, S., Lotfy, M. & O'Connell, K. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A Report from the WHOQOL Group. Qual Life Res 13, 299–310 (2004). https://doi.org/10.1023/B:QURE.0000018486.91360.00.	2004	Quantitative	11.830 adults from 23 countries
60	Soumani, A., Damigos, D., Oulis, P., Masdrakis, V., Ploumpidis, D., Mavreas, V., & Konstantakopoulos, G. (2011). Mental pain and suicide risk: Application of the greek version of the mental pain and the tolerance of mental pain scale. Psychiatriki, 22(4), 330–340.	2011	Quantitative	112 participants (73 women y 39 men). 18–65 years old
61	Rui C. Campos, Margarida Gomes, Ronald R. Holden, Margarida Piteira & Ana Rainha (2017) Does psychache mediate the relationship between general distress and suicide ideation?, Death Studies, 41:4, 241–245. doi: 10.1080/07481187.2016.1251510	2017	Quantitative	440 students

(Continued)

TABLE 1 | Continued

	Reviewed papers	Year	Type of study	Sample
62	Tossani, E., Ricci Garotti, M. G., Mikulincer, M., Giovagnoli, S., Calzolari, G., Landi, G., & Grandi, S. (2021). Psychometric evaluation of the Italian version of Orbach & Mikulincer mental pain scale in a non-clinical sample. Current Psychology, 40(4), 1903–1910. https://doi.org/10.1007/s12144-019-0128-4	2021	Quantitative	544 italian adults italianos, 18–85 years old
63	Troister T, Davis MP, Lowndes A, Holden RRA. Five-month longitudinal study of psychache and suicide ideation: replication in general and high-risk university students. Suicide Life Threat Behav (2013) 43(6):611–20. doi: 10.1111/sltb.12043	2013	Quantitative	4.499 students (80% women). 17–89 years old
64	Troister T, Holden RR. A two-year prospective study of psychache and its relationship to suicidality among high-rosk undergraduates. J Clin Psychol (2012) 68(9):1019–27. doi: 10.1002/jclp.21869	2012	Quantitative	41 students with suicide risk
65	Troister T, Holden RR. Comparing psychache, depression, and hopelessness in their associations with suicidality: a test of Shneidman's theory of suicide. Pers Individ Dif (2010) 49:689–93. doi: 10.1016/j.paid.2010.06.006	2010	Quantitative	1,475 student, 71% mujeres
66	Troister T, Holden RR. Factorial differentiation among depression, hopelessness, and psychache in statistically predicting suicidality. Meas Eval Couns Dev (2013) 46:50–63. doi: 10.1177/0748175612451744	2013	Quantitative	2.974 students (2.135 women, 769 men, 70 non-declared genre
67	Van Heeringen K, Van den Abbeele D, Vervaet M, Soenen L, Audenaert K. The functional neuroanatomy of mental pain in depression. Psychiatry Res (2010) 181:141–4. doi: 10.1016/j.pscychresns.2009.07.011	2010	Quantitative	39 patients (22 women, 17 men) diagnosed by depression
68	Xie W, Li H, Luo X, Fu R, Ying X, Wang N, et al. Anhedonia and pain avoidance in the suicidal mind: behavioral evidence for motivational manifestations of suicidal ideation in patients with major depressive disorder. J Clin Psychol (2014) 70(7):681–92. doi: 10.1002/jclp.22055	2014	Quantitative	40 outpacients and 20 control
69	Xuemei Sun, Huanhuan Li, Wei Song, Songyuan Jiang, Chengfeng Shen, Xiang Wang (2020). ROC analysis of three-dimensional psychological pain in suicide ideation and suicide attempt among patients with major depressive disorderJ. Clin. Psychol. 2020;76:210–227.doi: 10.1002/jclp.22870	2020	Quantitative	137 pacients (52 men, 38%; 85 women, 62%).
70	Yossi Levi-Belz, Yari Gvion, Alan Apter (2020). The Serious Suicide Attempts Approach for Understanding Suicide: Review of the Psychological Evidence. OMEGA—Journal of Death and Dying 1-18. doi: 10.1177/0030222820981235	2020	Review	Revision
71	You Z, Song J, Wu C, Qin P, Zhou Z. Effects of life satisfaction and psychache on risk for suicidal behaviour: a cross-sectional study based on data from Chinese undergraduates. BMJ Open (2014) 4:e004096. doi: 10.1136/bmjopen-2013-004096	2014	Cross-sectional study	5,988 university students
72	Berlim MT, Mattevi SB, Pavanello DP, Caldieraro MA, Fleck MPA, Wingate LR, et al. Psychache and sucidality in adults mood disordered outpatients in Brazil. Suicide Life Threat Behav (2003) 33(3):242–8. doi: 10.1521/suli.33.3.242.23220	2003	Quantitative	N = 60 outpatents, 50 women, 10 men

1) the clinical interview in the evaluation of patients with probable risk of suicide and

2) therapeutic interventions in different stages of the treatment of subjects with suicidal risk from the first clinical interview onwards (**Figure 4**).

RESULTS

The 73 studies reviewed had different characteristics, amongst which the following stand out:

The works included different methods and approaches. Most of them were done in adult samples. Not all studies detailed the sex and age of the patients, and some that obtained information from the internet were unable to establish the samples' demographic characteristics. There were 56 studies with quantitative methods, most of them comparing the results between different samples; 4 studies used qualitative analysis with smaller samples, and 2 studies used mixed methods. There were 4 reviews, 3 systematic reviews, 1 cross-sectional survey, and 2 studies that followed different methods. There were 2 studies in which a follow-up of close to 1 year was carried out. While most of the studies came from the United States, there were three Portuguese studies, two Canadian, and four Chinese. The reviewed studies are detailed in **Table 1**.

We analysed the information through an abstraction exercise that allowed us to classify different items in ordered groups under a common notion. The content analysis was structured based on the personality theory perspective of states and traits

FIGURE 1 | State of suicidal mental pain: Diagnosis.

FIGURE 2 | State of suicidal mental pain: Psychological experience.
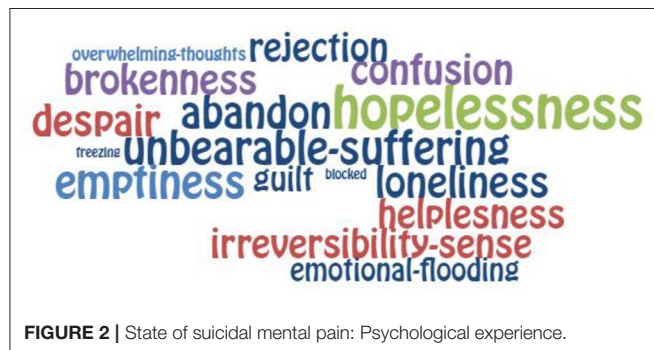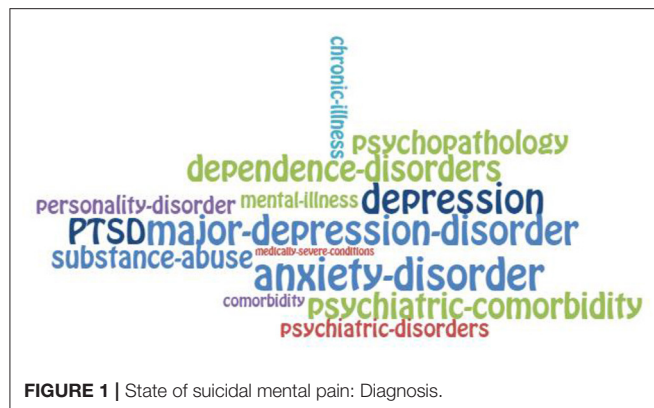
in suicidal mental pain. There are different factors that shape personality and can lead to dysfunctionalities in coping with areas of life: the genetic load that has been inherited from family biology; learning to deal problematically with emotions and interpersonal relationships in childhood; life events that cause prolonged stress; and traumatic childhood experiences, such as abuse, neglect, loss of caregivers, and bullying, among others. Dysfunctionalities can be increased or decreased, depending on history and context, leading to states of greater or lesser emotional well-being and impacting the relationship with oneself, interpersonal relationships, and quality of life (30).

The analysis provided a list of 607 variables, which an exercise of conceptual abstraction led us to group according to clinical criteria, differentiating those that are transitory from those that are relatively stable over time. The transient variables include the mental pain psychological states in suicide, and relatively stable variables include the mental pain psychological traits in suicide.

Mental Pain Psychological States in Suicide

1) Psychological states associated with a diagnosis of mental pain appearing at least 10 times in the analyses, resulting in 113 concepts. The cut-off point of 10 occurrences was chosen purely for the purpose of visibility in the diagramming of the concepts found. The diagnostic variables found were the following: Anxiety disorder, Chronic Illness, Comorbidity, Dependence

disorders, Major depression, Medically severe conditions, Mental Illness, Personality disorder, Psychiatric comorbidity, Psychiatric disorders, Psychopathology, Post-traumatic stress disorder (PTSD), and Substance abuse. These factors were abstracted into the grouping concept called Pathology.

2) Psychological states associated with a psychological experience of mental pain appearing at least 10 times in the analyses, resulting in 222 concepts. The psychological experience state variables found were as follows: Abandon, Blocked Sense, Brokenness, Confusion, Despair, Emotional Flooding, Emptiness, Freezing, Guilt, Helplessness, Hopelessness, Irreversibility Sense, Loneliness, Overwhelming Thoughts, Rejection, and Unbearable Suffering. These factors were abstracted under the grouping concept known as Unbearable Psychological Suffering.

Mental Pain Psychological Traits in Suicide

3) Psychological traits of mental pain appearing at least 10 times in the analysis, appearing 272 concepts. The psychological traits variables found were Alexithymia, Inability to Communicate Stress/ Painful Feelings/Thoughts, Lack of Control, Persistent Intolerance of Psychological Distress, and Sustained Emotional Dysregulation. These factors were abstracted under the grouping concept known as Emotional Dysregulation and Impairment in Recognising and Communicating Emotions.

Besides, the results showed other traits as Avoiding Rule-Learning, Inability in Help-Seeking Behaviours, Insecure Attachment Style, Difficulties with Interpersonal Abilities, Limited Help-Seeking Behaviours, and Schizoid Traits. These were abstracted under the grouping concept Troubled Interpersonal Relationships.

Other appearing traits were Impulsivity and Poorer Inclined Delay Rewards, which were named Impulsiveness. Also, we found Coping with Disability, Decision-Making Issues, Impaired Cognitive Control Rule Learning, and Rigid Conceptual Reasoning. These factors were abstracted under the concept Distorted Reasoning.

Both psychological states (transient) and subjective styles of experience (relatively stable personality) can be modified by psychotherapeutic work oriented toward aspects such as resignification of life history and broadening of coping styles.

These variables can be observed in **Table 2**, States in Mental Pain, and **Table 3**, Traits in Mental Pain.

For a graphic look at the weight of the concepts according to the number of repetitions that were observed in the analysis, we can observe (**Figures 1**–**3**).

Psychotherapeutic intervention in these cases can be developed with reflective exercises that add life history accounts and by encouraging adaptive responses to adverse events.

The ability to learn, to modify behaviour from new experiences, explains the usefulness of certain therapeutic interventions to modify the way of understanding and acting in response to various emotional stimuli (31). In the discussion, we will review some clinical interventions that would make it possible to reduce MP by expanding the repertoire of emotional
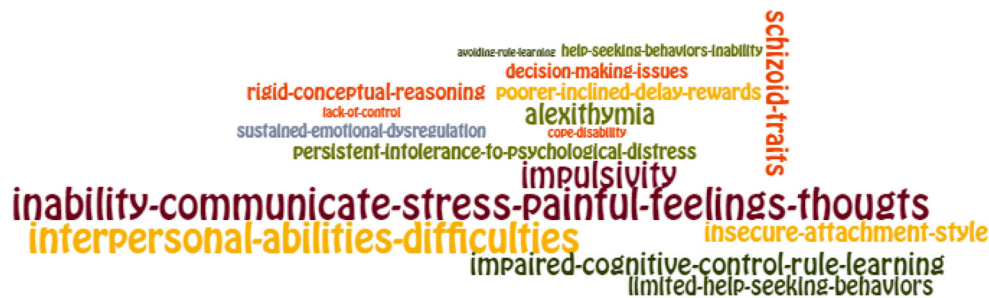
FIGURE 3 | Traits of suicidal mental pain.

and behavioural responses of a subject at risk of suicide (**Figure 3**).

DISCUSSION

The purpose of this paper is to contribute to the accuracy of the understanding of MP in suicide risk. Through a qualitative review of content, we have found variables which can be grouped corresponding to clinical criteria, differentiating between transitory variables associated with a psychological state in suicidal MP, including diagnostic variables on the one hand and subjective experience variables on the other.

In addition, we found relatively stable personality traits in suicidal MP. **Figure 3** shows the central elements of the evaluation of a patient who might be suffering from MP. Each of the factors is a reminder of the facts that are paramount in this task. We have collected the results of a number of studies to highlight those aspects that are most frequently observed in a clinical population. These facts can be assessed in the first interview and at different stages of the treatment after a suicide attempt. Our recommendations are based on the identification of mental pain as the event closest to suicidal action. One of the limitations of our study on SB is that the studies selected are those that include MP, which leaves out many very valuable papers conducted from different perspectives. We understand that the problem of suicide is extraordinarily complex, and therefore, when evaluating the experience of mental pain, we can recognise the manifestation of a diversity of facts in a similar state.

The main task for clinicians is to identify what contributes to encouraging or attenuating psychic pain in the subject's relationships with him/herself and with others. To reduce psychic pain, interventions must be directed at those factors that determine MP in everyone. The treatment of axis I disorders (DSM-V) is a priority and has been sufficiently described for each of the pathologies by means of various clinical guidelines and systematic reviews. We will review other state variables, such as hopelessness, unbearable suffering, loneliness, and psychological pain, when describing clinical strategies and the proper psychotherapeutic interventions.

The different groups of factors associated with suicide— namely personality and individual differences, cognitive factors, social factors, and adverse life events (1)—play roles in the
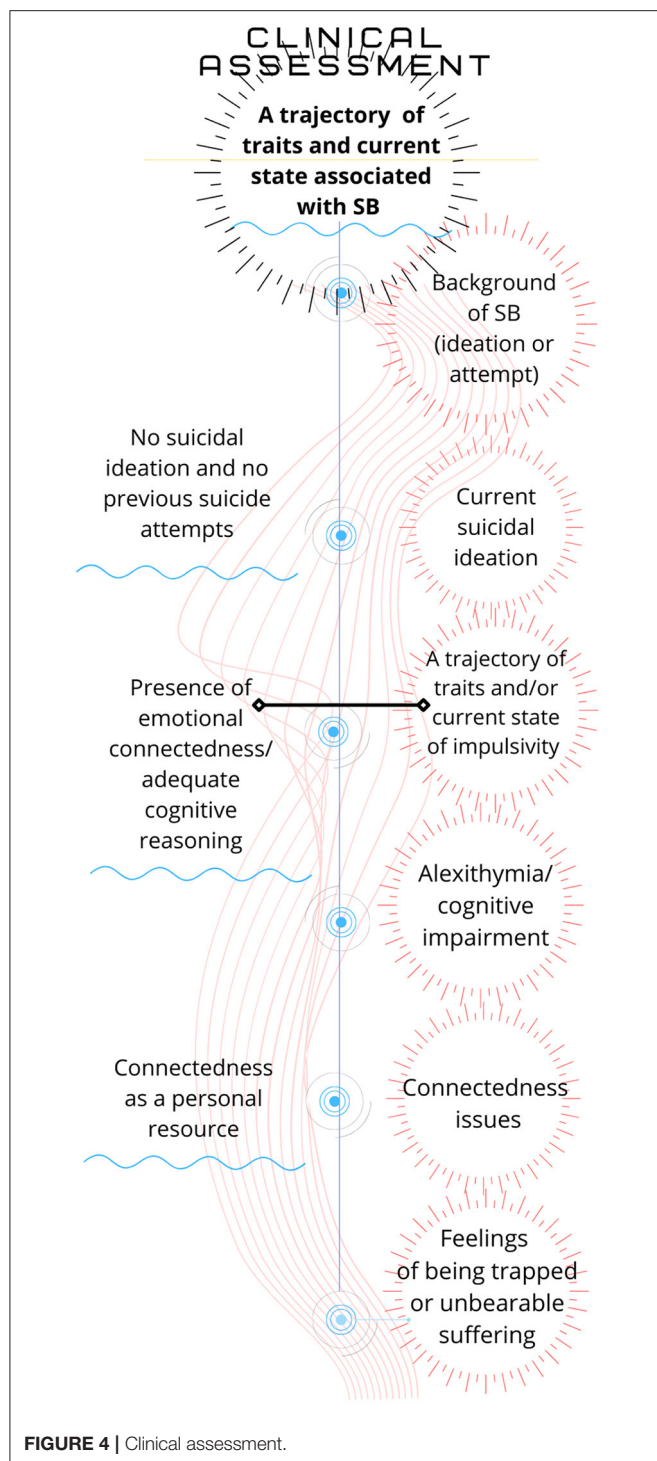
different stages of this behaviour. According to the integrated motivational-volitional model proposed by O'Connor, SB has a pre-motivational phase that includes background factors and triggering events: diathesis, environment, and life events; a motivational phase, in which ideation and intention build up; and a volitional phase, where the behaviour is enacted. MP takes place in the motivational phase, in which diverse psychological factors might lead a subject to experience a feeling of humiliation and defeat, followed by a perception of entrapment that might lead him/her to conceive of SB as the only way to alleviate mental pain. It is in the motivational phase where the presence or absence of factors might show a risk or a protective role. It is within that phase—which has a limited time frame—that those interventions might play a critical role in helping someone to avoid SB. The myriad of possible factors that might be relevant to someone's actions obliges us to select the most relevant ones leading to MP in each individual case. There doesn't seem to be a better way to approach this clinical plight. To prevent the subject from acting, we must single out the sources of individual psychological distress, addressing individual needs to foster preventive strategies (32).

State of Unbearable Psychological Suffering and Feelings of Hopelessness and Loneliness

In historical periods when the population has been exposed to unusual suffering under circumstances of great uncertainty and real threat, suicide has increased significantly. This is what happened in some parts of Germany after the end of World War II (33). But exceptional historical circumstances are not sufficient to explain what is eminently, rather, a matter of subjective experience. A sentimental break-up, an economic failure, and a severe illness are experiences associated with different responses. Each person finds his or her own way of adapting to adversity.

Unbearable suffering, along with depression, hopelessness, and impulsivity, is one of the most frequent emotional experiences in MP (34). This is consistent with our findings (**Figure 1**). A comprehensive model sustains that SB occurs in the presence of four factors: psychological pain, hopelessness, a feeling of connectedness, and suicide capacity. As summarised by Klonsky, "we believe that any effort to prevent or treat suicidality should target one or more of these four factors and will succeed

FIGURE 4 | Clinical assessment.

Our data support the joint role that these factors have in the experience of mental pain. The presence of unbearable pain and hopelessness (in **Figure 1**) has a similar relevance to "interpersonal difficulties" and "inability to communicate thoughts feelings" (**Figure 2**). Both capacities are expressed in the ease or difficulty of dealing with interpersonal differences and maintaining the bond with others (connectedness). There is a need to protect and activate cognitive and emotional resources using psychological interventions to foster a sense of emotional connexion with the people available in the patient's environment. In a suicidal crisis, patients may not visualise who could be part of their network. Nonetheless, this critical intervention can prevent suicidal ideation from escalating in intensity for those who are experiencing both pain and hopelessness. Also, when hopelessness is present, these interventions are often useful even if the patient is not depressed (35).

Emotional Dysregulation and Impairment in Recognising and Communicating Emotions

Alexithymia, defined as the inability to identify or express emotions (36), has been associated with SB. A recent systematic review and meta-analysis of the association between alexithymia and SB "found a large size effect (0.54) in the meta-correlation of alexithymia and suicide ideation, and a medium effect size (0.25) in the meta-correlation between alexithymia and SB" (37). Similarly, our review of the most frequent terms used in discussing mental pain highlights alexithymia as a trait that might interfere with the capacity to recognise the sources of mental pain. In such cases, when the pain becomes unbearable, the confusion and emotional overflow can be understood as a call for help and support (38, 39).

In the previous stages of treatment, it is necessary to do the task of naming the emotions that are usually expressed as physical sensations and emotional storms. This exercise of cognitive structuring allows the increase of emotional awareness, with the development of progressively more sophisticated abilities to differentiate and integrate the contents of emotional activity" (40).

Mentalisation treatment is helpful to understand mental states, such as beliefs, emotions, intentions, and desires, which are the basis of the relationships with oneself and others. The development of this skill is stimulated by the repetitive exercise of asking how the patient and the others may have felt in an interaction and what they thought and what they intended in a determined situation (41).

Troubled Interpersonal Relationships

Suicide attempters often have repeatedly experienced frustrated psychic needs in interpersonal interactions, with significantly increased victimisation in their historical contexts, including recurrent situations of physical and psychological abuse. These adverse events often interfere with the development of stable and harmonious interpersonal bonds, as the patients' processes of interpersonal trust, openness, and bonding in relationships have been traumatised (42). Depressive symptoms, such as psychache,

to the extent that one or more of these factors is changed for the better" (34). Moreover, "connectedness is most relevant to suicidal ideation as a protective factor among those high on pain and hopelessness, especially when one's connectedness exceeds one's pain" (34) Hence, pain, hopelessness, and connectedness contribute to SB interactively and jointly.

State variables

Diagnosis	Quantity	Percentage	Concepts abstraction	Psychological experience	Quantity	Percentage	Concepts abstraction
Anxiety disorder	18	15.93	**Pathology**	Abandonment	17	7.66	**Unbearable**
Chronic illness	4	3.54		Blocked	5	2.25	**Psychological**
Comorbidity	3	2.65		Brokenness	15	6.76	**suffering**
Dependence disorders	10	8.85		Confusion	15	6.76	
Depression	15	13.27		Despair	16	7.21	
Major depression disorder	14	12.39		Emotional flooding	10	4.50	
Medically severe conditions	2	1.77		Emptiness	18	8.11	
Mental illness	4	354		Freezing	5	2.25	
Personality disorder	5	4.42		Guilt	11	4.95	
Psychiatric comorbidity	10	8.85		Helplessness	14	6.31	
Psychiatric disorders	5	4.42		Hopelessness	28	12.61	
Psychopathology	8	7.08		Irreversibility sense	14	6.31	
PTSD	9	7.96		Loneliness	16	7.21	
Substance abuse	6	5.31		Overwhelming thoughts	6	2.70	
				Rejection	14	6.31	
				Unbearable suffering	18	8.11	
Total	**113**	**100.00**		**Total**	**222**	**100.00**	

thwarted belongingness, and perceived burdensomeness, are also related to suicidality through intrapersonal and interpersonal variables (43).

Clinical work can be guided by stimulating the patient's abilities to understand the context of the emotions arising in relationships (both one's own and those of others); to direct his/her attention to what is relevant for problem-solving; to adopt different points of view and multiple perspectives on issues; to discriminate the importance of events; to make his/her expectations flexible; and to concede and ask for changes to find agreed solutions (44). This ability can be obtained through joint reflection on different points of view and expectations. In addition, what the patient expects to happen and reflections on what he/she imagines others expect allow for greater flexibility in those particularly rigid views the subject may have about himself and others.

Impulsivity in Distorted Reasoning

Impulsivity has always been considered to play a major role in SB. However, it is difficult to determine its actual role in SB. A particularly complex task is to figure out its place within the sequence of events preceding suicide. For several authors, impulsivity is critical to explaining these actions. According to a recent study based on the Interpersonal Theory of suicide, "trait impulsivity is related to suicidal behaviour and the fluctuation of suicidal ideation, but not to suicidal ideation itself. Thus, trait impulsivity seems to act as a distal risk factor via capability for suicide and it seems to play a role for the dynamics of suicidal ideation" (45). However, impulsivity can manifest itself in different stages of behaviours leading to suicide, from the

moment in which the agent evaluates his or her difficulties and considers the options to solve them until the moment in which he or she decides to act. As we said before, SB is the result of a behaviour marked by ambivalence in which an individual conceives of actions without knowing the true consequences they would have for him/herself as well as for others. Not having the possibility of assessing the consequences of one action on another, the agent, motivated by the need to end his/her anguish and overwhelmed by the hopelessness of not finding a way out of his/her difficulties, will try to end his/her life. The action will occur under the motivational pre-eminence of one or several factors. A decision with irreversible consequences supported by a narrow view of the circumstances and encouraged by a state of emotional restraint almost always originates in an impulsive thought or behaviour. SB can be understood as acts that occur—in the presence of poor decision-making and impulsivity—when someone experiences unbearable suffering. This emotional state has been recognised as a condition that might stimulate someone to take their own life as a solution to the misery they are experiencing (46, 47).

In the clinical evaluation of patients at risk of SB, clinicians should take into consideration the patient's overall situation, avoiding a judgement based solely on a single aspect of it (**Figure 4**). Impulsivity might be a trait in someone's personal history, and yet, they may not have a history of SB. On the other hand, some patients may not have the trait of impulsivity in their personal history, but they might be suffering from some clinical conditions, such as a mixed bipolar state or psychosis, which by themselves increase the risk of decisions based on the patient's acute emotional status at a particular moment.

TABLE 3 | Subjective styles of experience (relatively stable personality) obtained in concepts analysis.

Trait variables in mental pain

Trait factors	Quantity	Percentage	Concepts Abstraction
Alexithymia	17	6.25	Emotional dysregulation and impairment in recognising and communicating emotions
Inability to communicate, stress, painful feelings/thoughts	42	15.44	
Lack of control	7	2.57	
Persistent intolerance of psychological distress	11	4.04	
Sustained emotional dysregulation	9	3.31	
Avoiding rule-learning	6	2.21	Troubled interpersonal relationships
Help-seeking behaviours inability	8	2.94	
Insecure attachment style	16	5.88	
Difficulties with interpersonal abilities	38	13.97	
Limited help-seeking behaviours	14	5.15	
Schizoid traits	18	6.62	
Impulsivity	26	9.56	Impulsiveness
Poorer inclined delay rewards	12	4.41	
Cope disability	7	2.57	Distorted reasoning
Decision-making issues	10	3.68	
Impaired cognitive control rule learning	19	6.99	
Rigid conceptual reasoning	12	4.41	
	272	100	

Highly lethal SB has been found in the presence of an overwhelming sense of entrapment with cognitive and emotional dysregulation (6). High-lethality suicide attempters, independent of depressive symptoms, may present executive function impairments, such as rigidity-shift setting and negative cognitive biases (48).

Suicidal individuals are more likely to inaccurately interpret stressors, use emotion-focused coping, and adopt an avoidant approach. In such cases, we must prioritise the application of techniques such as cognitive remediation and problem-solving (49, 50). Problem-solving efforts are multifaceted (social, psychological) and encompass a wide range of cognitive and emotional functions, such as autonomy, mastery of the environment, and development of a meaningful purpose in life (51).

Cognitive techniques aimed at reformulating and resolving intrapersonal and interpersonal conflicts are of great help for the subject to find adequate alternatives to understand and act whilst avoiding the feeling of entrapment. To do this, it will be necessary to look at each of the cognitive dimensions on which the most complex judgments are based. Among them are attention, memory, executive function, metacognition, and attribution of intentions. The goal of these interventions is to stabilise and generalise both intrapersonal and interpersonal functioning (52–64).

The study of suicidal behaviour is fraught with difficulties and limitations. In fact, it faces the same limitations that we find in the understanding of human behaviour and, particularly, of intention. An intentional action is one that someone performs for some reason. Human behaviour can have similar consequences for different reasons. But it is not possible to understand the reasons that led someone to act based solely on the consequences of their actions (65–73).

It is possible that in those subjects who are in treatment for mental health problems, as well as in those who have a history of previous suicide attempts, MP is the state closest to suicidal action. Therefore, if we concentrate our efforts on this group of patients, we may be able to intervene and prevent what would otherwise be inevitable (71, 74–80). We must be realistic that this is a subgroup of the total number of suicides. But it is precisely this group that is usually most within reach of our treatment.

The above clinical recommendations to address the state and trait aspects of the individual experience of MP can give clinicians (psychologists and psychiatrists) the appropriate means to alleviate psychological distress and prevent suicidal risk.

A limitation of the research is that it focused only on studies presented in English, without including scientific articles in other languages. Therefore, further research that expands the vocabulary may contribute to enriching the explanation of the subjective experience of suicidal behaviour. Likewise, it would be desirable to study the interventions proposed for states and traits in SB and to deepen the knowledge of the impact they have on decreasing the psychological distress of suicidal risk.

AUTHOR CONTRIBUTIONS

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Suicide in Healthcare Workers: Determinants, Challenges, and the Impact of COVID-19

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The Coronavirus disease-19 (COVID-19), which first appeared in Wuhan, China, and was later declared a pandemic, has caused significant morbidity and mortality worldwide. Numerous efforts have been made worldwide to understand the disease's physical manifestation. However, less emphasis has been placed on the pandemic's mental health challenges for healthcare workers (HCWs) who played a critical role in fighting the disease. Existing literature shows the detrimental psychological impact and increased incidence of depression and anxiety among HCWs. It is expected that the mental health crisis will become a serious issue affecting HCWs, with long-term negative consequences following COVID. Physicians and nurses already represent the highest risk groups of suicide among the general population, and suicide can be regarded as an occupational hazard in the healthcare industry. Increased workload, burnout and fatigue, multifaceted challenges women HCWs, and increased substance abuse are contributing factors to suicide ideation. In this article, we identify the risk factors of suicide among HCWs, discuss mental health challenges exacerbated by the pandemic and its impact on suicide ideation.

Keywords: COVID-19, healthcare workers, suicide, depression, anxiety, burnout, post-traumatic stress, substance abuse

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has completely transformed the lives of millions of people worldwide, putting enormous strain on society and healthcare systems. The disease has now affected 213,237,126 individuals, resulting in 4,452,903 deaths (1). The new reality of lockdown, self-isolation, fear, and uncertainty surrounding this disease has significantly harmed the mental health of many. During the pandemic, about 4 in 10 adults in the U.S. reported anxiety or depressive disorder symptoms (2). Similarly, a nationwide survey in China reported that 35% of

the respondents had experienced psychological distress due to the SARS-CoV-2 (3). The 2021 World Health Organization (WHO) annual health report recorded 7,00,000 deaths by suicide globally (4). Latest reports show that it is currently the 17th leading cause of death (5).

The trend of suicide occurrence observed globally does not show association with a particular age group; however, the vulnerability to suicide increases with age and puts older adults at the most significant risk (4). Moreover, despite being described as a "global phenomenon" by the WHO, 777% of the global burden of suicide stems from low-and middle-income countries (LMICs). Prevalent poverty and low socio-economic standing rapidly increased suicidal ideation amongst populations residing in LMICs (6).

Despite a disproportionate burden, the crude death rate is highest in the European region, with 12.8 deaths per 1,00,000 population (4). In the United States, a steady rise of 30% has been observed in the number of deaths by suicide during 2000–2016. In 2017, this rate increased to 14.0 per 1,00,000. The WHO annual statistics also show an apparent gender predisposition with crude death rates in men nearly twice women (4).

Recent reports from 2020 show that mental health amongst physicians and frontline workers has been affected by the current COVID-19 pandemic (7, 8). Despite the risk of infection and death, HCWs have been at the frontline in the global fight against the pandemic. Fear of exposure to infection and transmission, staff shortages, inadequate personal protective equipment, and work stress has added an extra burden to an already stressful lifestyle (8). All these factors eventually have led to a rapid progression to burnout and chronic fatigue, which can progress to post-traumatic stress disorder (PTSD). A systematic review assessing the mental health problems in HCWs since the pandemic reported that nurses, women workers, frontline health care workers, younger medical staff, and workers in areas with higher infection rates had faced the highest level of psychological distress (9).

As a result, it is critical to assess the repercussions of declining mental health, address and acknowledge the job strain, particularly for women, and identify high-risk individuals to implement early prevention initiatives. This article discusses the mental health issues that HCWs face and variation in suicide rates based on their age, gender, specialty, and working conditions. Furthermore, we address the underlying causes of burnout and emotional distress among HCWs due to the effects of the COVID-19 pandemic.

We believe that addressing these factors is critical in developing a comprehensive and targeted strategy for reducing the risk of Suicide among HCWs. Early prevention initiatives, identifying at-risk individuals, and focused treatment for those in need are all part of this strategy.

DIFFERENTIATING CHARACTERISTICS IN SUICIDE RATES

Different reports have been made available regarding suicide concerning age globally. According to a report from 2018, suicide

has been reported to be the most common cause of death during the second and third decades of life (10). Previous reports suggested an overall increase in the tendency to commit suicide; however, the evaluation of recent data suggests an increase in rates of suicide in 33 countries alongside a decrease observed in 15 countries. All reports have been classified according to gender, and a significant increase has been observed in females from 37 countries and in males from 33 countries. The effect of other factors on this trend was also described (11). Factors including the socio-economic status, mortality rate, income inequality in females, the proportion of Gross Domestic Product (GDP), and the per capita expenditure on healthcare significantly impacted age-related trends in suicide.

A review from 2004 suggests that the mortality ratio due to suicide amongst gender was markedly higher for female physicians than male physicians. (12) A recent meta-analysis has confirmed that the suicide mortality rate in male physicians was considerably lower than the general population. However, assessment of rates of suicide deduces male sex as a significant risk factor. Suicide is historically known as an aggressive behavior not to be observed amongst females. A study from 2008 suggested that white males are more likely to commit suicide, whereas, in China, Suicide is seen as a cry for help and is more common amongst females (13). Overall, less importance has been given to female statistics of suicide, and the limited literature on physician suicide does not highlight important risk factors. Multiple reports also confirm that females have a higher chance of experiencing suicidal ideation. Higher suicide rates were also reported in countries experiencing political reform and social environment changes. This validates a concern that females are more affected since reform changes gender roles, increasing the chances of burnout among females (14).

According to multiple reports, the risk of committing suicide correlates to the vocation individual works in. A study analyzing the different demographics of cases of suicide shows that the risk ranged from 2.73 in physicians to 0.44 in architects and engineers (15). When assessing the risk of suicide, easier access to means of suicide is a significant risk factor. According to a report, it was confirmed that healthcare professionals, including nurses, doctors, and pharmacists, are more inclined to use poisons as a means of suicide (16).

Within healthcare itself, multiple specialties are specifically associated with a higher frequency of suicide. The majority of studies deduce the effect of the quality of work affecting mental health by reporting symptoms of PTSD and depression in these workers. An additional factor leading to physician suicide can be attributed to the development of chronic mental health disorders such as post-traumatic stress disorder, substance abuse, and depressive mood disorder. Mental illness has always been associated as a risk factor for suicide.

Emergency responders are on the front line of trauma and experience highly stressful work-related conditions. They have often been exposed to critical medical situations and regularly witnessed fatalities. According to a review, 21.4–53.7% of emergency responders from the Great East Japan earthquake and Lebanon-Israel War fit the criteria for depression (17). The prevalence of PTSD among such groups was estimated to be

higher than predicted, exacerbated by certain risk factors. A responder's likelihood of developing PTSD includes having no social support, certain neurotic and distant personality types, and individuals with harmful coping mechanisms.

In healthcare, competitive specialties like general surgery, anesthesiology has a noticeably higher risk of suicide due to multiple factors such as access to drugs and a high-stress work environment, which increase the likelihood of suicide. A meta-analysis report by Dutheils et al. evaluating suicide amongst specialties deduced a higher incidence in internal medicine (16%) followed by psychiatry (11%) and anesthesiology (4%) (18).

WORK ASSOCIATED FACTORS FOR SUICIDE

Since hospital working conditions vary between and within regions, differences are expected in healthcare workers' mental health and suicide rates. Burnout is a psychological condition that develops when people are exposed to a stressful work environment with high job demands and limited resources (19, 20). Suicidal ideation was found to be higher among those with burnout than those without it, according to a cross-sectional survey of 2,734 female nurses working in Taiwanese hospitals. Similarly, burnout was predictive of suicidal ideation in a longitudinal study of U.S. medical students, even when depressive symptoms were not present (21, 22).

To avoid the unanticipated effects of exhaustion and burnout, it is critical to strike a balance between appropriate working hours for health care workers, including surgical trainees, physician assistants, psychiatrists, and nurses, while maintaining high-quality patient care. A study conducted in Taiwan has shown that the prevalence of high work-related burnout from highest to lowest was nurses (66%), physician assistants (61.8%), physicians (38.6%), administrative staff (36.1%), and medical technicians (31.9%), respectively (23).

Residents, in particular, have been reported to be at a higher risk of depression as a result of a transition in their job capacity from a medical student to a trainee, which now includes intensive training hours along with studies and research (24, 25). This is compounded by characteristics such as early employment uncertainty, competitive work environment, and being younger, all of which are risk factors for emotional distress and ultimately suicidal thoughts. (26) reported that working in a training set for more than 80 h per week considerably increases the resident's depressive symptoms. Another study of first-year Japanese residents has found that 22.6 percent of residents had newly developed depressive symptoms after three months of residency (27).

Some places, particularly in the developed Western world, recognize and address the need to promote a better work environment by reducing working hours for doctors. The European Working Time Directive (EWTD) is one such initiative that has had a significant impact on training and work schedules in countries such as New Zealand and Australia. For example, an agreement in New Zealand specifies regular working hours for surgical trainees as 40 h per week and no more than 8 h per day, with overtime permitted and compensation (28). The impact of such reforms can be seen in a meta-analysis that identified a higher incidence of physician suicide in North America than in Australia, New Zealand, and the Pacific, and that suicide has declined over time, particularly in Europe (18).

It is important to note that job uncertainty and a shorter duration of employment are associated with a higher risk of suicide among healthcare professionals. This correlation was discovered among diagnostic medical radiation workers in South Korea, who had a 2.74 and 4.66 times greater risk of suicide among male and female workers with <one year of employment, respectively, than those with more than 10 years of employment (29). As a result, it appears that the healthcare workers with short-term jobs are a vulnerable population who should be given enough assistance and a better working environment (29). In addition, factors such as limited resources, an insufficient workforce, and high job expectations contribute to suicide risk among HCWs, especially in developing countries. This issue is more pronounced among nurses, one of the most undervalued groups, even though they are the backbone of every healthcare system. Nurses' suicide rates have gone unnoticed for years, and there are several underlying contributing factors, including long working hours, being the primary caregiver for patients, such as in the ICU, and a lack of professional autonomy (30).

Furthermore, female nurses who form the majority of the workforce have dual profession and home responsibilities. Davis et al. reported that the suicide incidence among nurses was 17.1 per 1,00,000, compared to 8.6 per 1,00,000 among women in the general population, representing a doubling of risk (31). In addition, the increased rate of substance abuse, such as antidepressants, opiates, and amphetamines, which have been discovered to be more commonly used as poisoning methods for suicide attempts among this demographic, is an important issue to highlight (31, 32).

MENTAL HEALTH CHALLENGES FACED BY HEALTHCARE WORKERS

Literature regarding the mental well-being of healthcare workers was limited until 2016 (33); however, recent studies have started focusing on the challenges faced by healthcare workers. It has been noticed that constant amounts of stress negatively impact healthcare workers. Acute signs of anxiety, depression, and burnout have been noticed at all levels of training in the medical profession. According to a report from 2014, symptoms specific to depression have been noticed in medical students, whereas signs of burnout are highly probable amongst residents during their training (33). Seventy four percent of residents have reported signs of exhaustion in a study from 2015, thus highlighting the burnout epidemic in the medical community. It is described as a feeling of inefficacy, depersonalization coupled with signs of emotional exhaustion in the workplace (34). Another study has reported that constant exposure to intense and unpredictable working hours could lead to fatigue during training years, causing multiple mental health issues amongst health care workers (35).

Specific categories of physicians affected by PTSD include emergency physicians, medical personnel working in remote areas or warzones, physicians in training, those indirectly exposed to trauma, and malpractice litigation (36). The frequency of dealing with a higher burden of death in trauma care puts them at a higher risk for developing these symptoms. High-risk groups for suicide are often those with either a previous history of such instances or those with Post-traumatic stress disorder (PTSD). PTSD symptoms have been observed in 30% of the residents working in the emergency room, with symptoms increasing with training (37). A 4-factor model suggests association patterns between suicidal ideation and symptoms of PTSD, which include re-experiencing feelings, negative alterations in cognition and mood, and hyperarousal. A similar study has suggested a 7-factor model correlating PTSD and an increased risk for suicide (17). Exposure to critically ill patients also poses a higher risk of developing depression amongst residents (33). Similarly, nurses and staff from the emergency room have a higher risk of experiencing suicidal ideation due to the nature of cases they consult daily.

Work-related changes are believed to play a significant role in developing mental health issues in physicians. In a study conducted among intensive care unit staff, almost half reported symptoms consistent with a probable diagnosis of post-traumatic stress disorder, severe depression or anxiety, or problem drinking. In the previous two weeks, 13% of respondents reported having recurring thoughts of being better off dead or injuring themselves (38).

According to studies conducted in the United States, 10–15% of HCPs will misuse substances at some point in their careers, and prescription drug abuse and addiction rates are five times higher among physicians than in the general population benzodiazepine opioid abuse have exceptionally high rates (39). According to a 2010 inquiry into the Texas Board of Nursing, around a third of all disciplinary actions against nurses were related to drugs or alcohol (39). Many healthcare personnel uses these medicines to relieve stress, depression, and pain symptoms and improve their general work performance. However, these seemingly harmless medications frequently become a source of dependence or addiction in the user over time.

IMPACT OF THE COVID-19 PANDEMIC ON HEALTHCARE WORKERS' MENTAL HEALTH

As the world and healthcare institutions deal with the fallout from the 2019 Coronavirus pandemic, we are likely to see the impact on the mental health of all healthcare professionals who are facing the reality of constrained resources and unthinkable choices, working to exhaustion, and caring for patients while being at significant personal risk. Fear and uncertainty about the new virus, its devastating repercussions, exhausting working hours in the hospital, countless deaths, and shortage of PPE's have all been significant setbacks for the healthcare system and have led to emotional stress and depressive symptoms among HCWs during the early stages of the pandemic (40). Coping

with the COVID-19 pandemic has exacerbated HCWS's already-existing mental health issues and has placed extra strains on their well-being. Inevitably, this is bound to have a negative impact on the mental health of healthcare personnel, with long-term consequences.

Previous research has also shown that healthcare workers' mental health consequences of an epidemic or pandemic is long-term. Healthcare workers reported extreme emotional and traumatic stress and burnout, anxiety, and depressive symptoms during the SARS pandemic in 2003 and the MERS outbreak in 2015 (41, 42). Due to the nature of their job during the pandemic, HCWs, including nurses, emergency department staff, intensivists, and physicians, are among the most vulnerable groups to experience stressful events that can trigger a suicidal crisis (9). These individuals are already at risk for mental health issues such as post-traumatic stress disorder (PTSD), common among emergency room residents, intensivists, and surgeons (43).

According to studies, the COVID-19 epidemic has significantly increased stress, anxiety, depression, and insomnia among HCWs. The lack of standard treatment protocols or vaccines, work-related stress, the rapid spread of the virus, and fear of COVID-19 infection and transmission are major contributing factors leading to mental health disorders (44, 45). According to a study conducted among Malaysian HCWs, clinical depression has been the most significant predictor of present suicidal ideation, followed by mild (subthreshold) depression (46). Furthermore, it should be highlighted that female HCWs have appeared to be at a higher risk of suicidal behavior than their male counterparts during the current pandemic (47).

It concerns that a total of 26 worldwide COVID-19-related suicide cases among HCWs have been reported in a recent study; the affected persons consisted primarily of doctors, nurses, and paramedics, with more than half of them being female from India (45). In a similar report, multiple COVID-19-related suicides have been reported among nurses who have been on the frontlines caring for COVID-19 patients (48).

This emphasizes the importance of creating a supportive workplace environment for HCWs to maintain their mental well-being. It is critical to create less stressful schedules for HCWs in order to give them time to process and recover from their experiences, to recognize their vital contributions during this intense medical crisis, to remove the stigma around seeking help, and to provide timely and free psychological support to all HCWs.

RECOMMENDATIONS FOR SUICIDE PREVENTION

It comes as no surprise that physicians have the highest suicide rate among all professions and that burnout rates for healthcare workers show an undeniable trend that the majority, if not all, face extreme levels of stress and burnout (49). Paradoxically, doctors are the least likely to seek mental health treatment. Furthermore, gender disparities are common,

especially for women, when seeking care for psychological diseases and disclosing challenges like substance abuse. Men are more likely to seek specialized mental health treatment and primary inpatient care users (50). According to a survey, nearly half of female physicians who believed they fulfilled the criteria for a mental condition did not seek treatment (51). A tailored approach is required to break the stigma of seeking treatment based on gender stereotypes. While designing policies to remove barriers associated with mental health services, women healthcare workers' concerns about confidentiality and professional implications, such as effects on licensure status, should be considered. Hospital leadership and the medical community must develop and implement mental health and well-being strategies such as support groups, access to mental health professionals, and manageable schedules, as well as practicable workloads that will not only have a profound impact on the well-being of the physicians but will also help them provide higher quality care to their patients (44).

The Australian Medical Association's 'National Code of Practice – Hours of Work, Shiftwork and Rostering for Hospital Doctors' has been instrumental in changing attitudes to the ethics of safe hours and has decreased the proportion of doctors at high risk of fatigue (52).

Institutions and healthcare departments worldwide must develop comprehensive suicide prevention and mental health promotion plans in the future. Some integral components can include support and wellness programs for all healthcare workers, lifestyle and mental health screenings, and appropriate referrals for support or treatment. Ideally, at-risk behaviors should be identified via mental health screening, and interventions should be taken as early as possible by providing easier access to and communication with the mental health network. One example of such a suicide prevention initiative is the Healer Education Assessment and Referral (HEAR) program which provides education about risk factors and proactive screening focused on identifying, supporting, and referring clinicians for untreated depression and/or suicide risk (53).

Another concern that is necessary to address in the context of physician mental health and suicide risk is the reluctance of healthcare professionals in seeking help due to the risk of losing their medical license and higher medical liability insurance. Additionally, substance use is prevalent among HCWs, likely due to easy access to drugs (54). According to the Journal of Clinical Nursing, ∼20% of all nurses struggle with an addiction to drugs or alcohol (55). It has been noted that they are more likely to commit suicide from poisoning and substance abuse than other suicide methods (56). Hence, the responsibility falls upon the organizations to provide a safety net for the physicians to seek treatment for drug addiction while addressing license and disciplinary issues in the workplace.

CONCLUSIONS

It can be challenging to look beyond the immediate crisis during an emergency, but given the pandemic's long-term implications, we urge the healthcare community to address HCWs' mental health needs now and in the future. The ongoing pandemic stress-inducing factors are expected to exacerbate mental health concerns, including the increased risk of suicide.

As a result, it is critical to design and implement strategies that best support HCWs during crisis events; these interventions must be pragmatic, dynamic, and responsive according to individual needs. In addition, early prevention strategies, identification of at-risk individuals, and supportive workplace culture are essential to tackle the increased incidence of suicide among healthcare professionals.

AUTHOR CONTRIBUTIONS

All authors have contributed to the present review with equal efforts.

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Suicidality and Quality of Life in Treatment-Resistant Depression Patients in Latin America: Secondary Interim Analysis of the TRAL Study

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Background: A large proportion of patients with major depressive disorder (MDD) have treatment-resistant depression (TRD). The TRAL study examines the impact of TRD on suicidality and health-related quality of life (HRQoL) among MDD patients in 4 Latin American countries.

Methods: In this multicenter, prospective, observational study, MDD patients were recruited from 33 sites in Mexico, Colombia, Brazil, and Argentina. Patients were assessed for TRD, defined as failure to respond to ≥2 antidepressant medications of adequate dose and duration. Other assessments included current disease status, Mini International Neuropsychiatric Interview (MINI), Columbia-Suicide Severity Rating Scale (C-SSRS), 5 Level EQ-5D (EQ-5D-5L), Patient Health Questionnaire-9 (PHQ-9), and Sheehan Disability Scale (SDS).

Results: 1,475 MDD patients were included in the analysis (mean age, 45.6 years; 78% women), and 429 met criteria for TRD. Thoughts of suicide and suicide attempts were more common among TRD patients (38.7%) compared with non-TRD patients (24.9%; $P < 0.0001$), according to the current disease status questionnaire. The C-SSRS showed that lifetime suicidal behavior was significantly more common among TRD patients than non-TRD patients (13.8 vs. 10.0%; $P = 0.0384$). Compared with non-TRD patients, TRD patients showed significantly greater adverse impacts on QoL (EQ-5D-5L), more severe depression (PHQ-9), and greater functional impairment (SDS).

Conclusion: TRD patients in clinical sites from Mexico, Colombia, Brazil, and Argentina were more likely to experience suicidality and negative effects on HRQoL than non-TRD patients.

Keywords: treatment-resistant depression, major depressive disorder, suicidal ideation, quality of life, Latin America

INTRODUCTION

Major depressive disorder (MDD), which affects >300 million individuals worldwide, can severely impact functionality and quality of life (QoL) and may even be fatal (1, 2). Suicide is the cause of death for >800,000 individuals worldwide each year (3), and MDD patients are at increased risk for suicide (4). Compared with other psychiatric diagnoses, MDD and other depression-related diagnoses are associated with suicidal behavior and suicide at a higher rate (3, 5–7). According to suicide mortality data from 8 health care systems in the Mental Health Research Network, among those patients with mental health conditions who died by suicide, ~80% had depression; the risk of mortality from a suicide attempt was 7-fold greater in those with depression in comparison to those without depression in the general population (8). The presence of depression in the past year has been found to increase the risk of a suicide attempt 8-fold, and recent suicide attempts are significantly more common in those with a depressive disorder than in those without a depressive disorder after controlling for demographic factors (9). Increases in depression severity are associated with an increased risk of suicidal ideation and suicide attempts (10, 11). In one study, those with severe depression were 20 times more likely than those with no or mild depression to report suicidal ideation (10). In another study, those with the most severe depression symptoms had an 8-fold increased risk of a suicide attempt (11). Suicidal ideation and behavior can present significant treatment challenges, and identification of risk factors for suicide, including depression severity, is an important aspect of appropriate management of MDD patients (12). Recent work examining the genetic, physiological, and neurobiological underpinnings of suicidal ideation has provided some insight into relevant neurological pathways and identified potentially relevant biomarkers, but identifying at-risk patients remains a critical challenge (12, 13).

Approximately half of MDD patients do not respond to a first-line treatment; of those who continue to a second treatment, a further two-thirds do not respond (14). Treatment-resistant depression (TRD) is defined as failure to respond to ≥2 antidepressant regimens of adequate dose and duration (15, 16). Compared to treatment-responsive MDD patients (non-TRD), TRD patients have shown both increased suicidality (17) and lower health-related QoL (HRQoL) (17–19). The prevalence and burden of TRD in Latin America are not well documented, and more research is needed to understand the impact of MDD and TRD on suicidality and HRQoL in regions outside the United States and Europe. In Latin America, access to mental health care is more difficult, and gaps in access to care are more pronounced compared with the United States (20).

The TRAL study is a multicenter, prospective, observational, non-interventional study of TRD in 4 Latin American countries: Mexico, Colombia, Argentina, and Brazil. The study includes patients receiving care from clinical centers that treat mental disorders; it is not a population-based study. The primary objective of this study was to estimate the prevalence of TRD among MDD patients being treated in a psychiatry reference site. The secondary objectives were to describe the characteristics of MDD patients, including comorbidities, treatment standards,

severity of symptoms, and level of disability, and to evaluate suicidality risk (ideation and attempts) in TRD patients. The primary interim analysis of the first phase of the TRAL study revealed that 29% of MDD patients had TRD (21). Regional prevalence of TRD among MDD patients was as follows: 21% in Mexico, 32% in Colombia, 33% in Argentina, and 40% in Brazil. Results of the analysis showed that suicidality, anxiety, and work impairment were significantly greater among TRD patients than non-TRD patients (21). Here we report the secondary interim results from the first phase of the TRAL study, including detailed measures of suicidality, HRQoL, and related factors.

MATERIALS AND METHODS

Objectives
Objectives of the current analyses were to evaluate suicidal ideation, behavior, and related measures among TRD patients in comparison with non-TRD MDD patients being treated in a psychiatric reference site (clinic, ambulatory, hospital, day-hospital) in 4 Latin American countries (Mexico, Colombia, Brazil, and Argentina), and to evaluate HRQoL and related measures among TRD patients vs. non-TRD MDD patients.

Study Design and Population
This was a multicenter, prospective, observational, non-interventional study consisting of a screening phase, cross-sectional evaluation of demographic, symptom, suicidality, HRQoL, and functionality data (Phase 1); and 1-year follow up of the subset of TRD patients (Phase 2). Detailed study design methods have been described in the primary report and are briefly summarized here. Included patients were adult women and men (aged ≥18 years) with a diagnosis of MDD per the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* and confirmed by the Mini-International Neuropsychiatric Interview, version 7.0.2 (MINI). Patients had a new or continued episode of depression (treated or untreated) at the time of enrollment and were capable of completing study assessments. Diagnosis of TRD was based on the following criteria: treatment and adequate follow-up with ≥2 antidepressants, and lack of complete response to treatment based on the Montgomery-Asberg Depression Rating Scale (MADRS), where response was defined as 50% improvement in MADRS total score. MADRS is a 10-item depression scale designed to be responsive to treatment effects (22). Key exclusion criteria consisted of diagnosis of psychosis, schizophrenia, bipolar disorder, schizoaffective disorder, or dementia; serious substance dependence (as determined by the investigator); and current participation in another clinical study.

Data sources for the study were patient medical records, questionnaires, scales, and assessments completed by patients and investigators as part of the study.

Analyses
Suicidality and HRQoL variables were assessed among all MDD patients (TRD and non-TRD). These variables included suicidal ideation, behavior, and related measures, as assessed by current disease status (a questionnaire regarding the patient's

diagnosis, symptoms, and treatment), MINI (evaluated according to standards in which the presence or absence of suicidal thoughts and suicide attempts as well as feelings such as "hopelessness/pessimism" and "guilt/worthlessness/helplessness" were noted), and the Columbia-Suicide Severity Rating Scale (C-SSRS). Of note, on the C-SSRS suicidal ideation scale, only patients who answered "yes" to item 2 of the ideation scale (non-specific active suicidal thoughts [lifetime]) were asked subsequent questions on the ideation scale. Therefore, responses to items 3 through 5 of the scale are represented as percentages of the total number of patients responding "yes" to item 2 (lifetime) rather than as percentages of all respondents. HRQoL and related measures were assessed using the 5 Level EQ-5D (EQ-5D-5L; a health status questionnaire that provides a simple profile and an index value) (23), Patient Health Questionnaire-9 (PHQ-9; a measure of depression severity) (24), and Sheehan Disability Scale (SDS; a measure of disability and functional impairment) (25).

Statistical Analyses

Descriptive statistics were used to evaluate variables in all MDD patients and by group (non-TRD and TRD). Analysis of quantitative variables included calculation of mean, standard deviation (SD), or median and interquartile range (IQR) depending on the normal distribution of each variable. Analysis of qualitative variables included calculation of frequencies and percentages. Comparisons between groups for categorical variables were performed using the chi square test (CS) or Fisher Exact test. Comparisons between groups for quantitative variables were performed using the t-test for independent samples or the Mann-Whitney non-parametric test (MW), according to the assumption validations of the statistical tests. Partial dates were completed by investigators in a standardized fashion; no other imputation of missing data was performed.

RESULTS

Study Population and TRD Prevalence

Detailed prevalence information has been described in the primary report and is briefly summarized here. A total of

TABLE 1 | Suicidal ideation and behavior across scales.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
Current disease status				
Thoughts of suicide, suicide attempts, n (%)	426 (28.9%)	260 (24.9%)	166 (38.7%)	CS: <0.0001
MINI, meets criteria, n (%)				
Current suicidality (past month)	358 (24.3%)	207 (19.8%)	151 (35.2%)	CS: <0.0001
Lifetime attempt	265 (18.0%)	143 (13.7%)	122 (28.4%)	CS: <0.0001
Current suicidal behavior disorder	96 (6.5%)	59 (5.6%)	37 (8.6%)	CS: 0.0349
C-SSRS				
Suicidal ideation score*				MW: 0.9144
n	512	308	204	
Median	4.00	4.00	4.00	
Q1	3.00	3.00	3.00	
Q3	5.00	5.00	5.00	
IQR	2.00	2.00	2.00	
Suicidal behavior score[†]	356 (24.2%)	215 (20.6%)	141 (32.9%)	CS: <0.0001

MDD, major depressive disorder; TRD, treatment-resistant depression; CS, chi square test; MINI, Mini-International Neuropsychiatric Interview, version 7.0.2; C-SSRS, Columbia-Suicide Severity Rating Scale; MW, Mann-Whitney non-parametric test; Q, quartile; IQR, interquartile range.
Maximum suicidal ideation category (range: 1–5; 1 = wish to be dead; 2 = non-specific active suicidal thoughts; 3 = active suicidal ideation with any methods [not plan], without intent to act; 4 = active suicidal ideation with some intent to act, without specific plan; 5 = active suicidal ideation with specific plan and intent).
[†]*A "yes" answer to 1 of the 5 suicidal behavior questions.*

TABLE 2 | C-SSRS suicidal ideation and behavior scale.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
Suicidal ideation (1–5), n (%)*				
1) Wish to be dead	452 (30.7%)	263 (25.2%)	189 (44.1%)	CS: <0.0001
2) Non-specific active suicidal thoughts	278 (18.9%)	171 (16.4%)	107 (24.9%)	CS: 0.0001
3) Active suicidal ideation with any methods (not plan), without intent to act	214 (41.7%)	127 (41.2%)	87 (42.4%)	CS: 0.7863
4) Active suicidal ideation with some intent to act, without specific plan	156 (30.5%)	96 (31.2%)	60 (29.4%)	CS: 0.6724
5) Active suicidal ideation with specific plan and intent	94 (18.3%)	55 (17.9%)	39 (19.0%)	CS: 0.7378
Suicidal behavior (6–10), n (%)[†]				
6) Preparatory acts or behavior	65 (4.4%)	38 (3.6%)	27 (6.3%)	CS: 0.0228
7) Aborted attempt	34 (2.3%)	25 (2.4%)	9 (2.1%)	CS: 0.7396
8) Interrupted attempt	41 (2.8%)	28 (2.7%)	13 (3.0%)	CS: 0.6993
9) Non-fatal suicide attempt	87 (5.9%)	61 (5.8%)	26 (6.1%)	CS: 0.8526
10) Completed suicide	NA	NA	NA	NA

C-SSRS, Columbia-Suicide Severity Rating Scale; MDD, major depressive disorder; TRD, treatment-resistant depression; CS, chi square test; NA, not applicable.
Past 1 month.
[†]*Past 3 months.*
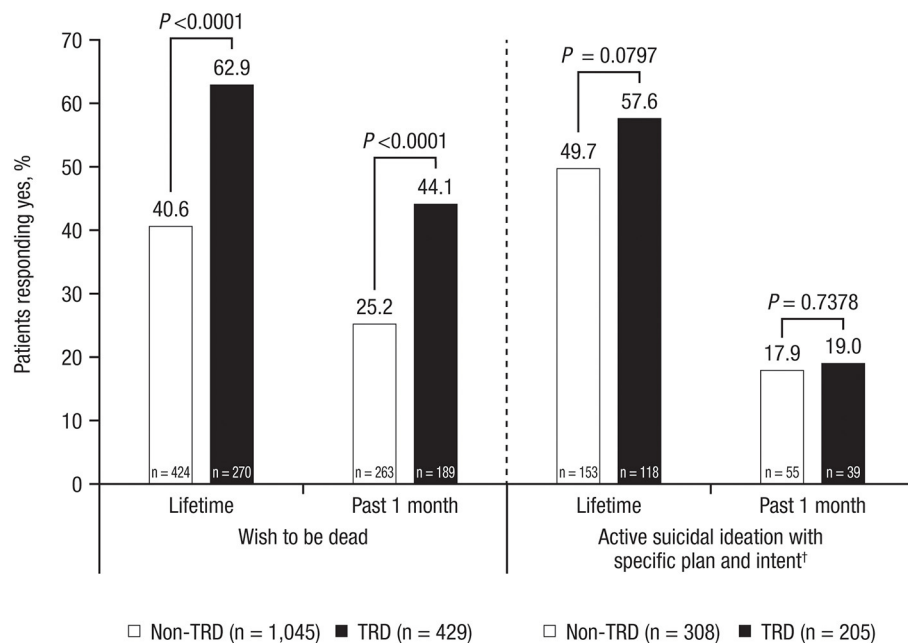
FIGURE 1 | Suicidal ideation in TRD patients vs. non-TRD patients, evaluated with C-SSRS*. TRD, treatment-resistant depression; C-SSRS, Columbia-Suicide Severity Rating Scale. *P-values represent differences between groups as measured by the chi square test. [†]Only patients who answered "yes" to having "non-specific active suicidal thoughts" were asked subsequent questions about intensity of ideation.

1,544 patients were screened and 1,475 (96%) were included in the Phase 1 analysis dataset. Patient data were collected from 33 centers in 4 countries: Mexico ($n = 697$; 47% of all patients), Colombia ($n = 162$; 11%), Brazil ($n = 396$; 27%), and Argentina ($n = 220$; 15%). In total, 429 patients had TRD [29% of all MDD patients; 95% confidence interval (CI), 27–31%]. Sociodemographic and clinical characteristics of all MDD patients have been reported previously (21).

Suicidality and Related Factors in Patients With Non-TRD and TRD

A comparison of suicidal ideation and behavior measures across scales is provided in **Table 1**. Among MDD patients, 28.9% had thoughts of suicide or suicide attempts, as measured by the current disease status questionnaire. Thoughts of suicide and suicide attempts were more common among TRD patients (38.7%) in comparison with non-TRD patients (24.9%; $P < 0.0001$). The questionnaire also allowed assessment of feelings such as "hopelessness and/or pessimism" and "guilt, worthlessness, and/or helplessness"; these were reported in 80.8 and 77.9% of MDD patients, respectively. TRD patients, vs. non-TRD patients, more frequently reported both hopelessness/pessimism (90.7 vs. 76.8%; CS, $P < 0.0001$) and guilt/worthlessness/helplessness (83.0 vs. 75.8%; CS, $P = 0.0026$).

According to results from the MINI, 24.3% of MDD patients met the criteria for current suicidality (score of ≥ 1 on the suicidality subscale) and 18.0% reported a lifetime suicide attempt. Both current suicidality and lifetime suicide attempts were significantly more common in TRD patients than in non-TRD patients (current, 35.2 vs. 19.8%; lifetime, 28.4 vs.

13.7%; both $P < 0.0001$). Among all MDD patients, 6.5% met the criteria for suicidal behavior disorder [defined as presence of a suicide attempt within the past 2 years (1)] and 5.2% were considered "in early remission" from this disorder. Current suicidal behavior disorder was also more common among TRD patients than non-TRD patients (8.6 vs. 5.6%; $P = 0.0349$). Furthermore, 9.3% of TRD patients were considered in early remission from suicidal behavior disorder in comparison to 3.5% of non-TRD patients ($P < 0.0001$), indicating that TRD patients were more likely to have a recent suicidal behavior disorder.

There were no statistically significant differences between groups for suicidal behavior disorder as a current primary diagnosis, but significantly more TRD patients, vs. non-TRD patients, had a primary diagnosis of early remission suicidal behavior disorder (2.1 vs. 0.6%; $P = 0.0175$). TRD patients, vs. non-TRD patients, also reported significantly higher prevalence of comorbid generalized anxiety disorder (GAD; 26.3 vs. 17.7%; $P = 0.0002$), post-traumatic stress disorder (PTSD; 6.5 vs. 3.3%; $P = 0.0061$), and substance use disorder (non-alcohol; 2.1 vs. 0.6%; $P = 0.0175$). Differences between groups for primary diagnosis of GAD, PTSD, or substance use disorder were not significant.

Among all MDD patients, the median suicidal ideation score on the C-SSRS was 4.0 (IQR, 3.0–5.0; **Table 1**). Over a lifetime, 47.1% of MDD patients had a "wish to be dead" (30.7% in the past 1 month; **Table 2**). Of the 513 MDD patients who reported at least non-specific active suicidal thoughts (lifetime), 52.8% had active suicidal ideation with specific plan and intent (18.3% in the past 1 month; **Table 2**). Median C-SSRS suicidal ideation score did not differ significantly between TRD patients and non-TRD
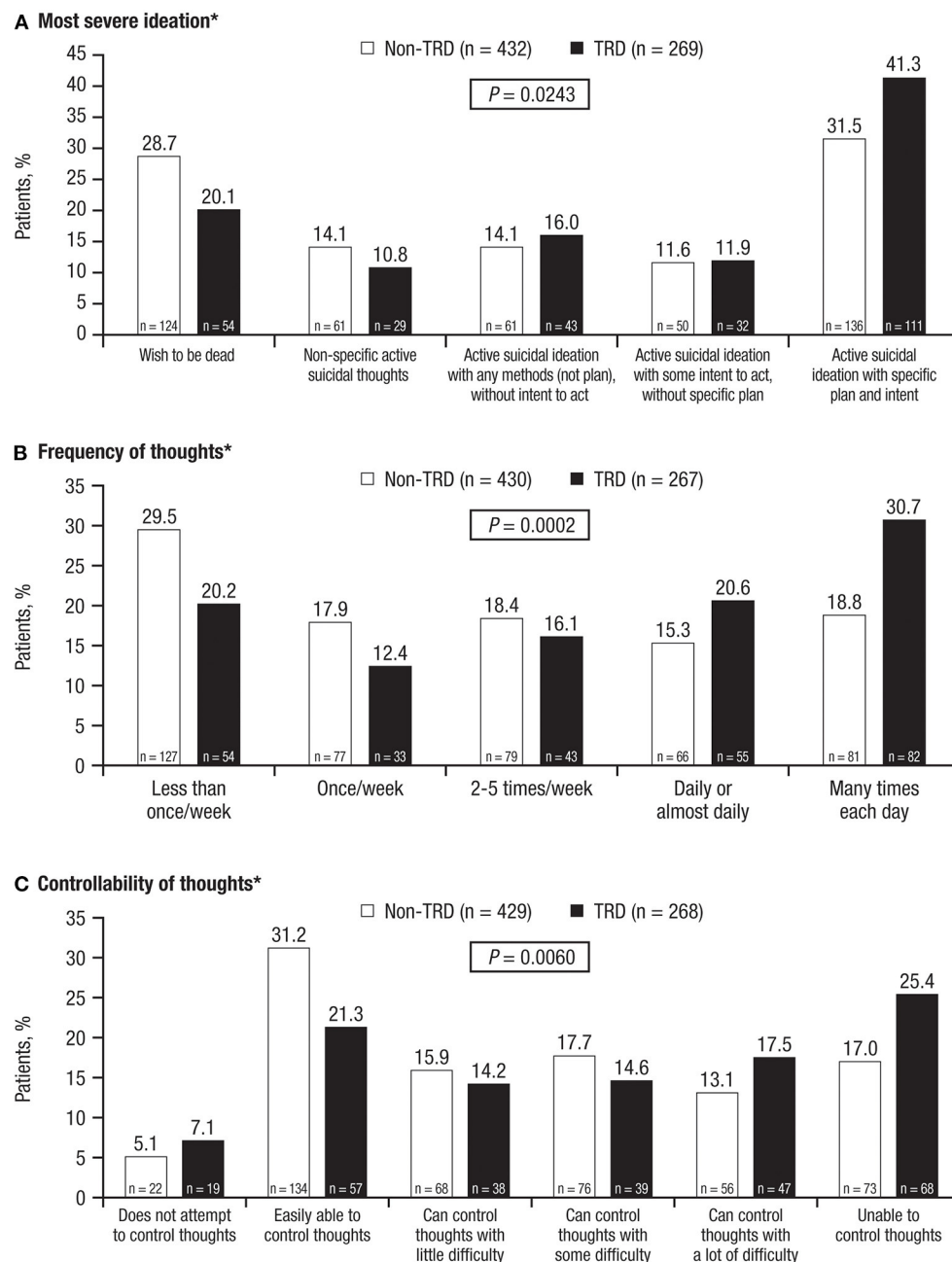
FIGURE 2 | Lifetime categories of suicidal ideation, evaluated with C-SSRS. **(A)** Most severe ideation, **(B)** Frequency of thoughts, and **(C)** Controllability of thoughts. TRD, treatment-resistant depression; C-SSRS, Columbia-Suicide Severity Rating Scale. *P-values represent differences between groups as measured by the chi square test.

patients (**Table 1**). However, TRD patients were more likely to have experienced a "wish to be dead" both over a lifetime (62.9 vs. 40.6%) and in the past month (44.1 vs. 25.2%; all $P < 0.0001$; **Figure 1**; **Table 2**).

TRD patients were also numerically more likely than non-TRD patients to report lifetime active suicidal ideation with specific plan and intent (57.6 vs. 49.7%; $P = 0.0797$). TRD patients reported more severe lifetime suicidal ideation, with significantly higher scores for "most severe ideation" (**Figure 2A**;

$P = 0.0243$), "frequency of thoughts" (**Figure 2B**; $P = 0.0002$), and "controllability of thoughts" (**Figure 2C**; $P = 0.0060$).

Among all MDD patients, 24.2% answered "yes" to ≥ 1 indicator of suicidal behavior, as measured by C-SSRS; a significantly greater proportion of TRD patients than non-TRD patients had ≥ 1 indicator of suicidal behavior (32.9 vs. 20.6%; $P < 0.0001$; **Table 1**). Among all MDD patients, 20.0% reported a lifetime suicide attempt, with a mean of 0.59 (range: 0.00–20.00) total attempts. Lifetime suicidal behavior was significantly more

FIGURE 3 | Lifetime suicidal behavior in TRD patients vs. non-TRD patients, evaluated with C-SSRS. **(A)** Lifetime presence of suicide attempts. **(B)** Lifetime number of suicide attempts. TRD, treatment-resistant depression; C-SSRS, Columbia-Suicide Severity Rating Scale. *P-value represents di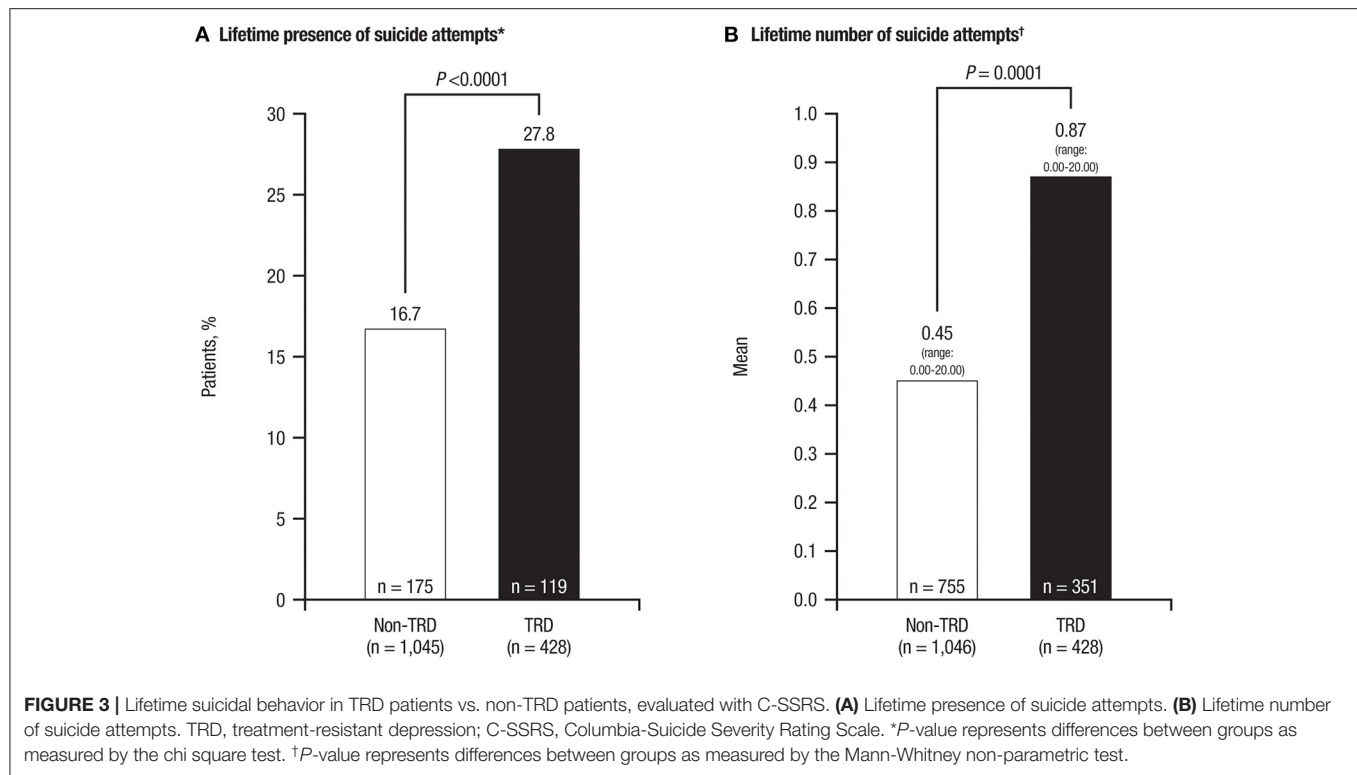fferences between groups as measured by the chi square test. [†]P-value represents differences between groups as measured by the Mann-Whitney non-parametric test.

common among TRD patients than non-TRD patients (13.8 vs. 10.0%; $P = 0.0384$). TRD patients, vs. non-TRD patients, were more likely to have made a lifetime suicide attempt (27.8 vs. 16.7%; $P < 0.0001$) and to have a higher number of lifetime attempts [mean number (range) 0.87 (0.00–20.00) vs. 0.45 (0.00–20.00); $P = 0.0001$; **Figure 3**]. Moreover, suicide attempts in TRD patients were significantly more likely to be fatal than in non-TRD patients (**Table 3**).

HRQoL and Related Measures in Patients With TRD and Non-TRD

Results from the EQ-5D-5L HRQoL questionnaire demonstrated that TRD patients in comparison to non-TRD patients were significantly more impacted on the mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and current health subscales (all $P < 0.0001$; **Table 4**). Among non-TRD patients, 66.4% reported no or slight pain or discomfort vs. 47.6% of TRD patients; in contrast, 23.5% of TRD patients reported severe or extreme pain or discomfort in comparison to 10.9% of non-TRD patients. Of non-TRD patients, 11.6% reported no feelings of anxiety or depression vs. 2.8% of TRD patients; 26.3% of non-TRD patients reported feeling severely or extremely anxious or depressed in comparison with 43.1% of TRD patients.

Depression severity scores on the PHQ-9 were higher in TRD patients ($P < 0.0001$), with 40.2% of TRD patients characterized as having severe depression (vs. 22.9% of non-TRD patients; **Figure 4**). Approximately two-thirds of TRD patients (vs. less than half of non-TRD patients) reported facing problems that made it "very difficult" or "extremely difficult" to do work, take care of things at home, or get along with other people (**Table 5**).

On the SDS, TRD patients reported higher levels of disruption to work/school, social life/leisure activities, and family/home responsibilities than did non-TRD patients (all $P < 0.0001$; **Table 6**). Of TRD patients, 17.4% responded that symptoms had extremely disrupted work/school (vs. 7.6% of non-TRD patients), 17.5% reported extremely disrupted social life/leisure activities (vs. 7.6% of non TRD patients), and 11.0% reported extremely disrupted family life/home responsibilities (vs. 6.0% of non-TRD patients). TRD patients also had higher median total SDS scores than did non-TRD patients [21.0 (IQR, 16.0–26.0) vs. 16.0 (IQR, 11.0–21.0); $P < 0.0001$]. TRD patients reported a greater median (IQR) number of days in the previous 7 days that they were unable to carry out normal daily responsibilities [1.00 (0.00–4.00) vs. 0.00 (0.00–2.00); $P < 0.0001$].

DISCUSSION

As presented in the primary interim analysis report, among all MDD patients in this study, 29% had TRD. In the current report, we present a deeper exploration of factors relating to MDD and TRD in Latin American countries, including comorbidities, suicidality, and HRQoL. Common comorbidities differentiating TRD patients from non-TRD patients included GAD, PTSD, and substance use disorder (non-alcohol).

TRD patients had higher suicidal ideation and behavior scores across scales than did non-TRD patients, although suicidality substantially contributed to disease burden in both TRD and non-TRD. These rates are comparable to those found in a systematic review of TRD in the United States, which showed 15% of TRD patients reported suicidal ideation (compared with

TABLE 3 | C-SSRS potential lethality of suicide attempts.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
Potential lethality				
Most recent attempt, n (%)				
0. Behavior not likely to result in injury	51 (55.4%)	40 (64.5%)	11 (36.7%)	CS: 0.0187
1. Behavior likely to result in injury but not likely to cause death	10 (10.9%)	7 (11.3%)	3 (10.0%)	
2. Behavior likely to result in death despite available medical care	31 (33.7%)	15 (24.2%)	16 (53.3%)	
Total	92	62	30	
Most lethal attempt, n (%)				
0. Behavior not likely to result in injury	49 (57.0%)	39 (67.2%)	10 (35.7%)	CS: 0.0115
1. Behavior likely to result in injury but not likely to cause death	9 (10.5%)	6 (10.3%)	3 (10.7%)	
2. Behavior likely to result in death despite available medical care	28 (32.6%)	13 (22.4%)	15 (53.6%)	
Total	86	58	28	
Initial/first attempt, n (%)				
0. Behavior not likely to result in injury	52 (55.9%)	40 (62.5%)	12 (41.4%)	CS: 0.0563
1. Behavior likely to result in injury but not likely to cause death	12 (12.9%)	9 (14.1%)	3 (10.3%)	
2. Behavior likely to result in death despite available medical care	29 (31.2%)	15 (23.4%)	14 (48.3%)	
Total	93	64	29	

C-SSRS, Columbia-Suicide Severity Rating Scale; MDD, major depressive disorder; TRD, treatment-resistant depression; CS, chi square test.

1% in the general population) and 17% of patients had a history of suicide attempt ([17]).

For all measures presented, TRD was associated with a higher risk of suicidal behavior vs. non-TRD. This was demonstrated in results from the current disease status questionnaire, the MINI, and the C-SSRS, which is considered

TABLE 4 | EQ-5D-5L HRQoL questionnaire.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
Mobility, n (%)				
I have no problems walking	954 (64.7%)	712 (68.1%)	242 (56.4%)	CS: <0.0001
I have slight problems walking	312 (21.2%)	231 (22.1%)	81 (18.9%)	
I have moderate problems walking	161 (10.9%)	81 (7.8%)	80 (18.6%)	
I have severe problems walking	42 (2.8%)	17 (1.6%)	25 (5.8%)	
I am unable to walk	5 (0.3%)	4 (0.4%)	1 (0.2%)	
Total	1,474	1,045	429	
Self-care, n (%)				
I have no problems washing or dressing myself	938 (63.6%)	697 (66.7%)	241 (56.2%)	CS: <0.0001
I have slight problems washing or dressing myself	320 (21.7%)	233 (22.3%)	87 (20.3%)	
I have moderate problems washing or dressing myself	162 (11.0%)	88 (8.4%)	74 (17.2%)	
I have severe problems washing or dressing myself	49 (3.3%)	22 (2.1%)	27 (6.3%)	
I am unable to wash or dress myself	5 (0.3%)	5 (0.5%)	0	
Total	1,474	1,045	429	
Usual activities, n (%)				
I have no problems doing my usual activities	375 (25.4%)	316 (30.2%)	59 (13.8%)	CS: <0.0001
I have slight problems doing my usual activities	435 (29.5%)	338 (32.3%)	97 (22.6%)	
I have moderate problems doing my usual activities	458 (31.1%)	275 (26.3%)	183 (42.7%)	
I have severe problems doing my usual activities	169 (11.5%)	96 (9.2%)	73 (17.0%)	
I am unable to do my usual activities	37 (2.5%)	20 (1.9%)	17 (4.0%)	
Total	1,474	1,045	429	
Pain/discomfort, n (%)				
I have no pain or discomfort	445 (30.2%)	346 (33.1%)	99 (23.1%)	CS: <0.0001
I have slight pain or discomfort	453 (30.7%)	348 (33.3%)	105 (24.5%)	
I have moderate pain or discomfort	361 (24.5%)	237 (22.7%)	124 (28.9%)	
I have severe pain or discomfort	182 (12.3%)	99 (9.5%)	83 (19.3%)	

(Continued)

TABLE 4 | Continued

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
I have extreme pain or discomfort	33 (2.2%)	15 (1.4%)	18 (4.2%)	
Total	1,474	1,045	429	
Anxiety/depression, n (%)				
I am not anxious or depressed	133 (9.0%)	121 (11.6%)	12 (2.8%)	CS: <0.0001
I am slightly anxious or depressed	338 (22.9%)	280 (26.8%)	58 (13.5%)	
I am moderately anxious or depressed	543 (36.8%)	369 (35.3%)	174 (40.6%)	
I am severely anxious or depressed	339 (23.0%)	206 (19.7%)	133 (31.0%)	
I am extremely anxious or depressed	121 (8.2%)	69 (6.6%)	52 (12.1%)	
Total	1,474	1,045	429	
Health in the current day*				
n	1,473	1,044	429	MW: <0.0001
Median	60.00	65.00	50.00	
Q1	50.00	50.00	40.00	
Q3	75.00	79.00	65.00	
IQR	25.00	29.00	25.00	

HRQoL, health-related quality of life; MDD, major depressive disorder; TRD, treatment-resistant depression; CS, chi square test; MW, Mann-Whitney non-parametric test; Q, quartile; IQR, interquartile range.
*Assessed using a visual analog scale ranging from 0 (worst health) to 100 (best health).

FIGURE 4 | Depression severity on the PHQ-9*. PHQ-9, Patient Health Questionnaire-9; MDD, major depressive disorder; TRD, treatment-resistant depression. *P-value represents chi square test.

TABLE 5 | Selected items from the PHQ-9.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
Total score*				
n	1,472	1,044	428	MW: <0.0001
Median	15.00	14.00	18.00	
Q1	10.00	9.00	13.00	
Q3	20.00	19.00	22.00	
IQR	10.00	10.00	9.00	
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?, n (%)				
Not difficult at all	152 (10.3%)	145 (13.9%)	7 (1.6%)	CS: <0.0001
Somewhat difficult	571 (38.8%)	437 (41.9%)	134 (31.3%)	
Very difficult	618 (42.0%)	392 (37.5%)	226 (52.8%)	
Extremely difficult	131 (8.9%)	70 (6.7%)	61 (14.3%)	
Total	1,472	1,044	428	

PHQ-9, Patient Health Questionnaire-9; MDD, major depressive disorder; TRD, treatment-resistant depression; MW, Mann-Whitney non-parametric test; Q, quartile; IQR, interquartile range; CS, chi square test.
*Total score ranges from 0 to 27; higher values indicate higher depression severity.

a complete instrument encompassing several dimensions of suicidal behavior. More than 90% of TRD patients reported feeling hopeless or pessimistic, and approximately 80% had feelings of guilt, worthlessness, or helplessness (vs. three-quarters of non-TRD patients in both cases), indicating a significantly increased disease burden for TRD patients. Compared with non-TRD patients, TRD patients were significantly more likely to report a "wish to be dead" (**Figure 1**), tended to have a greater degree of seriousness associated with suicidal thoughts/suicidality as well as significantly more intense suicidal ideation, as indicated by the most severe ideation, frequency of thoughts, and controllability of those thoughts on the C-SSRS (**Figure 2**). TRD patients were also more likely to display suicidal behavior. Significantly greater proportions of TRD patients had active suicidal behavior disorder per the MINI, answered "yes" to at least 1 of the C-SSRS suicidal behavior questions, and were significantly more likely to have had lifetime suicidal behavior, with nearly 3 in 10 reporting a lifetime attempt.

Although the burden of suicidality was greater for TRD patients, non-TRD patients reported suicidal ideation and behavior in substantial numbers, indicating that suicidality is a significant problem among all MDD patients in Latin America.
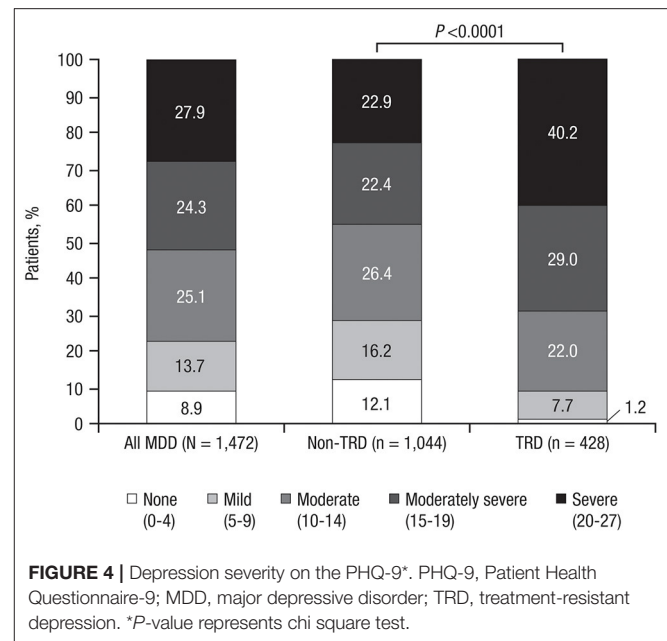
According to the World Health Organization, regional age-standardized suicide rates per 100,000 individuals in 2012 were 4.2 in Mexico, 5.4 in Colombia, 10.3 in Argentina, and 5.8 in Brazil ([3]). Differences among countries may be accounted for by societal and cultural risk factors, including health care access barriers, access to means of suicide, inappropriate media reporting and social media use, and stigma associated with help-seeking behavior. These risk factors for suicidality among TRD patients in Latin America underscore the need for

TABLE 6 | SDS questionnaire.

	All MDD (N = 1,475)	Non-TRD (n = 1,046)	TRD (n = 429)	P-value (non-TRD vs. TRD)
The symptoms have disrupted your work/school*				
n	1,134	794	340	MW: <0.0001
Median	6.00	5.00	7.00	
Q1	4.00	3.00	5.00	
Q3	8.00	7.00	9.00	
IQR	4.00	4.00	4.00	
The symptoms have disrupted your social life/leisure activities*				
n	1,473	1,044	429	MW: <0.0001
Median	6.00	5.00	7.00	
Q1	4.00	3.00	5.00	
Q3	8.00	7.00	9.00	
IQR	4.00	4.00	4.00	
The symptoms have disrupted your family life/home responsibilities*				
n	1,473	1,044	429	MW: <0.0001
Median	6.00	5.00	7.00	
Q1	4.00	3.00	5.00	
Q3	8.00	7.00	8.00	
IQR	4.00	4.00	3.00	
Total score				
n	1,134	794	340	MW: <0.0001
Median	18.00	16.00	21.00	
Q1	12.00	11.00	16.00	
Q3	23.00	21.00	26.00	
IQR	11.00	10.00	10.00	
On how many days in the past 7 days did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities?				
n	1,471	1,042	429	MW: <0.0001
Median	0.00	0.00	1.00	
Q1	0.00	0.00	0.00	
Q3	3.00	2.00	4.00	
IQR	3.00	2.00	4.00	
On how many days in the past 7 days did you feel so impaired by your symptoms that, even though you went to school or work or had other daily responsibilities, your productivity was reduced?				
n	1,472	1,043	429	MW: 0.0693
Median	2.00	2.00	2.00	
Q1	0.00	0.00	0.00	
Q3	4.00	3.00	4.00	
IQR	4.00	3.00	4.00	

SDS, Sheehan Disability Scale; MDD, major depressive disorder; TRD, treatment-resistant depression; MW, Mann-Whitney non-parametric test; Q, quartile; IQR, interquartile range.
**Scale value key: 0, not at all; 1–3, mildly; 4–6, moderately; 7–9, markedly; 10, extremely.*

appropriate management of TRD to ameliorate disease burden and potentially increase survival.

TRD also significantly impacted HRQoL, consistent with previous studies in TRD patients that demonstrated a negative impact of TRD on mental and physical well-being; TRD was also associated with greater work impairments and productivity loss, both in the primary interim analysis of this study and in other analyses (18, 19, 21). A previous study reported that worse

HRQoL was associated with higher suicidal ideation in MDD patients (26). In the present study, the EQ-5D-5L questionnaire revealed that patients with TRD were more likely to have problems walking, washing, dressing, or doing usual activities, and experienced more pain or discomfort and feelings of anxiety or depression; TRD patients also perceived themselves as being in significantly worse health than did non-TRD patients.

In our study, the difference in painful symptoms between the TRD and non-TRD groups was notable; more than twice the number of TRD patients (23.5%) reported severe or extreme pain or discomfort compared with non-TRD patients. Physical pain has been shown to be an important risk factor for suicide, pointing to a possible association with the relationship between treatment resistance and suicidal behavior (27, 28).

Results from the PHQ-9 demonstrated that TRD patients reported more severe depression than non-TRD patients and that this depression more severely impacted everyday activities and relationships; over two-thirds of TRD patients had problems that made it very or extremely difficult to work, take care of tasks at home, or get along with others in comparison with less than half of non-TRD patients. These results are comparable to those of the MADRS instrument employed in the primary interim analysis, which reported significantly more TRD patients with severe depression (MADRS total score >34) compared with non-TRD patients (21).

Responses to the SDS also showed that TRD patients, vs. non-TRD patients, were disproportionally disrupted in multiple functional domains, including work/school, social life/leisure activities, and family life/home responsibilities, and experienced more days in the previous week in which they found it impossible to carry out normal daily responsibilities. While there can be some debate as to whether HRQoL measures or symptomatic measures are better indicators of disease burden, results from this secondary interim analysis of the TRAL study showed that TRD patients in the Latin American countries studied are disproportionally impacted in both domains.

Based on the findings of this study, in which the severity of depression was greater in patients with TRD compared with non-TRD, clinicians in daily clinical practice could be more attentive in recognizing and diagnosing TRD in patients with severe depression. This is especially important in health care systems (in this case, those in Latin American countries) in which a practitioner may see a patient only once without the possibility of monitoring the same patient in the medium term. To this point, follow-up is a primary challenge in treating patients with TRD. Improving patient access to follow-up care as well as to continuity of care may have a positive impact on the quality of treatment, costs, and HRQoL for TRD patients, a group disproportionally affected by the potential for suicidality and detriments to daily activities, ranging from basic self-care to the ability to work and maintain relationships with others. In addition, new treatment options for TRD are needed to potentially improve outcomes in this underserved patient population.

A limitation of the present analysis is the lack of country-specific information about suicidality; country-based analyses of these data are currently in progress. Also, the current work represents an interim analysis; further information will be reported when the final analyses are complete.

Critically, TRAL is not a population-based study; patients enrolled in the study were recruited through regional centers that provide treatment and services for those with mental disorders (e.g., clinics and hospitals, as opposed to specialty treatment centers). This is an important caveat in a depression prevalence study, as many cases of depression may not be diagnosed in a general medicine practice. Diagnosis of MDD using the MINI, rather than presumptive diagnoses from patient registry databases, is a strength of this study. MDD may be underdiagnosed, but analysis of those with this diagnosis may provide important information about the differences between TRD patients and non-TRD patients.

Additionally, this study enrolled patients with a new or continued episode of depression, regardless of whether that episode was treated or untreated. This may have introduced a complicating factor into the current analysis, as those who perceive that they have an unmet need for mental health services (i.e., those who are un- or undertreated) are more likely to report suicidal ideation and behavior (29). However, only 11 out of 429 TRD patients were untreated at the time of enrollment (21), suggesting a minimal impact on the differences in suicidality between TRD and non-TRD patients.

CONCLUSIONS

TRD patients are more likely than non-TRD patients to experience suicidality and detriments to HRQoL. TRD represents a substantial unmet treatment need among MDD patients in Latin America.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. Requests to access the datasets should be directed to the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CEP HUPES, Comitê de Ética em Pesquisa do Hospital Universitário Walter Cantídio, COEP-UFMG, CEP- INC—Instituto de neurologia de Curitiba, Comite de Etica em pesquisa IPUB-UFRJ, Comitê de Ética em Pesquisa Investiga—Institutos de Pesquisa, Comitê de Ética em Pesquisa em Seres Humanos da Faculdade de Medicina da Universidade Federal de Pelotas, Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq, Comitê de Ética

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AUTHOR CONTRIBUTIONS

All authors meet the ICMJE authorship criteria, giving substantial contribution to the conception or design of the work, data acquisition and analysis, drafting or reviewing the work for intellectual content, and giving final approval of the version to be published. The authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Associations of Suicide Risk and Community Integration Among Patients With Treatment-Resistant Depression

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Introduction: Treatment-resistant depression (TRD) is one of the primary causes of disability and a major risk for suicide among patients living in the community. However, the suicide risks and care needs for safety among patients with TRD during the community reintegration process appear to be underestimated. This study aimed to investigate the association between community integration and suicide risks among patients with treatment-resistant depression (TRD) with sub-analysis by gender.

Methods: Patients diagnosed with major depressive disorder were recruited upon psychiatrists' referral in two general hospitals in northern Taiwan during 2018–2019. The participants who experienced more than two failed treatments of antidepressants with partial remission were defined as TRD. A structured questionnaire was used to collect socio-demographic, suicidality, and psychosocial information.

Results: In a total of 125 participants, gender difference was identified in certain community integration aspects such as home integration, productivity, and electronic social networking. The male participants appeared to have better involvement in social contact with internet but slightly less video link than women, while women had higher level of home integration in the past month. The participants who performed worse in the social integration and better home-based activity or productivity levels had higher suicide risks including suicide ideation and overall suicide risks.

Conclusions: Community integration levels of home, social, and productivity were associated with suicidality in terms of overall suicide risk and recent suicide ideation. Facilitation of community integration at home and life arrangements might reduce suicide risks in TRD patients.

Keywords: treatment-resistant depression, suicidal ideation, community integration (MeSH), gender differences, recovery

INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability. It is featured by its chronicity, recurrence, gender differences, and high-risk for suicide (1, 2). Approximately half of MDD patients would respond to an initial trial of an antidepressant, with only a third reaching clinical remission (3). Despite the varied definitions across the world, TRD has been defined and recognized as not responding to two adequate antidepressant medication regimens for patients with MDD (4). Further, two review and consensus studies of the Asian populations defined TRD as failure of at least two antidepressant trials at an adequate dose for 6–8 weeks during any MDD episode (5, 6). The management of disease and follow-up care among patients with TRD is put forward as an important issue.

More than 90% of people with completed suicide have been linked to a mental disorder (7), with MDD being the most common disease related to suicide (8, 9). Furthermore, history of suicide attempts and comorbid psychiatric disorders were the strongest risk factors for future attempts of those with TRD (10). Researchers identified the prevalence of suicide ideation among patients with TRD was 2-fold higher than in the non-TRD group (11). Apart from suicide risks, TRD patients had significantly lower productivity loss and activity impairment as compared to non-TRD and the general population (11). Moreover, a systematic review found that patients who admitted with suicidal thoughts or behaviors had near 200 times more risk of global suicide rate, even many years after discharge; in contrast, patients with previous psychiatric hospitalization have 30 times higher rates of suicide (12). Despite the continuous advancement in neuroscience and cutting-edge role of ketamine and ketamine treatment (9, 13) as well as in the knowledge of human behavior pathophysiology, currently, suicidal behavior represents a puzzling challenge. The complexity of suicidality in MDD has been explained by various possible pathophysiological factors as the role of neurobiological, neuroimmunological biomarkers, brain-derived neurotrophic factor, and other neuromodulators (9). However, the need of careful assessment and patient follow-ups with high risk of suicide in the community is less researched yet composed a critical part of suicide prevention in modern psychiatry (9).

Research in Taiwan indicated that during the trajectory of community life recovery, patients with TRD had difficulties integrating to social life due to multifactorial barriers including poor personal conditions and social adaptation skills (14). In this context, researchers in previous studies have introduced the concept of community reintegration for better recovery in TRD, including family life, productivity, social activities, and electronic social networks. A recent study suggested that well-integrated life in community was a protective factor associating with current suicide ideation in the past 2 weeks (15). Similarly, two prospective cohort studies addressed the negative correlation between suicide and social integration among both genders in the general population in the USA (16, 17). Although researchers excluded participants with poor mental health status, positive social integration was a potential protective factor for 2- and 3-fold reduction of suicide risk in men and women, respectively.

However, the evidence about the correlation between community integration and suicide risks was limited.

The study sought to examine whether community integration level was associated with suicidality among a cohort of TRD patients in northern Taiwan, with specific interest in exploring the gender differences in community integration features.

METHODS

Design

This cross-sectional study was nested in a 3-year prospective study investigating the psychosocial characteristics and non-pharmacological management for Taiwanese patients with TRD (Protocol ID: 201612198RINB). A cohort of TRD was established in 2018, with nurse-led group intervention and long-term follow-ups in the following 2 years. The current study analyzed the associations of suicide risks and the community integration levels of the TRD cohort.

Participants

The study participants were referred by psychiatrists at two general hospitals in northern Taiwan during January 2018 to October 2019. The sources of referral included psychiatric day-care service, outpatient department, or inpatient units. They were all confirmed with the diagnosis of MDD according to the 5th version of the Diagnostic and Statistical Manual and remitted partially in the recovery process for more than 2 years before participation in this study. All the patients were under medication treatment at the time of recruitment, albeit the existence of psychological or other therapeutic treatments. The inclusion criteria was an experience of two types of antidepressants in a recent episode of MDD according to the medical records. The exclusion criteria included cognitive impairment, communication barriers, and unstable disease conditions.

Data Collection

Before formal data collection, two psychiatrists of the research team underwent discussions of recruitment definition and procedures in two consensus meetings. The study was approved by two Ethics Committees in the study hospitals (201612198RINB and 20190106R). All the participants agreed to take part and signed the informed consent. A structured interview with questionnaire was conducted with each patient by the assistant and double-checked by the corresponding author.

Measurements

The measurements included socio-demographic and psychosocial information and the assessments toward suicidality and community integration status. Suicidality was defined as different suicide risk factors including the overall suicide risk, suicide ideation and suicide attempt in a week or lifetime.

The Socio-Demographic and Psychosocial Information

Participants' socio-demography was collected by variables such as gender, age, education years and level (below junior high/senior

high/above university), marital status (single/married or cohabited/others), occupation status (yes/no), religious belief (yes/no), and status of living alone (yes/no). Further, frequent feelings of hopelessness were inquired and recorded as yes/no.

Suicidality Measures

The term "suicidality" in this study was defined as including suicide ideation and suicide attempt. Two major scales were adopted to the assessment of suicidality, the five-item Brief Symptom Rating Scale (BSRS-5) and the nine-item Concise Mental Health Checklist (CMHC-9). The BSRS-5 was developed to identify recent psychiatric morbidity and suicide ideation in community subjects and psychiatric patients (18, 19). The scale contained the following five items of psychopathology and an additional item assessing suicide ideation: (1) having trouble falling asleep (insomnia); (2) feeling tense or keyed up (anxiety); (3) feeling easily annoyed or irritated (hostility); (4) feeling low in mood (depression); (5) feeling inferior to others (interpersonal hypersensitivity: inferiority). The additional item inquired, "Do you have suicide ideation in the past week?". The participants were asked to rate symptoms on a five-point Likert scale from 0, not at all; 1, a little bit; 2, moderately; 3, quite a bit; and 4, extremely. The total score was calculated by computing the first five items, with cut-off points of 5/6, 9/10, and 14/15 standing for mild/moderate/severe levels of mental distress. In this study, the Cronbach's alpha of BSRS-5 was 0.84.

The CMHC-9 was a nine-item short assessment of recent psychological distress and overall suicide risks in the community and clinical settings (20). It is a brief and effective tool for high-risk detection with satisfactory sensitivity (92%) and specificity (82%) in identifying recent suicide ideation. The nine items were divided into two core components of assessment, i.e., psychopathology/mental distress and major suicide risk factors. Each item was rated as 0 (no distress at all) or 1 (significant distress), with the timeframe spanning from past-week (5-item mental distress), lifetime (suicide attempt), and future (suicide intention) in order to objectively assess the overall risk of suicide. The total score ranges from 0 to 9, with the cutoff value over 4 points indicating higher suicide risk. The Cronbach's alpha for the scale in this study was 0.77.

The Revised Community Integration Questionnaire (CIQ-R)

The 18-item CIQ-R was used to assess life conditions across four components: home integration (items 1–5), social integration (items 6–11), productivity (items 12–15), and electronic social networking (items 16–18) (21). The original version of Community Integration Questionnaire has been widely utilized to measure community integration following traumatic brain injury and provide further direction for a clinical or research setting (22). It was also expanded to other target population as physical disability, spinal cord injury, brain tumors, and so on (21). The home integration component had scores from 0 to 2 points reflecting a person's autonomy in performing home activities; the score of 2 means mostly done by oneself, 1 means partly self or by family members, and 0 means all by the family. The assessment of social involvement or productivity in the past

month was based on performance frequency, dividing into 0 (never), 1 (1–4 times), or 2 (over 5 times). The electronic social networking included the frequency of contact to others using internet, online video link, or text message with scores as every day or most days = 2, almost every week = 1, and Seldom/never = 0. Higher scores of CIQ-R stand for better integration level or social activity involvement in actual or online community settings. The Cronbach's alpha was 0.66 in this study.

Data Analysis

Statistical calculations were carried out using SPSS 22.0. The means, standard deviations, and frequencies were calculated for quantitative variables; Cronbach's alpha was used to estimate the internal consistency of BSRS-5; CMHC-9, CIQ-R. Independent t-tests were adopted to explore the difference in each CIQ-R item between men and women and the difference of each CIQ-R subscale from suicidality variables. To examine a relationship between CIQ-R subscales and overall suicidality variables, Pearson correlation or t-test coefficients were obtained and computed. Statistical significance was set at a level of $p < 0.05$.

RESULTS

The Socio-Demographic and Suicidality Status

A total of 125 patients with TRD participated in this study. Three-fourth of all participants were women ($n = 91$, 72.8%). The mean age of patients was 55.4 (SD = 14.6) within a range of 20–80 years old. Nearly half of the samples ($n = 58$, 46.4%) had a degree above university with average education of 11.9 years. More than half of the people ($n = 68$, 54.4%) were married or cohabited. Two-thirds reported a religious belief ($n = 94$, 75.2%). Only one in five ($n = 26$, 20.8%) had a full-time job and closely one-third (31.2%) reported unemployment at the time of study. The vast majority of participants lived with at least one cohabitant ($n = 104$, 83.2%). More than half of participants felt hopeless of their future ($n = 85$, 68%). According to the scores of BSRS-5, the patients presented a higher level of mental distress (M = 10.8, SD = 5.4). Nearly all participants seriously considered suicide in their lifetime ($n = 118$, 94.4%), 52 patients (41.6%) revealed recent suicide ideation in the past week, and 70 (56%) had lifetime suicide attempt. Moreover, the severity of suicide ideation during the lifetime was self-rated as 7.2 points in average in a scale of 0–10. The overall suicide risk was high with 4.0 ± 2.6 points assessed by the CMHC-9 (**Table 1**).

The Association Between Psychosocial Factors, Suicidality, and Community Integration

In this study, suicidality was defined to represent the overall risk that includes both suicide ideation and suicide attempt. This section analyzed whether higher suicidality would be associated with community integration levels in terms of home, social, productivity, and electronic contact components. As seen in **Table 2**, patients with lifetime suicide ideation showed higher level of productivity ($t = -4.48$, $p < 0.001$). The significant

TABLE 1 | The socio-demographic and suicidality status of patients with treatment-resistant depression ($N = 125$).

Variable		n/Mean ± SD (range)	%
Gender	Female	91	72.8
	Male	34	27.2
Age group		55.4 ± 14.6 (20–80)	
	20–44	29	23.2
	45–64	54	43.2
	65–80	42	33.6
Education	Below junior high school	42	33.6
	Senior high school	25	20.0
	Above university	58	46.4
Education years		11.9 ± 4.8 (0–20)	
Marital status	Single	26	20.8
	Married/Cohabited	68	54.4
	Divorced/Separated	18	14.4
	Widowed	13	10.4
Religion	No	31	24.8
	Yes	94	75.2
Job	None	39	31.2
	Yes	86	68.8
Living alone	Yes	21	16.8
	No	104	83.2
Feeling hopeless	Yes	85	68.0
	No	40	32.0
Mental distress (BSRS-5)*	Total score	10.8 ± 5.4 (0–20)	
	Insomnia	99	79.2
	Anxiety	106	84.8
	Irritability	102	81.6
	Depression	108	86.4
	Inferiority	96	76.8
Suicide ideation (1 week)	Yes	52	41.6
	No	73	58.4
Lifetime suicide ideation	Yes	118	94.4
	No	7	5.6
Lifetime suicide attempt	Yes	70	56.0
	No	55	44.0
Overall suicide risk (CMHC-9)∧	Total score	4.0 ± 2.6 (0–9)	

*Each item in the BSRS-5 was scored ≥1 point in the 0–4 Likert scale.
∧CMHC-9: The nine-item Concise Mental Health Checklist.

correlation between home integration and social integration to the overall suicide risk score ($p < 0.05$) was also identified. This indicated that people who engaged more actively in home-based activities such as housework were more likely to demonstrate a higher rate of overall suicide risk. Specifically, those who had higher social integration scores were significantly associated with lower overall suicide risk ($p < 0.01$). Moreover, there was a significant difference in the mean score of social integration between patients who reported recent suicide ideation (M = 5.0,

SD = 2.1) compared to those without such ideation (M = 6.0, SD = 2.3) ($t = 2.61$, $p < 0.05$). That is, patients with recent suicide ideation performed worse in the social integration component than those without such ideation. These observations might be explained by the characteristics of TRD and are discussed further in the discussion section.

Gender Differences in Community Integration

Table 3 shows the gender differences in community integration features. Although male participants were much less than their female counterparts, the analysis revealed the current situation of female predominance in service-seeking behavior for depression. Gender inequality was found to be significant in specific items as preparing meals, housework, childcare, current work situation, and social contact using the internet by writing or video call ($p < 0.05$). For the specific question, "Who usually prepares meals in your household?", while a half of women (50.5%) prepared meals alone, around two-thirds of men (70.6%) had someone prepare for them ($p < 0.001$).

In the domain of home integration, male and female participants showed remarkably different performance in their reports. In the item, "In your home, who usually does normal everyday housework?", nearly half (49.5%) of women were active in doing normal everyday housework alone. On the other hand, only 8.8% men did the house work ($p < 0.001$). With patients who had children, we assessed, "Who usually cares for the children in your home?". Not any male participant took care of their children alone and only 11.8% ($n = 4$) of male patients could take care of their children together with another person. In contrast, 8.8% ($n = 8$) of women usually cared for their children alone and 17.6% ($n = 16$) could look after their children with another person ($p < 0.01$).

In the aspect of current work situation, two-thirds of women ($n = 67$, 73.6%) and half of men ($n = 18$, 52.9%) had neither job, learning, nor volunteer activities. Specifically, one-third of men ($n = 11$, 32.4%) attended school or worked full-time, but only 6.6% ($n = 6$) of women did so. Only 3% of women reached the highest level of current work situation; however, no male participant reported the same level ($p < 0.05$). Nearly five times of men were under employment or school learning as compared to women (32.4% vs. 6.6%), indicating the lower work conditions for women with TRD.

In addition, gender difference was found significant in the frequency of writing to people using the internet and using a video link for social contact ($p < 0.05$). Two-thirds of men (64.7%) wrote for social contact via the internet every day or most of the days, whereas less than one-thirds of women (31.9%) did. More than half of women (58.2%) seldom wrote to people for social contact. Finally, while no men reported using a video link for social contact every day, 7.9% women did so ($p < 0.05$).

DISCUSSION

Our findings highlighted that over ninety percent of patients with TRD seriously considered suicide in their lifetime and nearly

TABLE 2 | The associations between community integration conditions and suicidality ($N = 125$).

Mean (SD)	Overall suicide risks (r value)	Past-week suicide ideation		t	Lifetime suicide ideation		t	Lifetime suicide attempt		t
		Yes	No		Yes	No		Yes	No	
Home integration	0.19*	5.6 (3.8)	5.3 (3.3)	−0.54	5.4 (3.5)	6.6 (3.2)	0.88	5.7 (3.8)	5.1 (3.2)	−0.99
Social integration	−0.30**	5.0 (2.1)	6.0 (2.3)	2.61*	5.5 (2.3)	6.0 (1.4)	0.56	5.2 (2.2)	5.9 (2.2)	1.76
Productivity	0.11	3.0 (2.0)	2.6 (1.8)	−1.11	2.8 (1.9)	2.0 (0.0)	−4.48***	3.0 (1.9)	2.5 (1.8)	−1.57
Electronic Social networking	0.03	2.4 (1.8)	2.2 (1.8)	−0.55	2.3 (1.8)	1.4 (1.1)	−1.28	2.3 (1.8)	2.1 (1.7)	−0.68
CIQ-R total	0.05	17.1 (5.8)	17.1 (5.4)	0.01	17.2 (5.6)	17.7 (4.9)	0.26	17.6 (5.9)	16.7 (5.0)	−0.85

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. t/r: The values were derived from Independent t-tests or Pearson correlations.
SD, standard deviation.

half either revealed recent suicide ideation (in the past week) or history of self-harm/suicide attempts. Moreover, significant differences were identified in the levels of four components of the community integration assessment between male and female groups. For instance, male participants appeared to have better involvement in social contact with internet but slightly less video link than women; and women had higher level of home integration. In addition, TRD patients who had lower scores in the social integration and higher functioning in home integration were more likely to demonstrate higher scores in overall suicide risks. Those with TRD and recent suicide ideation were involved less in activities of social integration than those without recent ideation. Intriguingly, patients with lifetime suicide ideation presented significantly higher scores of productivities than those without that experience.

This study applied the CIQ-R to assess community life features in the recovery progress of patients with TRD. The issue was rarely investigated in the past when most prior evidence about TRD in Taiwan focused on epidemiology (23), pharmacological treatment (24, 25), and complementary treatment as transcranial magnetic stimulation or prefrontal theta-burst stimulation (26, 27). A previous study displayed long-term effects of functional impairment; severe depressive patients had higher rates of suicide (15) and higher all-cause mortality compared with non-TRD (28, 29). Whereas, in the present study, the majority of individuals with TRD presented high levels of mental distress which was assessed by the BSRS-5. Similar to previous study that compared to general population, psychiatric patients appeared to be 4.6–6.7-times more severe in psychological distress (14), and ~7.2-fold more severe for patients with TRD in this study. The results offer an evidence that chronic psychological distress is a significant concern that needs more attention for patients with TRD.

Gender difference of depression was found to be interpreted as related to presentation and precipitation of the disorder (30). Gender plays a role in community integration process of TRD, as evident in this study. Among 125 patients of our study, the number of women was 2.7-fold higher than men, which is consistent in ratio with other studies in Taiwan (23, 24), China (31), United States (27), and Sweden (10). Regarding the

gender issue, our study found significant differences in specific items of the community integration scale, such as preparing meals, housework, childcare, current work situation, and social contact using the internet by writing or video call. Women demonstrated significantly higher scores in home integration scale (preparing meals, housework, and childcare) than men, consistent with other reports (32, 33). However, this could be explained by the fact that Taiwanese women are more likely to take care of household chores whether they are in good health or not. Appealingly, it was found that patients who had higher functioning in the home integration domain showed higher score in the overall suicide risks. Of interest, various factors effected low involvement in home activities, including lack of necessity and motivation (32). One justifiable reason could be that even under severe depression and suicide risk, women with TRD still take responsibilities of house work in the society of Taiwan. These results suggest that in addition to providing different approaches in life skills training, healthcare providers could focus on reinforcement of a patient's motivation as well as promote the family members' shared responsibilities with the patients. Furthermore, mental health professionals should enhance sufficient knowledge in psychoeducation intervention and emotional support toward patients with TRD and their caregivers in order to decrease the conflict caused by and the burden from the family.

In the present study, low social integration was found to be significantly associated with higher level of overall suicide risk. Of interest, patients with recent suicide ideation got lower average scores in the domain of social integration (i.e., less frequent shopping, leisure activities, visiting friends/relatives, or hardly any confiding relationship) than those with no recent suicide ideation. Interestingly, these are entirely related to the concept of connectedness which has been demonstrated in various empirical studies regarding powerful protective factors to prevent suicide behavior (34, 35). The term social integration encompasses concepts such as social networks, social support, and social engagement, which were found to be positively associated with psychological integration in the communities during the pathway to recovery (36). Similar to the fact that well-integration in the community reflected lower risk in suicide

TABLE 3 | The descriptions of Community Integration Questionnaire-Revised items (*N* = 125).

Items		n (%)	Male (n = 34)	Female (n = 91)	χ^2
Home integration (item 1–6)					
1	Buying groceries	Yourself alone	9 (26.5)	37 (40.7)	1.37
		Yourself and someone else	12 (35.3)	27 (29.7)	
		Someone else	13 (38.2)	27 (29.7)	
2	Prepares meals	Yourself alone	5 (14.7)	46 (50.5)	4.79***
		Yourself and someone else	5 (14.7)	17 (18.7)	
		Someone else	24 (70.6)	28 (30.8)	
3	Housework	Yourself alone	3 (8.8)	45 (49.5)	4.75***
		Yourself and someone else	11 (32.4)	19 (20.9)	
		Someone else	20 (58.8)	27 (29.7)	
4	Child care	Yourself alone	0 (0)	8 (8.8)	3.12**
		Yourself and someone else	4 (11.8)	16 (17.6)	
		Someone else	10 (29.4)	18 (19.8)	
5	Social arrangements	Yourself alone	3 (8.8)	9 (9.9)	−1.30
		Yourself and someone else	11(32.4)	12 (13.2)	
		Someone else	20 (58.8)	70 (76.9)	
6	Financing	Yourself alone	19 (55.9)	43 (47.3)	−0.63
		Yourself and someone else	3 (8.8)	13 (14.3)	
		Someone else	12 (35.3)	35 (38.5)	
Social integration (item 7–11)					
7	Shopping	Never	3 (8.8)	18 (19.8)	−0.43
		1–4 times	18 (52.9)	34 (37.4)	
		5 or more	13 (38.2)	39 (42.9)	
8	Leisure activities	Never	5 (14.7)	23 (25.3)	−1.52
		1–4 times	14 (41.2)	39 (42.9)	
		5 or more	15 (44.1)	29 (31.9)	
9	Visiting friends/relatives	Never	20 (58.8)	56 (61.5)	0.24
		1–4 times	14 (41.2)	30 (33.0)	
		5 or more	0 (0)	5 (5.5)	
10	Companies when doing leisure activities	Mostly alone	10 (29.4)	19 (20.9)	0.59
		Mostly with friend	1 (2.9)	9 (9.9)	
		Mostly with family members	23 (67.6)	63 (69.2)	
11	Having a best friend with whom you confide	Yes	21 (61.8)	58 (63.7)	0.20
		No	13 (38.2)	33 (36.3)	
Productivity (item 12–15)					
12	Traveling outside	almost every day	28 (82.4)	69 (75.8)	−0.79
		almost every week	3 (8.8)	10 (11.0)	
		seldom/never	3 (8.8)	12 (13.2)	
13–15	Current work situation^	0	18 (52.9)	67 (73.6)	−2.16*
		1	1 (2.9)	2 (2.2)	
		2	1 (2.9)	5 (5.5)	
		3	3 (8.8)	8 (8.8)	
		4	11 (32.4)	6 (6.6)	
		5	0 (0)	3 (3.3)	
Electronic social networking (item 16–18)					
16	Frequency of writing to people using the Internet	Everyday/most days	22 (64.7)	29 (31.9)	−3.35**
		Almost every week	2 (5.9)	9 (9.9)	
		Seldom/never	10 (29.4)	53 (58.2)	

(Continued)

TABLE 3 | Continued

Items		n (%)	Male (n = 34)	Female (n = 91)	χ^2
17	Frequency of social contact with video link	Everyday/most days	0 (0)	7 (7.9)	1.10*
		Almost every week	3 (8.8)	8 (9.0)	
		Seldom/never	31 (91.2)	74 (83.1)	
18	Frequency of talking/messaging by phone	Everyday/most days	21 (61.8)	37 (41.6)	−1.74
		Almost every week	5 (14.7)	22 (24.7)	
		Seldom/never	8 (23.5)	30 (33.7)	

*$p \leq 0.05$ **$p < 0.01$ ***$p < 0.001$; t: The values were derived from independent t-tests. Scoring of each item was based on degree of autonomy or frequency, with higher score indicates more independence or social contact.
∧Current working status: 0 (Not working, not looking for work, not going to school, no volunteer activities), 1 (Volunteer 1–4 times and not working, not looking for work, not in school), 2 (Actively looking for work and/or volunteers 5 or more times), 3 (Attends school part-time or works part-time), 4 (Attends school full-time or work full-time), 5 (Works full-time and attends school part-time or attends school full-time and works part-time).

ideation, being alone and isolated were also evident in predicting the remission rate (1, 29), disability (37), and suicide attempts (10). The positive outcomes of friendship support for patient with serious mental illness were identified in studies related to social relationships (38). In contrast to friendship cooperation that requires both directions and reciprocity, the family members and healthcare providers are more likely to be one-sided in support for depressive patients. This robust evidence highlights the importance of social relationships as a target strategy for mental health staff to promote the importance of maintaining social connections of TRD patients for better quality of life or suicide prevention. In addition to providing enough information in psychotherapy programs and emphasizing the value of a healthy social relationship (39), healthcare providers can help the patients be aware and recognize harmful relationships which may worsen mental health development and deteriorate interpersonal relationship during the recovery process. Our finding lends support to suicide prevention guidelines in clinical settings regarding the importance of screening social integration level for suicide risk assessment (17).

Lastly, it was found that patients with lifetime suicide ideation responded with higher average scores in the productivity component (e.g., frequency of traveling outside the home and current performance status related to school, work, and volunteer activities). There was evidence that patients with suicide ideation appeared to have greater level of perfectionism and work performance compared to patients without suicidal ideation (40). Perfectionism is a multidimensional personality trait characterized by exceeding high personal performance standards by overly self-critical evaluation (41). Individuals with perfectionism attempt to perform perfectly to meet the social expectation, yet they may live with fear of mistake and self-criticism. Hence, the most frequently cited relationship with perfectionism was major depression, anxiety, obsessive-compulsive disorder, and suicidality in the previous studies. Therefore, our findings could support the fact that patients with TRD are struggling in work/life performances related to their social roles during the recovery process. According to Davidson and Roe (42) recovery is considered when a person is able to have a meaningful life while continuing to have a mental illness. That is a suggestion for mental health

providers to objectively assess and understand the ability, current needs, and personal characteristics of patients with TRD in order to identify facilitators for community reintegration and barriers to illness management during depression treatment. Finally, to reduce suicidality and build up better recovery for those with TRD, mental health policy should maintain a safe and supportive community environment for patients with TRD to adjust their life roles to adapt better in the community.

In interpreting these results, several limitations should be taken into consideration. First, the study simply analyzed cross-sectional data with a small sample size; selection bias and reverse causality might limit the generalizability of the findings. In addition, one-third of our sample was around 65–80 years old, which could affect to the level of community integration due to their functional impairment of TRD. Future studies are suggested to apply longitudinal designs in identifying the causal relationship between community integration and suicide risks. Finally, non-pharmacological intervention studies for patients with TRD may guide future development of better care quality in the trajectory of community recovery.

CONCLUSION

This was to our knowledge the first study which examined the association between community integration and suicidality among patients with TRD. Our results revealed a high suicide ideation and attempt rate among this patient group. It also highlighted that the community integration levels of home, social, and productivity were associated with overall suicide risk and recent suicide ideation with gender differences in an Asian context. Facilitation of community integration at home and life arrangements might reduce suicide risks in TRD patients. In conclusion, in order to enhance the quality of community life and mental health care for patients with TRD during recovery process, healthcare providers should actively empower their community involvement, social adaptation skills, as well as self-care needs between genders in the chronic illness trajectory.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the National Taiwan University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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Suicidal Ideation Is Associated With Reduced Functional Connectivity and White Matter Integrity in Drug-Naïve Patients With Major Depression

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Depression is a highly prevalent psychiatric disorder affecting millions of people worldwide. Depression is characterized by decreased mood or loss of interest in daily activities, changes in feeding and circadian rhythms and significant impairments in cognitive and executive function. In addition, the occurrence of recurrent thoughts of death and suicidal ideation confers depressed patients a higher risk of suicide than the general population. With this study, we aimed to explore the neural correlates of suicidal ideation in drug-naïve patients diagnosed with depression. Twenty-five patients were scanned using two-different magnetic resonance imaging (MRI) modalities, resting state functional MRI (fMRI) and diffusion tensor imaging (DTI). Resting state allowed the exploration of connectivity patterns in the absence of a specific stimulus and DTI allowed a detailed analysis of structural white matter integrity with measures like fractional anisotropy (FA). Probabilistic independent component analysis (PICA), network-based statistics and tract-based spatial statistics (TBSS) were applied to analyze resting-state fMRI and DTI data, respectively. Our results showed that, in our sample of drug-naïve patients, suicidal ideation was negatively associated with resting-state functional connectivity in the visual networks and with FA in the genu of corpus callosum and in the right anterior corona radiata. In addition, a significant association was identified between suicidal ideation and a functional connectivity network that included connections between regions in the superior and orbitofrontal cortex, the cerebellum, the cingulate gyrus as well as temporal and occipital regions. In conclusion, this work has expanded our knowledge about the possible functional and structural neuronal correlates of suicidal ideation in drug-naïve patients with depression, paving the way for future personalized therapeutic approaches.

Keywords: major depression, suicide, suicidal ideation, fMRI, DTI

INTRODUCTION

Depression affected nearly 300 million people around the world in 2019 (1) and it is considered by the world health organization (WHO) as the single largest contributor for disability worldwide (2). Nowadays, its prevalence might be even higher due to the challenges imposed by the COVID-19 pandemic (3, 4). The symptoms of depression include depressed mood or loss of interest in daily activities but also, changes in body weight, sleep disturbances, psychomotor retardation, fatigue, feelings of worthlessness, diminished ability to concentrate, recurrent thoughts of death and suicidal ideation (5). In fact, depression is one of the most common diagnosis at the time of death by suicide (6, 7) being depressed patients 20 times more likely to commit suicide than the general population (8, 9). It has been reported that more than 700,000 deaths are a result of suicide (10, 11) and it is estimated that for each death by suicide, there is a much higher number of suicidal attempts, increasing the personal, social, and economic burden of the disorder (8, 12).

Suicide is a complex phenomenon in which many factors could be implicated, especially in MDD patients. Even though the specific pathophysiological pathways of suicide are not yet fully understood, recent research suggest that suicide is a result of not a single factor but rather a complex interaction between genetic vulnerability as well as exogenous and endogenous stressors (13, 14).

The first step on this complex pathway is suicidal ideation, reported as one of the major risk factors for suicide (15). Its presence as a symptom of depression was previously associated with poorer treatment response (16) and deficits in cognitive functions, such as executive functions (17, 18) and verbal learning (19). One third of the patients experiencing suicidal ideation will act on their thoughts (20). Hence, suicidal ideation is a red flag for clinical concern, and it is an important part of the suicide risk assessment guidelines (21).

In the past decade, there has been an exponential growth of studies employing neuroimaging techniques to investigate structural, functional, and metabolic brain processes related to suicidal thoughts and behaviors (22). A commonly used neuroimaging technique is magnetic resonance imaging (MRI), given that its different modalities, such as structural MRI, diffusion tensor imaging (DTI) and functional MRI (fMRI), allow a wide characterization of the brain. Specifically, they provide information on gray and white matter anatomy, structure, as well as brain activity and connectivity. In the literature, these MRI modalities have been used to explore the neural correlates of suicidal ideation due to its importance on the suicide pathway.

At the functional level, previous studies have described the functional networks associated with suicidal ideation in depressed patients, showing a relation between decreased functional connectivity with suicidal ideation (23, 24). The functional networks included similar frontal brain regions, such as the orbitofrontal gyrus, but also distinct regions like the middle occipital gyrus, superior parietal gyrus, thalamus, and caudate (23, 24). Other studies, using seed-based approaches reported increased resting-state functional connectivity (rsFC) between both sides of hippocampus (23), amygdala-precuneus/cuneus

(25) and between the left habenula and the left cerebellum (26) when comparing depressed patients with and without suicidal ideation. In contrast, decreased rsFC between the right anterior cingulate cortex and the right middle temporal pole and the orbitomedial prefrontal cortex (27), as well as between the right habenula and the right precuneus and the left inferior frontal gyrus (26) were also described when comparing the same groups of patients with depression.

Alterations in gray and white matter have been reported in depressed patients with suicidal ideation (23, 28, 29). In particular, patients with suicidal ideation showed decreased cortical thickness in the left hemisphere, mainly in the insula when compared to patients without suicidal ideation (29); however, there were no statistically significant differences in their volumes (29). The authors also found that depressed patients with suicidal ideation presented increased radial diffusivity (RD) and decreased fractional anisotropy (FA) in the hippocampal part of the cingulum buddle, superior and posterior corona radiata (CR) as well as anterior thalamic radiation (ATR), when compared to depressed controls (29). These findings suggest a disruption in the white matter integrity of bundles described above, responsible to connect frontal brain regions and basal ganglia (29). Another study also reported decreased white matter integrity in depressed patients with suicidal ideation in tracts connecting frontal regions, namely corpus callosum (30). Indeed, Myung and collaborators (28) also identified a brain network with decreased structural connectivity in frontal, parietal, occipital, and subcortical regions (i.e., thalamus, caudate and pallidum).

These findings suggest that alterations in structure and function of frontal-subcortical networks are implied in suicidal ideation in MDD. Nevertheless, more studies are required in order to consolidate these results and establish the brain patterns related to suicidal ideation. Thus, combining multimodal MRI techniques seems crucial to level up the characterization of the pathophysiology and etiology of suicidal ideation in MDD, which may lead to the development of useful approaches to identify high-risk patients and targeted treatments for suicidal ideation.

In the present study, our main objective was to explore the neural correlates of suicidal ideation in drug-naïve depressed patients at the whole-brain level, using two different MRI modalities, namely resting-state fMRI, and DTI. For that purpose, probabilistic independent component analysis (PICA), network-based statistics (NBS) and tract-based spatial statistics (TBSS) were applied to analyze resting-state fMRI and DTI data, respectively. Our main hypothesis was that suicidal ideation would be associated with decreased functional connectivity as well as white matter integrity.

METHODOLOGY

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki (59th Amendment) and was approved by relevant local ethics review boards from University of Minho and Hospital de Braga (Braga, Portugal). The study goals, as well as the psychological and clinical assessments were explained

to the participants, of whom all gave informed consent. The anonymity and confidentiality of the participants in the study were guaranteed during all research activities.

Characterization of Participants

A sample of treatment-naïve (first depressive episode and without prior exposure to antidepressant treatment) MDD patients were recruited in the context of emergency psychiatric evaluations or the outpatient unit of the Psychiatry Department of the Hospital de Braga. The recruitment took place between January of 2016 and January of 2020. The diagnosis was confirmed with the SCID (structured clinical interview for DSM disorders) according to DSM-IV-TR (31).

The inclusion criteria were; being drug-naive, first-episode MDD patient, aged 18-65 years-old, without psychiatric or neurological comorbidities, The exclusion criteria were: age inferior to 18 years or superior to 65 years, presenting any MRI contradictions, comorbid psychiatric disorders (e.g., bipolar disorder, addictive disorders and schizophrenia), prior medical history of neurological disorders or traumatic brain injury and sign of cognitive impairment defined by scores below or equal to 24 in the Mini-Mental Sate Examination (MMSE) test (32).

In accordance with the established criteria, 32 patients were first selected. From these, 7 were not included in this analysis because either they were unable to perform the MRI, or they had to be excluded due to brain abnormalities. Therefore, a total of 25 MDD subjects (8 males, 17 females) were included in the final analysis of resting-state MRI data and 23 MDD subjects (7 males, 16 females) were included in the final analysis of diffusion data (2 subjects did not perform diffusion acquisitions) (**Supplementary Figure 1**).

All participants performed a psychological assessment in the same day of the MRI acquisition. 17-item Hamilton Depression Rating Scale HAM-D (33) and 14-item Hamilton Anxiety Rating Scale HAM-A (34) were used for the assessment of depression and anxiety severity in the past week, respectively. Both scales are clinician-administered. 10-item Perceived Stress Scale PSS-10 (35) was used to evaluate the global perceived stress in the past month. Beck Scale for Suicidal Ideation BSSI (36) is a self-reported scale used to detect and measure the severity of current suicidal ideation. It comprises 21 items: the first 19 items focus on several characteristics of suicidal ideation; the last two items assess the number of previous suicide attempts and the intention to die associated with it. Each item is rated on a 3-point scale (0–2). The total score is computed by adding the first 19 items of the scale, ranging from 0 to 38. There are no specific cut-off scores; higher total scores reflect higher severity of suicidal ideation.

MRI Acquisitions

MRI acquisitions were performed at Hospital de Braga with a clinical approved Siemens Magnetom Avanto 1.5 T (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel receive-only head coil. All patients underwent the same MRI acquisition protocol. Even though the protocol included other acquisitions, for the present study only the resting-state functional images and the diffusion-weighted imaging (DWI) sequences were considered.

Functional images were acquired using a BOLD sensitive echo-planar imaging (EPI) with the following parameters: 30 interleaved axial slices, repetition time (TR) = 2,000 ms, echo time (TE) = 50 ms, flip angle (FA) = 90°, slice thickness = 3.5 mm, slice gap = 0.48 mm, in-plane resolution = 3.5 × 3.5 mm^2, field of view (FoV) = 224 mm and 190 volumes. Also, a T1-weighted structural image for anatomical reference was obtained using a magnetization-prepared rapid acquisition (MPRAGE) by gradient echo sequence with voxel resolution 1.0 × 1.0 × 1.0 mm, FoV 234 × 234 mm^2, FA of 7°, 176 slices and TE/TR of 3.48/2,730 ms. During functional resting state acquisitions, participants were instructed to remain in an awake and calm state, with their eyes closed while trying not to focus on any particular thought.

DWI scans were performed using a spin echo–echo planar imaging (SE-EPI) sequence: TR = 8,800 ms, TE = 99 ms, FoV = 240 mm × 240 mm, acquisition matrix = 120 × 120, 61 two-millimeter axial slices with no gap, 30 non-collinear gradient directions with $b = 1,000$ s mm^{-2}, one $b = 0$ s mm^{-2} acquisition, and one repetition.

Before data pre-processing, the raw acquisitions from all participants were visually inspected to discard any brain lesions, critical head motion, or artifacts that could compromise the data.

MRI Data Pre-processing
Resting-State fMRI

Preprocessing of fMRI data was performed using custom scripts using FMRIB Software Library (FSL v6.01) tools (37). In order to exclude possible magnetic field inhomogeneities at the beginning of the acquisition, the first step of preprocessing was the removal of the first 5 volumes (10 s). Then, because fMRI is measured using 2D imaging, there are temporal offsets between volumes that needed to be corrected. The slice timing correction was done with a temporal data interpolation that used the first acquired volume as reference. The next step was correcting the head motion, by using a function from FSL that searches motion parameters and uses them to correct movement in the time-series. Motion correction is an important step in fMRI preprocessing as the slightest movement can induce motion related artifacts. To further reduce contamination on functional connectivity due to motion, motion scrubbing was also performed to identify and exclude time-points where head motion could be critical. A non-linear spatial normalization to Montreal Neurological Institute (MNI) standard space was performed to register the set of brains to a common space/template. The procedure involved: (i) skull stripping of the mean image of the functional acquisition; (ii) rigid-body registration of the mean functional image to the skull stripped structural scan; (iii) affine registration of the structural scan to the MNI T1 template; (iv) non-linear registration of the structural scan to the MNI T1 template using the affine transformation estimated previously as the initial alignment; (v) non-linear transformation of the functional acquisition to MNI standard space through the sequential application of the rigid-body transformation, followed by non-linear warp and resampling to 2 × 2 × 2 mm^3 voxel size. A linear regression using the mean of white matter and cerebrospinal fluid (CSF) signals

as well as motion outliers was performed, and the residuals of the regression were smoothed using a Gaussian kernel smoother with a full width half maximum of 6 mm ($\sigma = 2.55$ mm), band-pass temporal filtered (0.01–0.08 Hz) and used for the subsequent analysis.

Resting-State Networks

Probabilistic independent component analysis (PICA) was performed with MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components), distributed with FSL v6.01. PICA is a data driven analysis that isolates components or non-overlapping spatial maps corresponding to regions evidencing coherent time-courses (38, 39). The software estimates group-wise spatial maps that correspond mainly to Resting State Networks (RSNs). A total number of 30 independent components were used. In order to study subject-specific components, a dual regression analysis was performed as well.

Twelve RSNs (**Supplementary Figure 2**) of interest were identified by visual inspection in combination with spatial correlations between the obtained components and RSN templates available from a public dataset from the Functional Imaging in Neuropsychiatric Disorders (FIND) Lab at Stanford University (40).

Matrices of Functional Connectivity

The matrices of functional connectivity were constructed using the 116 cortical, subcortical, and cerebellar areas of the Anatomical Automatic Labeling (AAL) atlas (28). The mean signal for each brain region was extracted and the Pearson's correlations coefficients between each possible pair of regions were calculated, originating a symmetric adjacency matrix, R. Coefficients in matrix R were then transformed to Z-scores using Fisher's r-to-z transform.

DWI Image Pre-processing and Tensor Fitting

Diffusion data were pre-processed using the FMRIB Diffusion Toolbox (FDT) provided with FSL v6.0.3. DWI images were corrected for motion artifacts and eddy current distortions. Then, the affine transformations were used to register each volume and were applied to rotate gradient vectors. Afterwards, the first b_0 volume of each subject was extracted and skull stripped, creating a brain mask applied to the remaining volumes to remove non-brain structures.

Tensor fitting and the scalar maps computation steps were performed with DTIFIT, also included in the FDT toolbox. In this step, a diffusion tensor model is fitted at each voxel and scalar maps of FA and Mean Diffusivity (MD), as well as eigenvector and eigenvalue maps, were generated. Axial Diffusivity (AD) was defined as the principal diffusion eigenvalue, and RD was computed using the mean of the second and third eigenvalues.

Tract-Based Spatial Statistics

Voxel-wise analyses of the scalar maps between subjects were performed using TBSS procedures (41), also part of FSL. To remove potential outliers from the tensor fitting, all FA templates were slightly eroded, and the end slices were zeroed. Afterward, all the FA templates were non-linearly registered into a 1-mm

$\times$ 1-mm $\times$ 1-mm standard space. This step was performed by non-linearly registering each subject's FA template to each other to find the "most representative one" (i.e., the one that requires the least warping to align all images), subsequently used as the study-specific target image. Next, the selected target image was affine transformed into the MNI 152 standard space, and each subject's FA template was transformed into this standard space by combining the non-linear transformation to the study-specific target with the affine transformation into the MNI space. Then, the FA templates of all subjects were averaged, and the resulting image skeletonized. After visual inspection of the skeletonized image, we threshold it at 0.35 to remove from the skeleton regions encompassing other tissues, such as gray matter or CSF. Finally, all scalar maps (FA, AD, MD, and RD) were projected into this FA skeleton using the same transformation applied to the FA templates.

Statistics

Psychometric and Demographic Data

Descriptive statistics of psychometric and demographic data were performed using IBM® SPSS® Statistics (version 27; IBM Corp., Armonk, NY, United States). Normality was assessed using the Shapiro-Wilk Test. All demographic and psychometric variables followed a normal distribution except for the BSSI scale where the distribution was tailed toward left-hand. Correlations between non-parametric variables were performed using the Kendall's tau (τ). Results were considered significant for a *p-value* below 0.05.

RSN Analysis

RSN FC were correlated with the standardized score (z-score) obtained in the BSSI scale using a regression model with the non-parametric permutation procedure implemented in the *randomise* tool from FSL (42). Threshold-free cluster enhancement (TFCE) was used to detect widespread significant differences and control the family-wise error rate (FWE-R) at $\alpha = 0.05$. 5,000 permutations were performed for each contrast. Results were corrected for sex, age, and years of education.

Network Based Statistics

To assess whether suicidal ideation (BSSI score) was associated with the functional connectome, a regression model using the Network Based Statistics (NBS) was applied (31). The NBS method provides a correction for multiple comparisons equivalent to FWE-R by estimating the probability of identifying in a random permutation of the data, networks larger in extent than the ones identified by the hypothesis tested. The method consists in two parts. In the first part, the statistical hypothesis is tested for each connection, filtered by a user-chosen statistical edge threshold and significant network components are identified. In a significant network component, a node can be reached from any other through significant connections. The size of the component is calculated by the number of significant connections in it and although the user-defined threshold is not a determinant of the significance of the network, larger thresholds reveal more widespread networks and smaller thresholds produce smaller and more focused results. A set of different primary thresholds (0.005, 0.001, 0.0005

and 0.0001) was used, as suggested by the toolbox authors, to access different levels of sensibility. In the second part, random permutations of the data were created, and the same methodology described in the first part is applied to each permutation and the size of the network components found is calculated. The calculated distribution of components size is used to estimate the probability of finding random components with a size greater than the one found in our hypothesis. A total of 5,000 permutations were used, together with a FWE corrected network significance of 0.05. Results were corrected for sex, age, and years of education.

Diffusion Data

In a similar way to the analyses performed with RSN FC, non-parametric permutation methods were employed using the *randomise* tool from FSL (42), in order to analyze the skeletonized maps of FA, AD, MD, and RD. Particularly, linear regression models were performed to investigate whether WM microstructure measures were associate with suicidal ideation (z-scores of BSSI score). These models were adjusted for age, gender/sex and years of education.

Widespread significant differences were detected with TFCE, and multiple comparisons were corrected using FWE-R at $\alpha = 0.05$ and cluster extent threshold of $K > 50$. Clusters showing significant results were identified using the John Hopkins University ICBM-DTI-81 WM Labels Atlas and dilated with the *tbss_fill* tool (included in FSL) for visualization purposes.

RESULTS

Psychometric and Demographic Data

Descriptive statistics of psychometric and demographic data are detailed in **Table 1**. Our cohort was composed of 25 drug-naïve MDD patients (9 males and 16 females) with an age mean of 37 years (ranging from 19 to 59 years of age). In our sample 10 patients presented no current suicidal ideation (BSSI score = 0) and 22 patients presented no previous history of suicide attempt.

In our cohort, suicidal ideation (BSSI) was not found to be significantly correlated with depression (HAM-D, $\tau = 0.155$, $p = 0.375$), anxiety (HAM-A, $\tau = 0.069$, $p = 0.659$) or perceived stress (PSS-10, $\tau = 0.083$, $p = 0.602$) as well as demographic variables such as years of education ($\tau = 0.165$, $p = 0.292$) or age ($\tau = 0.101$, $p = 0.511$).

RS-FC Correlates of Suicidal Ideation in Drug-Naïve MDD

Resting State Networks

Thirty independent components were obtained using the MELODIC approach. From these components, 12 were consistent with the typical and identifiable RSN (**Supplementary Figure 2**) (43).

Our results revealed positive and negative correlations between suicidal ideation and functional connectivity to the primary and high visual networks (**Figure 1**). Statistical analysis revealed that in our cohort of drug naïve MDD patients, the FC between the high visual network and the right inferior occipital gyrus was positively correlated with suicidal ideation

(FWE-corrected p value = 0.013, **Figures 1A,C**). In the other hand, the FC between the same network and the left precuneus and cerebellum were negatively correlated with suicidal ideation (FWE-corrected p-value = 0.011, FWE-corrected p-value = 0.007, respectively, **Figures 1A,C**). As for the primary visual network, the connectivity to the right cuneus had a positive association with suicidal ideation, inversely the connectivity to the frontal superior orbital gyrus was negatively correlated (FWE-corrected p-value = 0.015, FWE-corrected p-value = 0.007, respectively, **Figures 1B,C**). **Figure 1C** presents details on statistical analysis obtained for each cluster (including MNI coordinates, FWE-corrected peak p-values and cluster sizes).

Network-Based Statistics

From the connectivity analysis performed using the NBS method, a single network was found to be significantly correlated with suicidal ideation (BSSI). In our cohort of MDD patients, a higher FC in this network was related to lower scores in the BSSI scale. The NBS analysis was performed using thresholds between 0.005 and 0.0001 (**Supplementary Tables 1, 2**). In **Figure 2**, we present the results found for the significant threshold p-value = 0.001 $t_{(threshold)}$ = 3.78, df = 23, p-value (network) = 0.025, 15 nodes and 15 edges. From the set of tested thresholds this was the network that showed a higher mean FC for the lowest p-value.

Of this network we emphasize the connections between the cerebellum (node #106) and the nodes in the left superior frontal gyrus (node #3), the frontal middle orbital cortex (nodes #25 and #26), the rectus (nodes #27 and #28) and the right inferior and superior occipital gyrus (nodes #54 and #50). This network also presented relevant connections between the left superior frontal gyrus (node #3) and the left middle temporal gyrus (node #85) and the cuneus (nodes #45 and #46) and the posterior cingulate gyrus (nodes #35 and #36).

WM Microstructure Correlates of Suicidal Ideation in Drug-Naïve MDD

The statistical analysis of the skeletonized maps revealed a statistically significant negative correlation between suicidal ideation scores and FA maps (**Figure 3A**). Patients with higher suicidal ideation scores showed a significant decrease in FA maps in clusters including the genu of the Corpus Callosum and the right anterior Corona Radiata (**Figure 3B**). **Figure 3C** presents details on statistical analysis obtained for each cluster (including MNI coordinates, FWE-corrected peak p-values and cluster sizes). No significant correlations were found between suicidal ideation score and AD, MD, and RD maps.

DISCUSSION

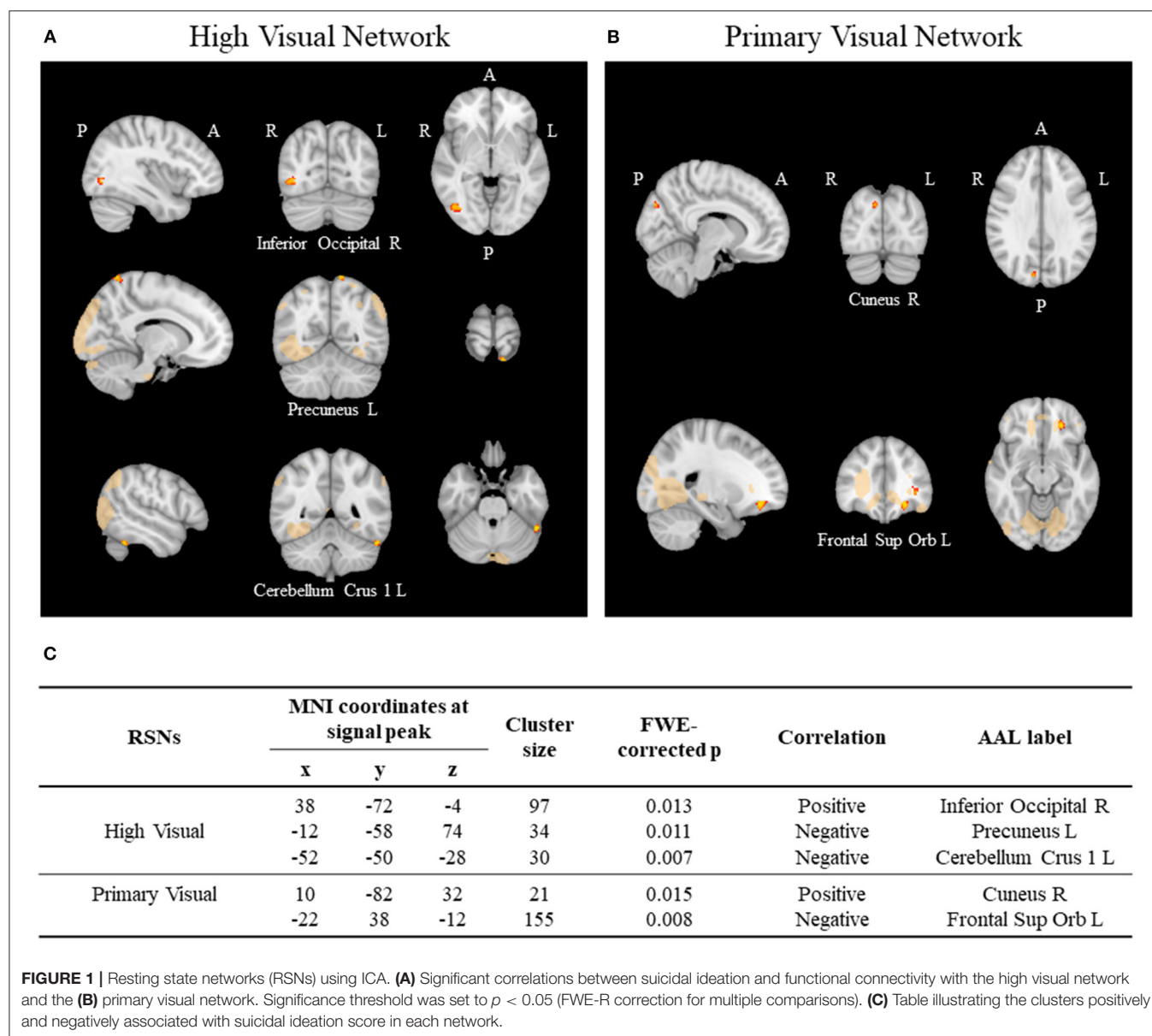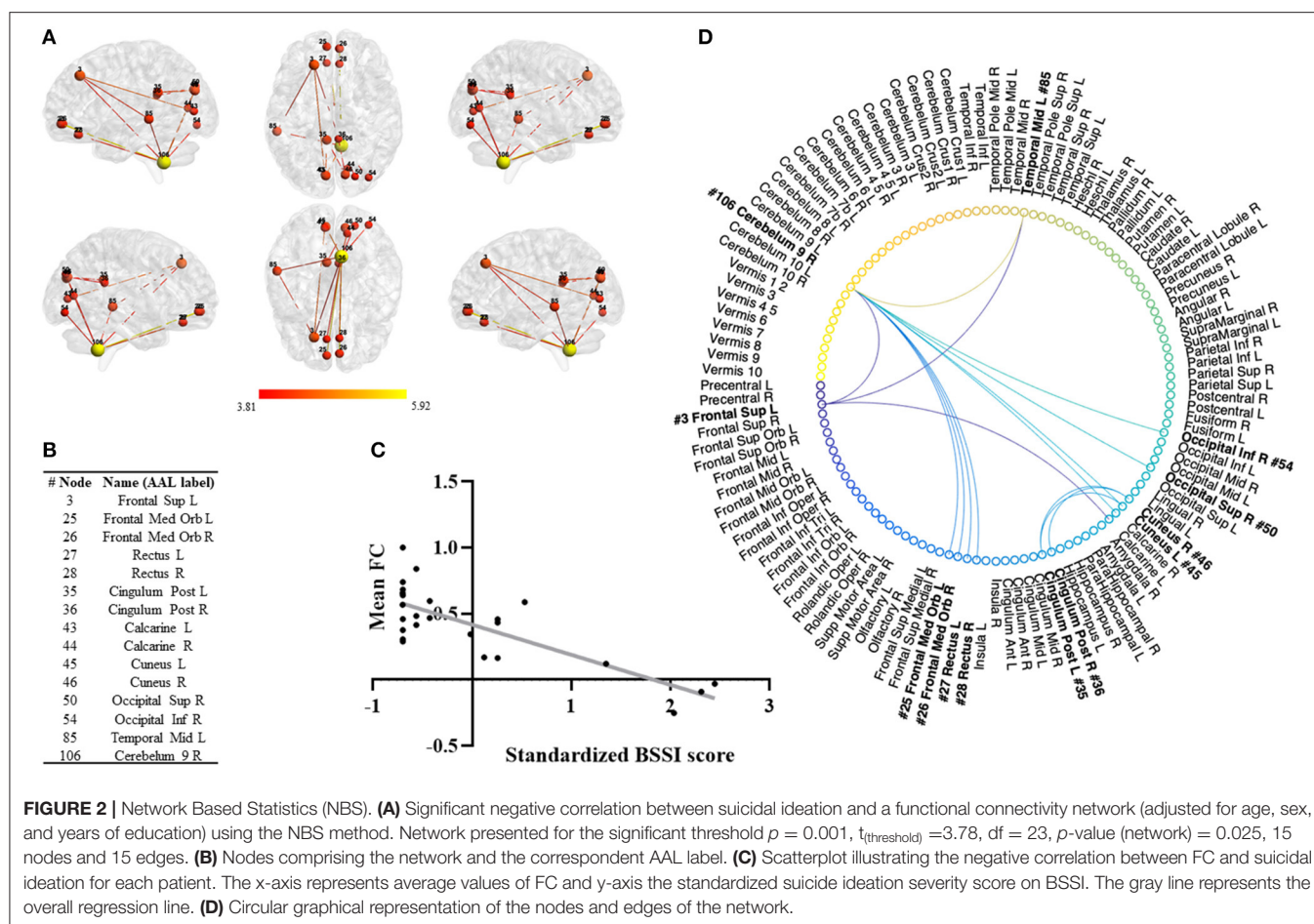The present study aimed to investigate the neuronal correlates of suicidal ideation in drug-naïve depressed patients using a multimodal MRI approach, specifically resting-state fMRI, and DTI. In our sample of MDD patients, three (12%) reported previous history of suicide attempt, whereas in previous studies including drug-naïve depressed patients 16%-20% reported suicide attempts in the past (44–46).

TABLE 1 | Demographic and psychological characterization of the sample.

	N	Mean	Std. error mean	95% CI lower	95% CI upper	Min	Max
Age (years)	25	37.44	2.47	32.35	42.53	19	59
Sex (Male/Female)	9/16						
Education (years)	25	11.64	0.99	9.6	13.68	4	20
HAM-D	25	20.72	1.45	17.72	23.72	9	33
HAM-A	25	22.96	1.77	19.3	26.62	8	40
PSS-10	25	27.36	1.07	25.15	29.57	17	36
BSSI	25	5.12	1.46	2.1	8.14	0	23
Previous SA	3						

HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; PSS-10, Perceived Stress Scale 10 items; BSSI, Beck Suicidal Ideation Scale; SA, suicide attempts; CI, confidence interval; Min, minimum; Max, maximum.
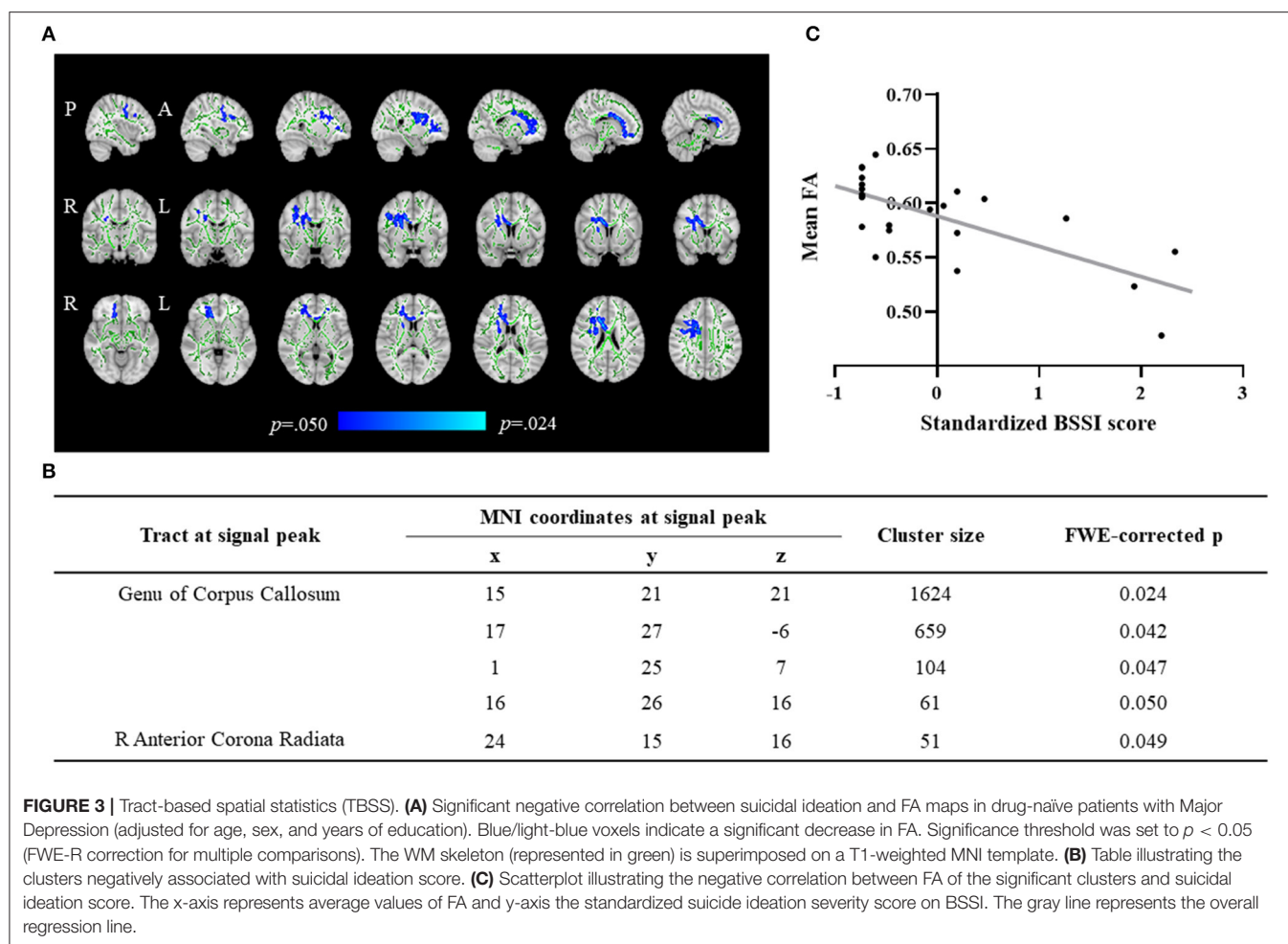

C

RSNs	MNI coordinates at signal peak			Cluster size	FWE-corrected p	Correlation	AAL label
	x	y	z				
High Visual	38	-72	-4	97	0.013	Positive	Inferior Occipital R
	-12	-58	74	34	0.011	Negative	Precuneus L
	-52	-50	-28	30	0.007	Negative	Cerebellum Crus 1 L
Primary Visual	10	-82	32	21	0.015	Positive	Cuneus R
	-22	38	-12	155	0.008	Negative	Frontal Sup Orb L

FIGURE 1 | Resting state networks (RSNs) using ICA. **(A)** Significant correlations between suicidal ideation and functional connectivity with the high visual network and the **(B)** primary visual network. Significance threshold was set to *p* < 0.05 (FWE-R correction for multiple comparisons). **(C)** Table illustrating the clusters positively and negatively associated with suicidal ideation score in each network.

FIGURE 2 | Network Based Statistics (NBS). **(A)** Significant negative correlation between suicidal ideation and a functional connectivity network (adjusted for age, sex, and years of education) using the NBS method. Network presented for the significant threshold $p = 0.001$, $t_{(threshold)} = 3.78$, df = 23, p-value (network) = 0.025, 15 nodes and 15 edges. **(B)** Nodes comprising the network and the correspondent AAL label. **(C)** Scatterplot illustrating the negative correlation between FC and suicidal ideation for each patient. The x-axis represents average values of FC and y-axis the standardized suicide ideation severity score on BSSI. The gray line represents the overall regression line. **(D)** Circular graphical representation of the nodes and edges of the network.

Our results showed that, in our cohort of MDD patients, suicidal ideation was negatively correlated with rsFC in the visual networks and FA in the genu of corpus callosum and the right anterior CR. Moreover, we identified a specific rsFC network associated with suicidal ideation that included connections between regions in the superior and orbitofrontal cortex, the cerebellum, as well as temporal and occipital regions. Moreover, patients' scores on HAM-D were not correlated with BSSI scores, suggesting that in our cohort of patients with depression, higher suicidal ideation is not associated with higher depression severity.

Regarding the functional correlates of suicidal ideation in MDD, the results in our cohort showed that suicidal ideation was correlated with functional connectivity with the visual RSN, both high and primary visual networks. These results seem to indicate a dysregulation in rsFC involving brain regions such as the right inferior occipital gyrus (positive correlation), the left precuneus and cerebellum (negative correlation) and their interaction with the regions that compose the high visual network. In accordance, the connectivity between primary visual network and the right cuneus was positively correlated with suicidal ideation. Finally, the connectivity between left frontal superior orbital gyrus and the primary visual network was negatively correlated with the suicidal ideation in MDD. These results in the RSN seem to be in line with the ones obtained using a different approach

to FC. In fact, the NBS method revealed a network of FC that was also shown to be negatively correlated with suicidal ideation in our cohort of MDD patients before the initiation of an antidepressant. The regions of this network overlap, to some extent, with the ones previously found using the typical RSNs, reinforcing the idea of their involvement in the suicidal ideation processes. The areas that compose this network range from regions involved in higher order cognitive functions (such as the medial frontal orbital gyrus, left frontal superior gyrus, posterior cingulate and rectus) to visual processing functions (such as the calcarine, superior and inferior left occipital gyrus and cuneus) and semantic and conceptual processing (left middle temporal gyrus) and motor control (cerebellum).

In a previous study using NBS, Chen et al. reported a specific network of FC that distinguished MDD patients with and without suicidal ideation (23). The reported network was composed by areas that overlap partially with the network found in our cohort, specifically the orbital frontal gyrus, the posterior cingulate cortex, the rectus, and the occipital gyrus. Moreover, another study by Kim et al., also using NBS (24), reported a network of FC that distinguished MDD patients with and without suicidal ideation. That network also presents some regions that overlap with our observations, specifically the left middle temporal gyrus, the middle frontal orbitofrontal gyrus and the superior frontal

FIGURE 3 | Tract-based spatial statistics (TBSS). **(A)** Significant negative correlation between suicidal ideation and FA maps in drug-naïve patients with Major Depression (adjusted for age, sex, and years of education). Blue/light-blue voxels indicate a significant decrease in FA. Significance threshold was set to $p < 0.05$ (FWE-R correction for multiple comparisons). The WM skeleton (represented in green) is superimposed on a T1-weighted MNI template. **(B)** Table illustrating the clusters negatively associated with suicidal ideation score. **(C)** Scatterplot illustrating the negative correlation between FA of the significant clusters and suicidal ideation score. The x-axis represents average values of FA and y-axis the standardized suicide ideation severity score on BSSI. The gray line represents the overall regression line.

gyrus. Thus, together with previous evidence, our results seem to indicate a possible involvement of a specific network of rsFC in the suicidal ideation processes.

Differently, our results showed a possible involvement of the cerebellum in the network of functional connectivity associated with suicidal ideation. The association between the cerebellum and suicidal ideation has been previously hypothesized, however its involvement in the process is still unclear. Our findings seem to be in line with previous studies that revealed that the cerebellum plays a role in higher order cognitive processes but also mood regulation in disorders such as major depression and bipolar disorder (BD) (47, 48) with reported reduced cerebellar volumes in BD patients with previous suicide attempts (49). Also in line with our results, Shaffer et al. suggested a role of the cerebellum in the neuronal circuits involved in suicidal behavior (50).

Regarding the white matter microstructure, our findings revealed that increased suicidal ideation was associated with decreased FA in the genu of corpus callosum and the anterior CR, mainly in the right hemisphere. These findings suggest that alterations in the white matter microstructure are associated with higher suicidal ideation in MDD. Taylor et al. (29) also

suggested alterations in the white matter microstructure in depressed patients with suicidal ideation, although they reported widespread alterations in CgH, superior and posterior CR, and ATR. The incongruent findings between the studies might be explained by the characteristics of the sample (first depressive episode vs. recurrent depressive episodes), previous exposure to antidepressants (drug-naïve vs. drug washout for at least 1 month), or even the characteristics of the diffusion acquisition (30 directions vs. 20 directions). Moreover, in line with our results, Chen and colleagues (30) reported decreased generalized fractional anisotropy and normalized quantitative anisotropy values in corpus callosum and anterior cingulate in depressed patients with suicidal ideation, suggesting focal alterations in the white matter integrity associated with suicidal ideation.

The genu of the corpus callosum and the anterior CR were the 2 major white matter structures displaying a significant association with suicidal ideation. The genu of the corpus callosum comprises fibers from orbital, medial, and dorsolateral frontal cortex, whereas the anterior CR is formed by thalamic and motor projections from the internal capsule to the cortex (51). Previous studies reported a decreased FA in the genu of the corpus callosum associated with an increased number

of suicide attempts in depressed and bipolar patients (52), as well as reduced number of projecting fibers from the internal capsule to orbitofrontal cortex and thalamus in depressed suicide attempters when compared with depressed controls (53). Taken together with our findings, these observations suggest that alterations in the white matter microstructure and connections of these bundles might contribute to an increased suicide risk, given its association with both suicidal ideation and behaviors. Also supporting this hypothesis, Myung and collaborators (28) described that depressed patients with suicidal ideation present a reduced structural connectivity in a specific network, including the orbitofrontal cortex and thalamus.

The present work has expanded our knowledge into the possible neuronal correlates of suicidal ideation in MDD patients before antidepressant medication is initiated. Besides the alterations in the white-matter integrity (in the genu of corpus callosum and the right anterior CR), our results also revealed abnormal functional connectivity in the visual RSN but also in a specific network composed by frontal, cerebellar, occipital, and parietal regions. Importantly, in our cohort of MDD patients, suicidal ideation was not found to be associated with worse depression severity and thus suggesting that these results were specific to suicidal ideation. It is often difficult to separate the suicidal ideation process from factors such as disease severity, duration of illness and medication status as these variables are often clinically linked and not independent.

The present study presents some important limitations, first being the limited sample size and the strength of the MRI magnetic field being 1.5 Tesla that limited the quality of the signal and the number of directions considered in the DTI acquisitions, as well as the absence of a control group. Due to these limitations, caution should be applied when interpreting these results as more studies should be done in the sense of replication of the patterns presented in this paper. The present study shared some light into the brain alterations associated with suicidal ideation in MDD patients. Such knowledge could be at use in the guidance of better treatments that could target deregulations linked to suicidal ideation in MDD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Hospital of Braga and Ethics Committee of University of Minho. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.838111/full#supplementary-material

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