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Research paper

Prevalence of suicidality in clinically stable patients with major depressive disorder during the COVID-19 pandemic



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ABSTRACT

Background: The COVID-19 pandemic is associated with an increased risk of mental health problems including suicide in many subpopulations, but its influence on stable patients with major depressive disorder (MDD) has been studied fleetingly. This study examined the one-year prevalence of suicidality including suicidal ideation (SI), suicide plans (SP), and suicide attempts (SA) as well as their correlates in clinically stable MDD patients during the COVID-19 pandemic.

Methods: A cross-sectional, observational study was conducted between October 1, 2020, and October 15, 2021, in six tertiary psychiatric hospitals. Socio-demographic information, clinical data and one-year prevalence of suicidality were recorded.

Results: Altogether, 1718 participants who met the eligibility criteria were included. The overall one-year prevalence of suicidality during the COVID-19 pandemic was 68.04% (95% confidence intervals (CI) = 65.84–70.25%), with one-year SI prevalence of 66.4% (95%CI = 64.18–68.65%), SP prevalence of 36.26% (95%CI = 33.99–38.54%), and SA prevalence of 39.35% (95%CI = 37.04–41.66%). Binary logistic regression analyses revealed male gender, married marital status, college education level and above and age were negatively associated with risk of suicidality. Urban residence, unemployed work status, experiences of cyberbullying, a history of suicide among family members or friends, and more severe fatigue, physical pain, and residual depressive symptoms were positively associated with risk of suicidality.

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Conclusions: Suicidality is common among clinically stable MDD patients during the COVID-19 pandemic. Regular suicide screening and preventive measures should be provided to clinically stable MDD patients during the pandemic.

1. Introduction

Suicide is a major global public health challenge. The WHO estimated that the global suicide rate is around 10.6 per 100,000 population (7.7 for females and 13.5 for males) (World Health Organization, 2020). Suicidality reflects a continuum that includes suicidal ideation (SI), suicide plans (SP), suicide attempts (SA) and suicide. SI, SP, and SA, respectively, refer to thoughts or wishes about ending one's life, making plans to end one's life, and self-destructive actions with at least some intent to end one's own life (Kao et al., 2012; Posner et al., 2007). Compared to other psychiatric disorders, major depressive disorder (MDD) is more likely to cause suicidality (Hawton et al., 2013). Approximately 90% of suicide victims suffer from one or more mental illnesses (Cavanagh et al., 2003; Nordentoft et al., 2011), with MDD alone accounting for 59–87% of all suicides (Cavanagh et al., 2003; Nordentoft et al., 2011). A meta-analysis revealed that global prevalence rates of SI, SP and SA among MDD patients are 37.7% (95% CI = 32.3–43.4%), 15.1% (95% CI = 8.0–26.8%) (Cai et al., 2021) and 31% (95%CI = 27–34%) (Dong et al., 2019), respectively.

The COVID-19 pandemic itself and related negative outcomes such as social isolation and economic recession are associated with increased likelihood of mental health problems (Zhao et al., 2021) that may increase risk of suicidality (Reger et al., 2020; Sinyor et al., 2021). Previous studies have found that the overall prevalence of SI is 16.4% in the general population of China during the COVID-19 pandemic (Shi et al., 2021). Moreover, 19.2% of veterans with pre-existing psychiatric conditions in the US screened positive for SI during the peri-pandemic period (Na et al., 2021). A multivariable analysis has also linked greater pre-pandemic psychiatric symptom severity, past-year SI, lifetime SA, psychosocial difficulties, COVID-19 infection, and past-year increases in psychiatric symptom severity to peri-pandemic SI (Na et al., 2021). In addition, individuals with psychiatric disorders have a 1.64-fold higher risk of SI compared to those without disorders (Papadopoulou et al., 2021).

One limitation of the literature on suicidality during the COVID-19 pandemic is that studies have tended to focus exclusively upon SI (Na et al., 2021; Shi et al., 2021), even though suicidality also comprises SP and SA (Tuisku et al., 2006). In addition, studies have tended to assess risk in heterogeneous populations so less is known about prevalence and predictors within certain diagnostic groups such as people with MDD. Although evaluating suicidality is an integral part of suicide risk assessment and prevention for patients with MDD, we could not identify studies that considered prevalence of SI, SP and SA in MDD patients during the COVID-19 pandemic, particularly among those who are clinically stable and account for the majority of this population. To reduce the risk of future suicide in patients with MDD, it is important to document the pattern of suicidality and its correlates in a more comprehensive manner.

In this study, we examined the one-year prevalence of SI, SP and SA in clinically stable MDD patients during the COVID-19 pandemic as well as sociodemographic, psychiatric, and well-being correlates of suicidality in this population. We hypothesized that SI, SP and SA in clinically stable MDD patients during the COVID-19 pandemic would be more common compared to the corresponding figures documented in this subpopulation prior to the pandemic.

2. Method

2.1. Study design

This was a cross-sectional, observational study conducted between October 1, 2020 and October 15, 2021 in six tertiary psychiatric hospitals distributed in east, west, south, and north regions of China (i.e., Beijing, Guangxi, Jiangsu, Fujian, Gansu, and Anhui). All patients who attended outpatient and inpatient services in participating psychiatric hospitals during the study period were consecutively invited to participate in this study. Patients were invited to scan a Quick Response code (QR Code) linked to the study introduction and invitation with their own or a guardian's smartphone. After providing electronic written informed consent, patients could access the data collection form and questionnaire. To be eligible, participants needed to meet the following criteria: 1) aged 18 years or older, 2) diagnosed with MDD, 3) able to read and understand Chinese, and 4) clinically stable as judged by their psychiatrists. Based on previous studies (Lobana et al., 2001; Ma et al., 2020), "clinically stable" is defined as a change in the dose of antidepressant medications that is less than 50% during the past three months based on a comparison between the highest and lowest antidepressant doses. The study protocol was centrally approved by the ethics committees of Beijing Anding Hospital and other participating hospitals.

2.2. Data collection and measures

Socio-demographic data collected using a pre-designed data collection sheet, included gender, age, place of residence, marital status, living with family or alone, employment status, health insurance, education level, perceived health status, subjective economic status, family history of psychiatric disorders, experience of cyberbullying, and history of suicide among family members or friends. Following previous studies (Li et al., 2017), SI was assessed with a standard question ("Over the past year, have you thought that you would be better off dead?") that included a binary response option (yes/no). SP was assessed with a standard question ("Over the past year, have you made a plan for suicide?") featuring a binary response option (yes/no). SA was evaluated with a standard question ("Over the past year, have you attempted suicide?"), including a binary response option (yes/no). If a patient responded "yes" to any of the above three questions, he or she was defined as "having suicidality".

Severity of residual depressive symptoms was measured using the validated Chinese version of the Patient Health Questionnaire-2 (PHQ-2) (Kroenke et al., 2003; Liu et al., 2016). PHQ-2 total scores ranged from 0 to 6, with higher scores representing more severe depressive symptoms. Severity of fatigue was assessed using a single item fatigue numeric rating scale with options ranging from '0' (no fatigue) to '10' (extreme fatigue) (Gladman et al., 2020). Severity of physical pain was measured using a one-item Visual Analog Scale for Pain (VAS) (Hawker et al., 2011) with anchors of '0' (no pain at all) and '10' (worst pain imaginable). Finally, global quality of life (QOL) was measured with the first 2 items of the World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF): "How do you assess your quality of life?" and "Are you satisfied with your current health?" (Cheung et al., 2019; Skevington et al., 2004). Higher scores reflected better QOL.

2.3. Statistical analysis

2.3.1. Univariate and multivariate analyses

Data analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA). Distributions of all continuous variables were checked for normality using P–P plots. Chi-square tests, independent samples *t*-tests, and Mann-Whitney *U* tests were used, as appropriate, to compare MDD patients with suicidality versus those without suicidality in terms of sociodemographic and clinical variables. Analysis of covariance (ANCOVA) was used to compare QOL between patients with and without suicidality after adjusting for variables with significant group differences in univariate analyses. Binary logistic regression analyses with the “enter” method were used to examine independent correlates of suicide behaviors. SI, SP, and SA were entered as separate dependent variables while measures with significant suicidality versus no suicidality group differences in univariate analyses were independent variables after controlling for the impact of study site on responses. The level of significance level was set as $p < 0.05$ (two-tailed).

3. Results

3.1. Social-demographic and clinical characteristics

Altogether, 1749 patients were invited to participate in the survey during the predefined study period. Of these, 1718 met eligibility criteria and were included, generating a participation rate of 97.9%. Socio-demographic and clinical characteristics of participants are presented in Table 1. The overall one-year prevalence of suicidality during the COVID-19 pandemic was 68.04% (95%CI = 65.84–70.25%), with a SI prevalence of 66.4% (95%CI = 64.18–68.65%), SP prevalence of 36.26% (95%CI = 33.99–38.54%), and SA prevalence of 39.35% (95%CI = 37.04–41.66%).

Table 2 presents results of binary logistic regression analyses. Male gender was negatively associated with SI (OR = 0.648, 95%CI = 0.503–0.835, $P = 0.001$), SP (OR = 0.699, 95%CI = 0.542–0.903, $P = 0.006$) and SA (OR = 0.767, 95%CI = 0.599–0.982, $P = 0.036$). “Married” relationship status was negatively associated with SI (OR = 0.530, 95%CI = 0.383–0.736, $P < 0.001$) and SP (OR = 0.620, 95%CI = 0.438–0.876, $P = 0.007$). “College and above” education level was negatively associated with SP (OR = 0.765, 95%CI = 0.597–0.980, $P = 0.034$) and SA (OR = 0.725, 95%CI = 0.570–0.924, $P = 0.009$). In addition, age was negatively associated with SI (OR = 0.972, 95%CI = 0.953–0.991, $P = 0.004$), SP (OR = 0.967, 95%CI = 0.949–0.986, $P < 0.001$) and SA (OR = 0.959, 95%CI = 0.941–0.978, $P < 0.001$).

Urban residence was positively associated with SI (OR = 1.450, 95%CI = 1.117–1.882, $P = 0.005$) and SP (OR = 1.468, 95%CI = 1.132–1.908, $P = 0.004$). “Unemployed” work status was positively associated with SI (OR = 1.404, 95%CI = 1.081–1.823, $P = 0.011$), SP (OR = 1.790, 95%CI = 1.370–2.340, $P < 0.001$) and SA (OR = 1.582, 95%CI = 1.221–2.050, $P = 0.001$). Reports of being a victim of cyberbullying were positively associated with SP (OR = 1.703, 95%CI = 1.204–2.411, $P = 0.003$). History of suicide among family members or friends were positively associated with SI (OR = 4.126, 95%CI = 2.898–5.875, $P < 0.001$), SP (OR = 2.248, 95%CI = 1.743–2.899, $P < 0.001$) and SA (OR = 2.230, 95%CI = 1.732–2.870, $P < 0.001$). More severe fatigue was associated with higher risk of SI (OR = 1.109, 95%CI = 1.044–1.177, $P = 0.001$), SP (OR = 1.129, 95%CI = 1.062–1.201, $P < 0.001$) and SA (OR = 1.091, 95%CI = 1.028–1.158, $P = 0.004$). More severe physical pain scores were associated with higher risk of SP (OR = 1.058, 95%CI = 1.004–1.115, $P = 0.035$) and SA (OR = 1.068, 95%CI = 1.015–1.123, $P = 0.011$). PHQ-2 total scores were positively associated with SI (OR = 1.196, 95%CI = 1.111–1.289, $P < 0.001$), SP (OR = 1.101, 95%CI = 1.025–1.184, $P = 0.009$) and SA (OR = 1.097, 95%CI = 1.022–1.177, $P = 0.010$) (Table 2).

ANCOVAs revealed that, even after controlling for significant correlates of suicidality in univariate analyses, significantly lower QOL

scores were observed among MDD patients with SI ($F_{(1, 1718)} = 54.875$, $P < 0.001$), SP ($F_{(1, 1718)} = 54.849$, $P < 0.001$), and SA ($F_{(1, 1718)} = 55.037$, $P < 0.001$) compared to those without suicidality.

4. Discussion

To the best of our knowledge, this was the first study to examine the one-year prevalence and correlates of suicidality in clinically stable patients with MDD during the COVID-19 pandemic. The overall one-year prevalence of suicidality during the COVID-19 pandemic was 68.04% (95%CI = 65.84–70.25%), with SI, SP and SA rates of 66.4% (95%CI = 64.18–68.65%), 36.26% (95%CI = 33.99–38.54%), and 39.35% (95%CI = 37.04–41.66%), respectively. Our prevalence findings were substantially higher than corresponding figures among MDD patients prior to the COVID-19 pandemic. For instance, previous studies found that the pre-pandemic one-year prevalence of SI, SP, and SA among MDD patients were 20.3% (Omary, 2020), 14.4% (Lee et al., 2020), and 2.7% (Hegerl et al., 2013), respectively. A meta-analysis found that prevalence rates of SI, SP, and SA were 37.7% (95%CI = 32.3–43.4%), 15.1% (95%CI = 8.0–26.8%) (Cai et al., 2021a) and 31% (95%CI = 27–34%) among MDD patients prior to the pandemic (Cai et al., 2021; Dong et al., 2019), respectively. In addition, the prevalence of SI in our sample was elevated compared to rates in a U.S. sample of veterans with pre-existing psychiatric conditions (19.2%) and a general population sample (16.4%) from China during the COVID-19 pandemic (Na et al., 2021; Shi et al., 2021). It should be noted that the timeframes are different between studies; therefore, the direct comparisons should be made with caution.

As such, our findings underscore how the one-year suicidality rate in MDD patients is noticeably elevated during the COVID-19 pandemic even though respondents were clinically stable. There are several possible reasons for these elevations. First, some clinically stable patients may have experienced deteriorations in mental and/or physical health conditions as maintenance treatments were interrupted or discontinued due to insufficient access to hospital services during the pandemic (Li et al., 2020). Second, to reduce the risk of COVID-19 infection, strict public health measures were adopted in many countries including China. Such lockdowns may have increased social isolation, loneliness, personal and economic losses, all of which could increase the risk of suicidality, particularly within at-risk groups such as MDD patients (Gunnell et al., 2020; Moutier, 2021; Reger et al., 2020).

Female gender, younger age, and unmarried relationship status were associated with higher risk of suicidality among MDD patients in this study. Gender differences exist in the psychopathology, prevalence and course of depression, behaviors of seeking help, and the response to treatment among MDD patients (Gagne et al., 2014; Picco et al., 2017). Previous studies have implicated biological susceptibility (e.g., higher levels of inflammatory, neurotrophic, and serotonergic markers in women (Labaka et al., 2018)), higher risk of sexual and physical abuse, lower self-esteem, more severe interpersonal violence, and exposure to stress associated with gender inequity as factors that contribute to higher risk of suicidality among women, at least with reference to attempts (Riecher-Rössler, 2017). Compared with their older counterparts, younger MDD patients were also more likely to have suicidality, which aligns with previous findings indicating that younger people are more prone than older cohorts to depression, anxiety, insomnia, acute stress, and suicidality related to attempts (Shi et al., 2020; Shi et al., 2021). Furthermore, social isolation and lack of physical activity during the COVID-19 pandemic may increase the likelihood of suicidality in younger people (Shi et al., 2021; Vancampfort et al., 2018). Unmarried MDD patients were more likely to report suicidality during the COVID-19 pandemic, which is consistent with some (Fitzpatrick et al., 2020; Islam et al., 2021) but not studies (Na et al., 2021). For instance, two studies found that unmarried persons reported higher suicidality compared to married peers (Fitzpatrick et al., 2020; Islam et al., 2021). Conversely, among U.S. veterans with pre-existing psychiatric problems,

Table 1
Demographic and clinical characteristics of participants.

Variables	Total (N = 1718)	Suicidal ideation					Suicide plan					Suicide attempt							
		No (N = 577)		Yes (N = 1141)	Statistics			No (N = 1095)		Yes (N = 623)	Statistics			No (N = 1042)		Yes (N = 676)	Statistics		
		N (%)	N (%)	N (%)	χ^2	df	P	N (%)	N (%)	χ^2	df	P	N (%)	N (%)	χ^2	df	P		
Male gender	479 (27.9)	191 (33.1)	288 (25.2)	11.778	1	0.001	335 (30.6)	144 (23.1)	11.048	1	0.001	317 (30.4)	162 (24.0)	8.503	1	0.004			
Urban	1205 (70.1)	371 (64.3)	834 (73.1)	14.155	1	<0.001	742 (67.8)	463 (74.3)	8.147	1	0.004	726 (69.7)	479 (70.9)	0.275	1	0.600			
Married	685 (39.9)	349 (60.5)	336 (29.4)	153.980	1	<0.001	552 (50.4)	133 (21.3)	139.896	1	<0.001	527 (50.6)	158 (23.4)	126.556	1	<0.001			
College and above	893 (52.0)	274 (47.5)	619 (54.3)	7.023	1	0.008	574 (52.4)	319 (51.2)	0.235	1	0.628	555 (53.3)	338 (50.0)	1.749	1	0.186			
Living with family numbers	1328 (77.3)	474 (82.1)	854 (74.8)	11.645	1	0.001	865 (79.0)	463 (74.3)	4.951	1	0.026	823 (79.0)	505 (74.7)	4.277	1	0.039			
Unemployed	992 (57.7)	254 (44.0)	738 (64.7)	67.030	1	<0.001	533 (48.7)	459 (73.7)	101.708	1	<0.001	502 (48.2)	490 (72.5)	99.291	1	<0.001			
Health insurance	1400 (81.5)	495 (85.8)	905 (79.3)	10.642	1	0.001	912 (83.3)	488 (78.3)	6.469	1	0.011	883 (84.7)	517 (76.5)	18.553	1	<0.001			
Poor perceived health status	1446 (84.2)	471 (81.6)	975 (85.5)	4.201	1	0.040	914 (83.5)	532 (85.4)	1.102	1	0.294	856 (82.1)	590 (87.3)	8.092	1	0.004			
Poor perceived economic status	1590 (92.5)	530 (91.9)	1060 (92.9)	0.609	1	0.435	1016 (92.8)	574 (92.1)	0.244	1	0.622	960 (92.1)	630 (93.2)	0.674	1	0.412			
Family history of psychiatric disorders	155 (9.0)	41 (7.1)	114 (10.0)	3.887	1	0.049	83 (7.6)	108 (17.3)	38.244	1	<0.001	90 (8.6)	65 (9.6)	0.478	1	0.489			
Cyberbullying	191 (11.1)	39 (6.8)	152 (13.3)	16.702	1	<0.001	88 (8.0)	67 (10.8)	3.574	1	0.059	91 (8.7)	100 (14.8)	15.236	1	<0.001			
Inpatients	210 (12.2)	65 (11.3)	145 (12.7)	0.744	1	0.388	138 (12.6)	72 (11.6)	0.405	1	0.525	120 (11.5)	90 (13.3)	1.234	1	0.267			
Family members or friends' suicide	414 (24.1)	44 (7.6)	370 (32.4)	128.879	1	<0.001	178 (16.3)	236 (37.9)	101.527	1	<0.001	168 (16.1)	246 (36.4)	92.081	1	<0.001			
	Mean (SD)	Mean (SD)	Mean (SD)	t/Z	df	P	Mean (SD)	Mean (SD)	t/Z	df	P	Mean (SD)	Mean (SD)	t/Z	df	P			
Age (Years)	31.59 (14.43)	38.22 (15.38)	28.23 (12.67)	14.338	1716	<0.001	34.94 (14.99)	25.69 (11.16)	13.437	1716	<0.001	35.26 (15.01)	25.93 (11.37)	13.787	1716	<0.001			
First age of onset (years)	29.71 (14.66)	35.65 (15.21)	26.71 (13.41)	12.468	1716	<0.001	32.72 (14.77)	24.43 (12.86)	11.722	1716	<0.001	32.92 (14.77)	24.77 (13.03)	11.706	1716	<0.001			
Fatigue	5.53 (2.51)	4.60 (2.50)	6.00 (2.39)	-11.189	1716	<0.001	5.07 (2.50)	6.34 (2.34)	-10.314	—*	<0.001	5.08 (2.49)	6.23 (2.39)	-9.628	—*	<0.001			
Physical pain	3.08 (2.49)	2.59 (2.42)	3.33 (2.48)	-6.237	—*	<0.001	2.78 (2.39)	3.62 (2.56)	-6.832	—*	<0.001	2.74 (2.37)	3.61 (2.57)	-7.099	—*	<0.001			
PHQ-2 total	3.11 (1.90)	2.46 (1.84)	3.44 (1.84)	-10.043	—*	<0.001	2.84 (1.89)	3.59 (1.82)	-7.868	—*	<0.001	2.82 (1.87)	3.54 (1.85)	-7.548	—*	<0.001			
Global QOL	5.04 (1.70)	5.37 (1.68)	4.87 (1.69)	5.803	1716	<0.001	5.18 (1.68)	4.80 (1.71)	4.492	1716	<0.001	5.23 (1.66)	4.76 (1.73)	5.613	1716	<0.001			

Bolded values: <0.05; M: mean; SD: standard deviation; PHQ-2: 2-item Patient Health Questionnaire; QOL: Quality of Life; * Mann-Whitney U test.

Table 2
Independent correlates of suicidality by multiple logistic regression analyses.

Variables	Suicidal ideation			Suicide plan			Suicide attempt		
	P values	OR	95%CI	P values	OR	95%CI	P values	OR	95%CI
Male gender	0.001	0.648	0.503–0.835	0.006	0.699	0.542–0.903	0.036	0.767	0.599–0.982
Urban	0.005	1.450	1.117–1.882	0.004	1.468	1.132–1.908	0.590	1.071	0.834–1.377
Married	<0.001	0.530	0.383–0.736	0.007	0.620	0.438–0.876	0.061	0.727	0.521–1.015
College and above	0.726	0.954	0.733–1.242	0.034	0.765	0.597–0.980	0.009	0.725	0.570–0.924
Living with family numbers	0.118	1.286	0.938–1.763	0.227	1.192	0.897–1.583	0.203	1.198	0.907–1.584
Unemployed	0.011	1.404	1.081–1.823	<0.001	1.790	1.370–2.340	0.001	1.582	1.221–2.050
Health insurance	0.932	0.986	0.717–1.357	0.318	1.155	0.871–1.532	0.393	0.887	0.672–1.169
Poor perceived health status	0.705	0.940	0.682–1.296	0.302	1.186	0.858–1.642	0.174	0.801	0.582–1.103
Family history of psychiatric disorders	0.384	1.208	0.790–1.848	0.315	1.215	0.831–1.778	0.814	0.956	0.657–1.392
Cyberbullying	0.176	1.334	0.878–2.027	0.003	1.703	1.204–2.411	0.520	1.119	0.794–1.578
Family members or friends' suicide	<0.001	4.126	2.898–5.875	<0.001	2.248	1.743–2.899	<0.001	2.230	1.732–2.870
Age (Years)	0.004	0.972	0.953–0.991	0.001	0.967	0.949–0.986	<0.001	0.959	0.941–0.978
First age of onset (years)	0.812	1.002	0.984–1.020	0.620	1.004	0.988–1.020	0.376	1.007	0.991–1.024
Fatigue	0.001	1.109	1.044–1.177	<0.001	1.129	1.062–1.201	0.004	1.091	1.028–1.158
Physical pain	0.298	1.030	0.974–1.088	0.035	1.058	1.004–1.115	0.011	1.068	1.015–1.123
PHQ-2 total	<0.001	1.196	1.111–1.289	0.009	1.101	1.025–1.184	0.010	1.097	1.022–1.177

Bolded values: <0.05; CI: confidential interval; OR: odds ratio; PHQ-2: 2-item Patient Health Questionnaire.

marital status did not influence suicidality during the COVID-19 pandemic (Na et al., 2021).

We found that urban residence, unemployment, and having history of suicide among family members or friends were associated with higher risk of suicidality. MDD patients living in urban appeared more prone to having suicidality during the COVID-19 pandemic, which replicates the positive association between urban living and suicidality found among Bangladeshi university students during the COVID-19 pandemic (Tasnim et al., 2020). Compared to those in rural areas, urban residents may experience more disruptions to daily life due to suspended public services such as public transportation, which may further worsen their psychiatric symptoms and increase the risk of suicidality. Unemployed patients were more likely to report suicidality, as a probable result of significant economic losses during the pandemic (Gunnell et al., 2020) and the deprivation of important psychosocial needs that employment provides (Zechmann and Paul, 2019). The relationship between unemployment and increased suicidality has been well documented previously (Fergusson et al., 2007; Lee et al., 2018). MDD patients who reported a history of suicide among family members or friends had higher risk of suicidality, which is consistent with previous findings. MDD patients may have learned maladaptive responses to coping with stressors from observing responses of significant others (Nanayakkara et al., 2013; Tasnim et al., 2020). Conversely, genetic susceptibility may also increase risk. A study on genetic factors and their relationships with behavioral and clinical factors among depressed patients with or without suicides revealed that the STin2 locus might contribute to the observed familial aggregation of suicidal behavior (de Lara et al., 2006).

During the COVID-19 pandemic, due to a range of public health measures, Internet use and online activities have increased sharply (Dost et al., 2020) for both professional and personal purposes (Hawdon et al., 2020). Increased Internet use could also increase risk for being a target of cyberbullying. Cyberbullying is associated with a range of negative outcomes in victims, including physical comorbidities and psychological distress (Al Qudah et al., 2020; Sampasa-Kanyinga et al., 2018), impaired social functioning, poor quality of clinical care, lowered QOL (Diomidous et al., 2016; Hellfeldt et al., 2019) and even higher risk of suicidality (Hinduja and Patchin, 2010). In this study, we found that MDD patients who were targets of cyberbullying were more likely to experience suicidality during the pandemic.

As expected, elevations in current fatigue, pain, and residual depressive symptoms were associated with higher risk of suicidality among MDD patients in this study; these data support the notion that more severe somatic symptoms and psychiatric problems increase risk of suicidality in MDD patients (Park et al., 2010; Zalpuri and Rothschild, 2016). Recent findings also indicate that more severe psychiatric

symptoms are linked to higher suicide risk in both the general population and those with pre-existing psychiatric conditions during the pandemic (Fitzpatrick et al., 2020; Na et al., 2021). Residual psychiatric symptoms such as fatigue, pain, and depressive symptoms may be reflections of past suicidality or serve as prognosticators for worse outcomes, including increased risk for relapse, recurrence, and suicidality (Judd et al., 2000; Kennedy and Paykel, 2004). Hence, these symptoms should be addressed in maintenance treatment and rehabilitation for clinically stable psychiatric patients during the pandemic.

In this study, MDD patients who had suicidality reported lower overall QOL scores compared to those who did not experience suicidality. Psychiatric patients with suicidality often have lower socioeconomic status (e.g., low income), poor social support, and more severe physical problems (Fergusson et al., 2007; Fitzpatrick et al., 2020; Lee et al., 2020; Na et al., 2021). Therefore, it is reasonable to assume that patients with suicidality were more likely to have lower QOL in line with our results, which echo previous findings (Asrat et al., 2020; Li et al., 2017; Woo et al., 2014; Zhou et al., 2017).

The strengths of this study included its large sample size, a multi-center study design from different regions of China that could increase the representativeness of the study sample, and the assessment of suicidal ideation, planning, and attempts, rather than a single index of suicidality during the COVID-19 pandemic. However, its main limitations should be noted as well. First, due to the cross-sectional study design, causal relationships between suicidality and other variables (e.g., fatigue, pain, depression and QOL) could not be established. Second, for logistical reasons, participants were recruited based on a consecutive sampling, rather than a random sampling method, which may limit the generalizability of the findings. Third, this study focused on clinically stable MDD patients; therefore the findings could not be generalized to less clinically stable or remitted patients with MDD. Fourth, potentially important influences, such as the use of psychotropic medications and perceived social support, were not assessed in an effort to maintain reasonable response burdens for unpaid research volunteers. Fifth, because the study was initiated as a direct response to the COVID-19 pandemic, pre-pandemic rates of suicidality were not assessed and changes in rates as a result of the pandemic could not be assessed directly within the current sample. Future prospective studies should be conducted to facilitate comparisons of suicidality between different stages of the COVID-19 pandemic. Finally, although different sociocultural and economic contexts between study sites could bias results to an uncertain extent, study site was used as a covariate in multiple logistic regression analyses to control for related confounding effects.

In conclusion, this study found that suicidality is common among clinically stable MDD patients during the COVID-19 pandemic with

notably higher rates than those from similar studies conducted prior to the pandemic. In addition, particular demographic factors and measures of distress severity were identified as associated factors of suicidality. Together, these findings provide a comprehensive profile of suicidality in the MDD patients and highlight the importance of regularly screening for suicidality (e.g., at least once per month and in response to significant stressors in patients' lives) using relevant interviewer-rated or self-reported standardized questions and/or scales as well as the need for ongoing clinical care, even when MDD patients are clinically stable during the pandemic. Timely effective treatments are critical for those who experience suicidality during pandemics.

CRedit authorship contribution statement

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Conflict of Interest

The authors have no conflicts of interest to declare.

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References

- Al Qudah, M.F., Al-Barashdi, H.S., Hassan, E., Albursan, I.S., Heilat, M.Q., Bakhtiet, S.F. A., Al-Khadher, M.A., 2020. Psychological security, psychological loneliness, and age as the predictors of cyber-bullying among university students. *Community Ment. Health J.* 56 (3), 393–403.
- Asrat, B., Lund, C., Ambaw, F., Garman, E.C., Schneider, M., 2020. Major depressive disorder and its association with adherence to antiretroviral therapy and quality of life: cross-sectional survey of people living with HIV/AIDS in Northwest Ethiopia. *BMC Psychiatry* 20 (1), 1–13.
- Cai, H., Jin, Y., Liu, S., Zhang, Q., Zhang, L., Cheung, T., Balbuena, L., Xiang, Y.-T., 2021. Prevalence of suicidal ideation and planning in patients with major depressive disorder: a meta-analysis of observation studies. *J. Affect. Disord.* 293, 148–158.
- Cavanagh, J.T.C., A. J., Sharpe, M., Lawrie, S.M., 2003. Psychological autopsy studies of suicide: a systematic review. *Psychol. Med.* 33 (3), 395–405.
- Cheung, Y.B., Yeo, K.K., Chong, K.J., Khoo, E.Y.H., Wee, H.L., 2019. Measurement equivalence of the english, chinese and malay versions of the World Health Organization quality of life (WHOQOL-BREF) questionnaires. *Health Qual. Life Outcomes* 17 (1), 67.
- Diomidous, M., Chardalias, K., Magita, A., Koutonias, P., Panagiotopoulou, P., Mantas, J., 2016. Social and psychological effects of the internet use. *Acta Inform. Med.* 24 (1), 66–68.
- Dong, Zeng, L.N., Lu, L., Li, X.H., Ungvari, G.S., Ng, C.H., Chow, I.H.I., Zhang, L., Zhou, Y., Xiang, Y.T., 2019. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. *Psychol. Med.* 49 (10), 1691–1704.
- Dost, S., Hossain, A., Shehab, M., Abdelwahed, A., Al-Nusair, L., 2020. Perceptions of medical students towards online teaching during the COVID-19 pandemic: a national cross-sectional survey of 2721 UK medical students. *BMJ Open* 10 (11), e042378.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2007. Unemployment and suicidal behavior in a New Zealand birth cohort: a fixed effects regression analysis. *Crisis* 28 (2), 95–101.
- Fitzpatrick, K.M., Harris, C., Drawwe, G., 2020. How bad is it? Suicidality in the middle of the COVID-19 pandemic. *Suicide Life Threat. Behav.* 50 (6), 1241–1249.
- Gagne, S.V., H. M., Preville, M., 2014. Gender differences in general and specialty outpatient mental health service use for depression. *BMC Psychiatry* 14, 135.
- Gladman, D., Nash, P., Goto, H., Birt, J.A., Lin, C.-Y., Orbai, A.-M., Kvien, T.K., 2020. Fatigue numeric rating scale validity, discrimination and responder definition in patients with psoriatic arthritis. *RMD Open* 6 (1), e000928.
- Gunnell, D., Appleby, L., Arensman, E., Hawton, K., John, A., Kapur, N., Khan, M., O'Connor, R.C., Pirkis, J., Caine, E.D., 2020. Suicide risk and prevention during the COVID-19 pandemic. *Lancet Psychiatry* 7 (6), 468–471.
- Hawdon, J., Parti, K., Dearden, T.E., 2020. Cybercrime in America amid COVID-19: the initial results from a natural experiment. *Am. J. Crim. Justice* 1–17.
- Hawker, G.A., Mian, S., Kendzerska, T., French, M., 2011. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short-Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res.* 63 (Suppl. 11), S240–S252.
- Hawton, K., i Comabella, C.C., Haw, C., Saunders, K., 2013. Risk factors for suicide in individuals with depression: a systematic review. *J. Affect. Disord.* 147 (1–3), 17–28.
- Hegerl, U., Mergl, R., Quail, D., Schneider, E., Strauß, M., Hundemer, H.-P., Linden, M., 2013. Fast versus slow onset of depressive episodes: a clinical criterion for subtyping patients with major depression. *Eur. Psychiatry* 28 (5), 288–292.
- Hellfeldt, K., López-Romero, L., Andershed, H., 2019. Cyberbullying and psychological well-being in young adolescence: the potential protective mediation effects of social support from family, friends, and teachers. *Int. J. Environ. Res. Public Health* 17 (1).
- Hinduja, S., Patchin, J.W., 2010. Bullying, cyberbullying, and suicide. *Archiv. Suicide Res.* 14 (3), 206–221.
- Islam, M.S., Tasnim, R., Sujana, M.S.H., Ferdous, M.Z., Sikder, M.T., Masud, J.H.B., Kundu, S., Tahsin, P., Mosaddek, A.S.M., Griffiths, M.D., 2021. Depressive symptoms associated with COVID-19 preventive practice measures, daily activities in home quarantine and suicidal behaviors: findings from a large-scale online survey in Bangladesh. *BMC Psychiatry* 21 (1), 1–12.
- Judd, L.L., Paulus, M.J., Schettler, P.J., Akiskal, H.S., Endicott, J., Leon, A.C., Maser, J. D., Mueller, T., Solomon, D.A., Keller, M.B., 2000. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am. J. Psychiatry* 157 (9), 1501–1504.
- Kao, Y.-C., Liu, Y.-P., Cheng, T.-H., Chou, M.-K., 2012. Subjective quality of life and suicidal behavior among Taiwanese schizophrenia patients. *Soc. Psychiatry Psychiatr. Epidemiol.* 47 (4), 523–532.
- Kennedy, N., Paykel, E., 2004. Residual symptoms at remission from depression: impact on long-term outcome. *J. Affect. Disord.* 80 (2–3), 135–144.
- Kronke, K., Spitzer, R.L., Williams, J.B., 2003. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med. Care* 41 (11), 1284–1292.
- Labaka, A., Goñi-Balentiaga, O., Lebeña, A., Pérez-Tejada, J., 2018. Biological sex differences in depression: a systematic review. *Biol. Res. Nurs.* 20 (4), 383–392.
- de Lara, C.L., Dumais, A., Rouleau, G., Lesage, A., Dumont, M., Chawky, N., Alda, M., Benkelfat, C., Turecki, G., 2006. STin2 variant and family history of suicide as significant predictors of suicide completion in major depression. *Biol. Psychiatry* 59 (2), 114–120.
- Lee, E.H.M., Hui, C.L.M., Chan, P.Y., Chang, W.C., Chan, S.K.W., Chen, E.Y.H., 2018. Suicide rates, psychiatric hospital bed numbers, and unemployment rates from 1999 to 2015: a population-based study in Hong Kong. *Am. J. Psychiatry* 175 (3), 285–286.
- Lee, S.W., Yang, J.M., Moon, S.Y., Yoo, I.K., Ha, E.K., Kim, S.Y., Park, U.M., Choi, S., Lee, S.-H., Ahn, Y.M., 2020. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *Lancet Psychiatry* 7 (12), 1025–1031.
- Li, H., Luo, X., Ke, X., Dai, Q., Zheng, W., Zhang, C., Cassidy, R.M., Soares, J.C., Zhang, X., Ning, Y., 2017. Major depressive disorder and suicide risk among adult outpatients at several general hospitals in a Chinese Han population. *PLoS ONE* 12 (10), e0186143.
- Li, W., Yang, Y., Liu, Z.-H., Zhao, Y.-J., Zhang, Q., Zhang, L., Cheung, T., Xiang, Y.-T., 2020. Progression of mental health services during the COVID-19 outbreak in China. *Int. J. Biol. Sci.* 16 (10), 1732.
- Liu, Z.W., Yu, Y., Hu, M., Liu, H.M., Zhou, L., Xiao, S.Y., 2016. PHQ-9 and PHQ-2 for screening depression in Chinese rural elderly. *PLoS One* 11 (3), e0151042.
- Lobana, A., Mattoo, S.K., Basu, D., Gupta, N., 2001. Quality of life in schizophrenia in India: comparison of three approaches. *Acta Psychiatr. Scand.* 104 (1), 51–55.
- Ma, Y.F., Li, W., Deng, H.B., Wang, L., Wang, Y., Wang, P.H., Bo, H.X., Cao, J., Wang, Y., Zhu, L.Y., Yang, Y., Cheung, T., Ng, C.H., Wu, X., Xiang, Y.T., 2020. Prevalence of depression and its association with quality of life in clinically stable patients with COVID-19. *J. Affect. Disord.* 275, 145–148.
- Moutier, C., 2021. Suicide prevention in the COVID-19 era: transforming threat into opportunity. *JAMA Psychiatry* 78 (4), 433–438.
- Na, P.J., Tsai, J., Hill, M.L., Nichter, B., Norman, S.B., Southwick, S.M., Pietrzak, R.H., 2021. Prevalence, risk and protective factors associated with suicidal ideation during the COVID-19 pandemic in US military veterans with pre-existing psychiatric conditions. *J. Psychiatr. Res.* 137, 351–359.
- Nanayakkara, S., Misch, D., Chang, L., Henry, D., 2013. Depression and exposure to suicide predict suicide attempt. *Depression Anxiety* 30 (10), 991–996.
- Nordentoft, M.M., P. B., Pedersen, C.B., 2011. Absolute risk of suicide after first hospital contact in mental disorder. *Arch. Gen. Psychiatry* 68 (10), 1058–1064.
- Omari, A., 2020. Predictors and confounders of suicidal ideation and suicide attempts among adults with and without depression. *Psychiatr. Q.* 92, 331–345.
- Papadopoulou, A., Efstathiou, V., Yotsidi, V., Pomini, V., Michopoulos, I., Markopoulou, E., Papadopoulou, M., Tsigkaropoulou, E., Kalem, G., Tournikioti, K.,

- Douzenis, A., Gournellis, R., 2021. Suicidal ideation during COVID-19 lockdown in Greece: prevalence in the community, risk and protective factors. *Psychiatry Res.* 297, 113713.
- Park, M.-H., Kim, T.-S., Yim, H.-W., Jeong, S.H., Lee, C., Lee, C.-U., Kim, J.-M., Jung, S.-W., Lee, M.-S., Jun, T.-Y., 2010. Clinical characteristics of depressed patients with a history of suicide attempts: results from the CRESCEND study in South Korea. *J. Nerv. Ment. Dis.* 198 (10), 748–754.
- Picco, L.S., M., Abdin, E., Vaingankar, J.A., Chong, S.A., 2017. Gender differences in major depressive disorder: findings from the Singapore Mental Health Study. *Singapore Med. J.* 58 (11), 649–655.
- Posner, K.O., M. A., Gould, M., Stanley, B., Davies, M., 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am. J. Psychiatry* 164 (7), 1035–1043.
- Reger, M.A., Stanley, I.H., Joiner, T.E., 2020. Suicide mortality and coronavirus disease 2019—a perfect storm? *JAMA Psychiatry* 77 (11), 1093–1094.
- Riecher-Rössler, A., 2017. Sex and gender differences in mental disorders. *Lancet Psychiatry* 4 (1), 8–9.
- Sampasa-Kanyinga, H., Chaput, J.P., Hamilton, H.A., Colman, I., 2018. Bullying involvement, psychological distress, and short sleep duration among adolescents. *Soc. Psychiatry Psychiatr. Epidemiol.* 53 (12), 1371–1380.
- Shi, L., Lu, Z.-A., Que, J.-Y., Huang, X.-L., Liu, L., Ran, M.-S., Gong, Y.-M., Yuan, K., Yan, W., Sun, Y.-K., 2020. Prevalence of and risk factors associated with mental health symptoms among the general population in China during the coronavirus disease 2019 pandemic. *JAMA Netw. Open* 3 (7), e2014053.
- Shi, L., Que, J.-Y., Lu, Z.-A., Gong, Y.-M., Liu, L., Wang, Y.-H., Ran, M.-S., Ravindran, N., Ravindran, A.V., Fazel, S., 2021. Prevalence and correlates of suicidal ideation among the general population in China during the COVID-19 pandemic. *Eur. Psychiatry* 64 (1).
- Sinyor, M., Knipe, D., Borges, G., Ueda, M., Pirkis, J., Phillips, M.R., Gunnell, D., <collab>Collaboration, I.C.-S.P.R.</collab>, 2021. Suicide risk and prevention during the COVID-19 pandemic: one year on. *Arch. Suicide Res.* 1–6.
- Skevington, S.M., Lotfy, M., O'Connell, K.A., <collab>Group, W.collab, 2004. 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 (2), 299–310.
- Tasnim, R., Islam, M.S., Sujon, M.S.H., Sikder, M.T., Potenza, M.N., 2020. Suicidal ideation among Bangladeshi university students early during the COVID-19 pandemic: prevalence estimates and correlates. *Child Youth Serv. Rev.* 119, 105703.
- Tuisku, V., Pelkonen, M., Karlsson, L., Kiviruusu, O., Holi, M., Ruuttu, T., Punamaki, R.L., Marttunen, M., 2006. Suicidal ideation, deliberate self-harm behaviour and suicide attempts among adolescent outpatients with depressive mood disorders and comorbid axis I disorders. *Eur. Child Adolesc. Psychiatry* 15 (4), 199–206.
- Vancampfort, D., Hallgren, M., Firth, J., Rosenbaum, S., Schuch, F.B., Mugisha, J., Probst, M., Van Damme, T., Carvalho, A.F., Stubbs, B., 2018. Physical activity and suicidal ideation: a systematic review and meta-analysis. *J. Affect. Disord.* 225, 438–448.
- Woo, J.-M., Jeon, H.J., Noh, E., Kim, H.-J., Lee, S.W., Lee, K.K., Kim, S.H., Hong, J.P., 2014. Importance of remission and residual somatic symptoms in health-related quality of life among outpatients with major depressive disorder: a cross-sectional study. *Health Qual. Life Outcomes* 12 (1), 1–10.
- World Health Organization, 2020. Suicide prevention. https://www.who.int/health-topics/suicide#tab=tab_1. Available at:
- Zalpuri, I., Rothschild, A.J., 2016. Does psychosis increase the risk of suicide in patients with major depression? A systematic review. *J. Affect. Disord.* 198, 23–31.
- Zechmann, A., Paul, K.I., 2019. Why do individuals suffer during unemployment? Analyzing the role of deprived psychological needs in a six-wave longitudinal study. *J. Occup. Health Psychol.* 24 (6), 641.
- Zhao, Y.-J., Jin, Y., Rao, W.-W., Li, W., Zhao, N., Cheung, T., Ng, C.H., Wang, Y.-Y., Zhang, Q.-E., Xiang, Y.-T., 2021. The prevalence of psychiatric comorbidities during the SARS and COVID-19 epidemics: a systematic review and meta-analysis of observational studies. *J. Affect. Disord.* 287, 145–157.
- Zhou, Y., Cao, Z., Yang, M., Xi, X., Guo, Y., Fang, M., Cheng, L., Du, Y., 2017. Comorbid generalized anxiety disorder and its association with quality of life in patients with major depressive disorder. *Sci. Rep.* 7 (1), 1–8.