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Association between chronic fatigue syndrome and suicidality among survivors of Middle East respiratory syndrome over a 2-year follow-up period

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ABSTRACT

Suicide is an important public health issue during the current pandemic of emerging infectious diseases (EIDs). In EIDs, various symptoms persist even after recovery, and chronic fatigue is among those that are commonly reported. The aim of this study was to examine the effects of chronic fatigue syndrome on suicidality during the recovery phase among survivors of Middle East respiratory syndrome (MERS). MERS survivors were recruited from five centers and prospectively followed up for 2 years. In total, 63 participants were registered at 12 months (T1), of whom 53 and 50 completed the assessments at 18 months (T2) and 24 months (T3), respectively. Suicidality and chronic fatigue were evaluated using the suicidality module of the Mini-International Neuropsychiatric Interview (MINI) and the Fatigue Severity Scale (FSS), respectively. We analyzed the relationship between chronic fatigue and suicidality during the follow-up period using the generalized estimating equation (GEE). The suicidality rates were 22.2% (n = 14), 15.1% (n = 8), and 10.0% (n = 5) at T1–T3, respectively. Of the 63 participants, 29 had chronic fatigue syndrome at T1. The group that reported chronic fatigue syndrome at T1 was more likely to experience suicidality during the 2-year follow-up than the group that reported otherwise (RR: 7.5, 95% CI: 2.4–23.1). This association was present even after adjusting for potential confounders (RR: 7.6, 95% CI: 2.2–26.0). Chronic fatigue syndrome and suicide risk among emerging infectious disease (EID) survivors should be acknowledged, and effective interventions must be developed.

1. Introduction

Emerging infectious diseases (EIDs) are a major global health challenge. We are currently experiencing a pandemic of Coronavirus disease-2019 (COVID-19), caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19

pandemic is increasing the risk of mental health problems through the unpredictability and uncertainty it has created. According to a recent meta-analysis, the prevalence of stress, anxiety, and depression in the general population during the COVID-19 pandemic is high, at 29.6%, 31.9%, and 33.7%, respectively (Salari et al., 2020). Currently, about 20 million people around the world have recovered from the disease, but

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persistent symptoms post-infection have been reported. It appears that many patients are likely to suffer from long-term consequences, both physical and mental (del Rio et al., 2020).

A significant outbreak of Middle East respiratory syndrome (MERS), caused by another Coronavirus, occurred in South Korea in 2015. In 217 days, the MERS epidemic resulted in 186 confirmed cases and 36 deaths, and 16,693 people experienced quarantine (Cho et al., 2016). A retrospective chart review of 24 confirmed MERS cases from the 2015 MERS outbreak in Korea found that they experienced psychiatric symptoms such as insomnia, depressive mood, tension, disorientation, impaired memory, auditory hallucinations, and aggressive outbursts (Kim et al., 2018). A prospective cohort study suggested that MERS survivors continued to experience significant psychiatric problems a year after recovering from MERS (Shin et al., 2019). We need to pay attention to the long-term impacts on mental health, as EIDs are reportedly associated with severe mental illness burdens in both the acute and post-disease phases (Rogers et al., 2020).

Suicide is an important mental health issue. Previous reports have identified an association between viral infectious diseases and suicide (Honigsbaum, 2010; Wasserman, 1992). The 2003 SARS epidemic was associated with an increased suicide rate among older females in Hong Kong (Chan et al., 2006). Furthermore, survivors of Ebola infection (Keita et al., 2017) and those with influenza B seropositivity (Okusaga et al., 2011) both showed higher rates of suicide attempts. These findings suggest that suicide rates will increase due to the COVID-19 pandemic (Gunnell et al., 2020).

Chronic fatigue is reportedly associated with increased risk of suicidal ideation and early mortality (Jason et al., 2006), and functional impairment is among the modulators of this association (Johnson et al., 2020). Reports of chronic fatigue have been common in association with EID recovery and may persist for long periods in survivors (Tansey et al., 2007; Wing and Leung, 2012). A follow-up study of Korean MERS survivors suggested that depression may mediate chronic fatigue and post-traumatic stress symptoms (Lee et al., 2019). Fatigue is also a long-term sequela of post-Ebola syndrome (PES). Among Ebola virus disease (EVD) survivors in the United States, 75% reported unusual tiredness (Epstein et al., 2015). Furthermore, in a cross-sectional study of EVD survivors, unusual tiredness was one of the most common symptoms persisting for longer than 10 months (Wilson et al., 2018). A study of COVID-19 survivors also reported fatigue as the most common symptom of recovery and emphasized long-term tracking of survivors (Kamal et al., 2020).

However, little is known about the relationship between chronic fatigue and suicidality in the context of EIDs, particularly among MERS survivors. Moreover, since mental health consequences are likely to persist beyond the actual pandemic (Gunnell et al., 2020), long-term follow-up observational data are required. Thus, we investigated psychological variables in survivors of MERS after 12 and 24 months, and the relationships among them. The aim of this study was to examine the effects of chronic fatigue on suicidality.

2. Materials and method

2.1. Participants

This study involved a 2-year prospective follow-up of MERS survivors at five centers in the Republic of Korea. All participants had been diagnosed with MERS during the 2015 outbreak, were treated, and had recovered. MERS survivors were recruited from the National Medical Center, Seoul National University Hospital, Chungnam National University Hospital, Seoul Medical Center, and Dankook University, and were followed up via e-mail and in person. In total, 63 participants were registered and evaluated at 12 months (T1). Of these participants, 53 and 50 completed the assessments at 18 months (T2), and 24 months (T3), respectively. All participants consented to participate in for study and completed the questionnaires independently. The data collection

process was carried out in accordance with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Boards of Chungnam National University Hospital (2015-08-029-007), Dankook University (2016-02-014), National Medical Center (H-1510-059-007), Seoul Medical Center (2015-12-102), and Seoul National University Hospital (1511-117-723).

2.2. Measures

Socio-demographic data (age, sex, marital status, and occupation) and use of psychotropics were collected. Clinical variables pertaining to the period of MERS infection included pneumonia status, oxygen supply status, significant physical comorbidities, quarantine, status, hospitalization duration, and the interval between symptoms and confirmed diagnosis.

The post-MERS variables evaluated were suicidality, chronic fatigue, depression, anxiety, alcohol use, coping strategies, difficulties in daily life due to poor physical health, financial support, social support, and stigma associated with MERS.

The suicidality module of the Mini-International Neuropsychiatric Interview (MINI) (Leclercq et al., 1997; Yoo et al., 2006) was used to assess suicidality. This module includes six sets of weighted items: desire for death (weight of 1), desire to self-harm (weight of 2), lifetime suicide attempts (weight of 4), suicidal thoughts (weight of 6), suicide plan (weight of 10), and suicide attempts within the past month (weight of 10). The weighted scores were summed to derive the total score; scores ≥ 6 are considered to indicate a moderate-to-high degree of risk.

The Fatigue Severity Scale (FSS) (Krupp et al., 1989) comprises nine items that assess the severity of fatigue experienced during the past week, rated on a Likert scale ranging from 1 to 7. It includes statements such as “My motivation is lower when I am fatigued” and “Fatigue is among my three most disabling symptoms”. The average score for all items is obtained, with higher scores indicating greater impairment due to fatigue. The Korean version of the FSS (Chung and Song, 2001), which has a composite cut-off score of 3.22, showed a sensitivity of 84.1% and specificity of 85.7%. The correlations between FSS scores and depressive symptomatology were weak (Krupp et al., 1989).

To assess core depressive symptoms, the Patient Health Questionnaire-2 (PHQ-2) (Kroenke et al., 2003; Manea et al., 2016) was used instead of the Patient Health Questionnaire-9 (PHQ-9) because some depressive items on the PHQ-9 could overlap with fatigue-related symptoms. The PHQ-2 consists of two items that represent the core symptoms of major depressive disorder listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), each of which is scored from 0 to 3. The PHQ-2 has been translated and validated in Korean (Shin et al., 2013) and has shown good validity and reliability. The optimal cut-off score for depression is 3.

The Generalized Anxiety Disorder-7 (GAD-7) scale (Spitzer et al., 2006) is a screening tool used to measure the severity of anxiety over the preceding 2 weeks. The scale consists of seven items rated using a four-point Likert-type scale (0 points for “Not at all” and 3 points for “Nearly every day”). A total score ≥ 10 is considered clinically significant.

The Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993) is a simple screening tool to assess hazardous and harmful alcohol consumption, and identify cases of dependence during the preceding year. A shorter version (Seong et al., 2009), the Alcohol Use Disorder Identification Test –Consumption (AUDIT-C), consisting of three items assessing the frequency and amount of drinking, and binge drinking, was used in this study.

The Brief Coping Inventory (Brief COPE) (Carver, 1997) measures the three main coping strategies: emotion-focused, problem-focused, and dysfunctional. This questionnaire comprises 28 items scored on a four-point Likert scale ranging from 0 (“Not used at all”) to 3 (“Used frequently”).

The stigma associated with MERS infection was assessed using a

modified version of the Berger's Human Immunodeficiency Virus (HIV) Stigma Scale (Berger et al., 2001), and the short version of the HIV Stigma Scale (Wiklander et al., 2013). These questionnaires include eight items rated on a four-point Likert scale and assess the four categories of stigma: personalized stigma, disclosure concerns, negative self-image, and concern regarding public attitudes (Table 1).

The Medical Outcome Study Social Support Survey (MOS-SSS) (Sherbourne and Stewart, 1991) was used to assess the extent to which the participants are supported by others when facing stressful situations. This scale comprises 19 items and the initial instruction: "If you need it, how often can you depend on somebody to help?" There are five response options (five-point Likert scale; 0, "Never"; 4, "Always"). Higher total scores indicate greater perceived support.

2.3. Statistical analysis

The participants' socio-demographic and MERS-related clinical characteristics are presented as either mean \pm SD or numbers and percentages. The participants were divided into two groups based on the presence of chronic fatigue syndrome at baseline. Group differences were calculated either by t-tests for continuous variables or Chi-square tests for categorical variables.

To evaluate the association between chronic fatigue syndrome and suicidality among MERS survivors over the 2-year follow-up period, we applied a generalized estimating equation (GEE) to a binomial regression model, with a logit link function and an unstructured correlation matrix data. Univariate GEE analyses were used to determine the associations of chronic fatigue syndrome with suicidality among MERS survivors over the 2-year follow-up period in Model I. In the multivariable GEE analysis, we adjusted for age and sex in Model II and all potential confounders in Model III. The confounding variables for the model III analysis were selected from variables with p-values less than 0.1 in model I; sex was additionally selected as it regularly shows clinically meaningful effects in suicidality studies. Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). All p-values were two-sided.

3. Results

Of the 63 participants, 29 and 34 were classified as having and not having chronic fatigue syndrome at baseline, respectively. No group difference was observed in baseline socio-demographic or clinical characteristics during the period of MERS infection (Table 2 and Table 3).

The 12-, 18-, and 24-month suicidality follow-up assessments were completed by 63 (100%), 53 (81.1%), and 50 (79.4%) participants, respectively. The suicidality prevalence rates were 14 (22.2%), 8 (15.1%), and 5 (10.0%) at 12, 18, and 24 months, respectively (Fig. 1).

Compared to the group that reported no chronic fatigue syndrome at baseline, those who reported chronic fatigue syndrome showed a 7.5-fold (RR: 7.5, 95% CI: 2.4–23.1) increase in suicidality over the 2-year follow-up period, according to Model I. In the multivariate model,

Table 1
Items assessing the stigma associated with MERS infection.

Items
1 . I feel isolated from the world since I became a MERS survivor.
2 . I should be very careful about not revealing that I'm a MERS survivor.
3 . I worry that people would discriminate against me if they knew that I am a MERS survivor.
4 . Most MERS survivors are rejected when others learn about it.
5 . I work hard to keep the fact that I am a MERS survivor a secret.
6 . When people know that I am MERS survivor, they feel uncomfortable sitting next to me.
7 . I have been hurt by people's reactions to learning that I am a MERS survivor.
8 . I don't feel at all ashamed that I am a MERS survivor

Table 2
Baseline Socio-demographic characteristics of participants (n = 63).

Variables	Total (n = 63)	Having chronic fatigue syndrome (n = 29)	No chronic fatigue syndrome (n = 34)	P value
	Mean \pm SD or n (%)	Mean \pm SD or n (%)	Mean \pm SD or n (%)	
Age	49.21 \pm 12.57	49.34 \pm 11.77	49.09 \pm 13.39	0.936
Age (cat)				0.995
20–39	17 (27.0)	8 (27.6)	9 (26.5)	
40–49	17 (27.0)	8 (27.6)	9 (26.5)	
50–59	15 (23.8)	7 (24.1)	8 (23.5)	
60+	14 (22.2)	6 (20.7)	8 (23.5)	
Sex				0.980
male	39 (61.9)	18 (62.1)	21 (61.8)	
female	24 (38.1)	11 (37.9)	13 (38.2)	
Marriage				0.900
unmarried	8 (12.7)	3 (10.3)	5 (14.7)	
married	50 (79.4)	24 (82.8)	26 (76.5)	
divorced or bereaved	5 (7.9)	2 (6.9)	3 (8.8)	
Living with children				0.966
yes	52 (82.5)	24 (82.8)	28 (82.4)	
no	11 (17.5)	5 (17.2)	6 (17.7)	
Religion				0.130
yes	44 (69.8)	23 (79.3)	21 (61.8)	
no	19 (30.2)	6 (20.7)	13 (38.2)	
Job				0.618
yes	59 (93.7)	28 (96.6)	31 (91.2)	
no	4 (6.3)	1 (3.5)	3 (8.8)	
Monthly income (US dollar) ^a				0.136
below 1500	20 (32.8)	6 (20.7)	14 (43.8)	
1500–3000	18 (29.5)	11 (37.9)	7 (21.9)	
above 3000	23 (37.7)	12 (41.4)	11 (34.4)	
Education				0.267
below middle school	11 (17.5)	3 (10.3)	8 (23.5)	
high school	19 (30.2)	8 (27.6)	11 (32.4)	
university	33 (52.4)	18 (62.1)	15 (44.1)	
above				

^a 1 US dollar = 1200 Korean Won.

Table 3
Clinical status during the MERS-infected period.

Variables	Total (n = 63)	Having chronic fatigue syndrome (n = 29)	No chronic fatigue syndrome (n = 34)	P value
	Mean \pm SD or n (%)	Mean \pm SD or n (%)	Mean \pm SD or n (%)	
Status at the point of infection				0.725
patients	20 (31.7)	8 (27.6)	12 (35.3)	
health care workers	15 (23.8)	7 (24.1)	8 (23.5)	
caregivers	11 (17.5)	5 (45.5)	6 (54.6)	
visitors	11 (17.5)	7 (24.1)	4 (11.8)	
others	6 (9.5)	2 (6.9)	4 (11.8)	
Pneumonia (yes)	21 (33.3)	11 (37.9)	10 (29.4)	0.475
Ventilator (yes)	12 (19.0)	8 (27.6)	4 (11.8)	0.111
ECMO (yes)	4 (6.3)	3 (10.3)	1 (6.4)	0.326
Comorbidities (yes)	20	10 (34.5)	10 (29.4)	0.667
Quarantine (yes)	50	23 (82.1)	27 (81.8)	0.974
Days of hospitalization	25.71 \pm 20.09	31.07 \pm 27.34	21.14 \pm 8.79	0.070
Days from symptoms to confirmed dx	5.23 \pm 3.99	6.24 \pm 4.16	4.33 \pm 3.66	0.060

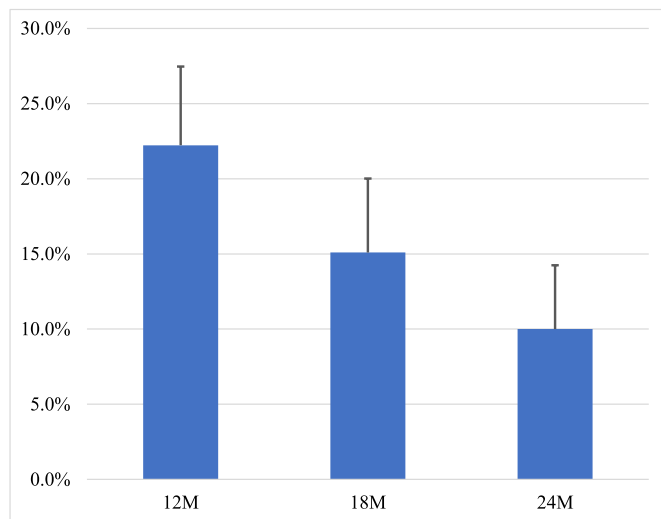


Fig. 1. Proportion of suicidality each follow-up point.

baseline chronic fatigue syndrome was independently associated with the presence of suicidality throughout the 2-year follow-up period, after adjusting for age and sex (Model II, RR: 8.3, 95% CI: 2.8–24.4), and for potential confounders (Model III, RR: 7.6, 95% CI: 2.2–26.0) (Table 4).

4. Discussion

To the best of our knowledge, our study is the first prospective investigation of suicidality among MERS survivors. We found that the prevalence rate of suicidality in MERS survivors was 10–22.2% during the 2-year follow-up period. Baseline chronic fatigue syndrome was independently associated with the presence of suicidality throughout the 2-year follow-up.

Our findings are consistent with those of previous studies showing that suicidality may persist after recovery from EIDs (Keita et al., 2017; Secor et al., 2020), although the prevalence rate of suicidality may have differed between this study and previous ones because of differences in the recovery periods and suicidality assessment instruments. A retrospective cohort study of EVD survivors found that 3 years after the outbreak, EVD survivors reported consistently high levels of post-traumatic stress disorder, depression, anxiety, and suicide attempts in comparison with non-survivors, with 39 out of 116 (34%) respondents reporting suicide attempts (Niederkrötenhaler et al., 2020). In a cohort study involving 256 of the 1270 EVD survivors of the 2013–2016 epidemic, 33 were referred to psychiatrists during the recovery phase, one of whom was experiencing suicidal ideation and three of whom had attempted suicide (Keita et al., 2017). A cross-sectional survey conducted during the survivors' recovery period in the three countries affected by EVD showed that 10–20% of the respondents reported self-harm or suicidal ideation (Secor et al., 2020). In a 4-year survey following the SARS outbreak in Hong Kong, 42.5% of the survivors (77/181) reported at least one diagnosable psychiatric disorder, and 40.3% reported chronic fatigue (Lam et al., 2009). Suicide is among the most important public health issues. We suggest that this study is particularly meaningful at this time, given that the need for suicide prevention is being highlighted, and the prospect that the suicide rate will increase (Gunnell et al., 2020) due to the ongoing EID epidemic caused by COVID-19.

We found that chronic fatigue among survivors at 12 months after MERS predicted suicidality over the 2-year follow-up. An adult health survey conducted in an urban area in Iceland reported that fatigue was related to suicidal ideation (Vilhjalmsson et al., 1998), while an earlier US study reported an increase in suicide mortality among people with fatigue symptoms (Smith et al., 2006). However, depression confounds

Table 4

Relative risks and 95% confidence intervals of univariate and multivariate GEE analyses on association between chronic fatigue syndrome and suicidality among MERS survivors.

Predictors	Model I	Model II	Model III
Chronic fatigue syndrome	7.5 (2.4–23.1)*	8.3 (2.8–24.4)*	7.6 (2.2–26.6)*
Age	1.0 (1.0–1.1)	1.0 (1.0–1.1)	
Female (ref = male)	2.2 (0.7–6.7)	2.0 (0.6–6.3)	2.5 (0.7–9.6)
Without spouse (ref = with spouse)	1.9 (0.6–6.1)	1.9 (0.6–6.1)	
No job (ref = Having job)	0.8 (0.1–6.2)	0.6 (0.1–3.1)	
Depressive symptoms (ref = PHQ-2 < 3)	4.8 (1.2–3.0) *	4.9 (1.2–19.3)*	1.5 (0.4–5.7)
Anxiety symptoms (ref = GAD7 < 10)	10.3 (3.0–36.4)*	10.3 (2.4–44.1)*	3.2 (0.6–16.3)
Without Financial support	1.0 (0.3–3.1)	1.3 (0.4–4.1)	
Social support (ref = lower group)	1.2 (0.4–3.5)	1.0 (0.3–3.2)	
Problem focused coping strategy (ref = lower group)	0.2 (0.08–0.7)*	0.3 (0.08–0.9)*	0.2 (0.04–0.8)*
Emotion-focused coping strategy (ref = lower group)	0.5 (0.2–1.5)	0.5 (0.1–1.4)	
Dysfunctional coping strategy (ref = lower group)	2.4 (0.8–7.2)	3.8 (1.2–12.2)*	
Difficulties in daily life due to physical health (ref = no)	2.7 (0.7–10.0)	2.8 (0.7–11.1)	
MERS Stigma (ref = lower group)	1.1 (0.4–3.2)	0.8 (0.3–2.6)	
Alcohol Use Disorder Identification Test-Consumption	0.2 (0.04–1.0)	0.2 (0.1–1.2)	
Psychotropic medication	7.4 (1.2–44.5)*	10.3 (1.6–65.0)*	2.8 (0.4–19.0)

Model I: Crude RRs.

Model II: Adjusted for age and sex.

Model III: Adjusted for sex, depressive symptoms, anxiety symptoms, problem focused coping strategy, and psychotropics.

Chronic fatigue syndrome was assessed by FSS (Fatigue severity scale) with the cut off score was 3.22.

Anxiety symptoms were assessed by GAD-7 (Generalized Anxiety Disorder-7). Social support was assessed by MOS-SSS (Medical Outcomes Study-Social Support Survey) and the higher group defined as the above of the median score (72). Coping strategy was assessed by brief coping inventory and it was analyzed by dividing into three main domains (emotion-focused, problem-focused, and dysfunctional).

Bold values denote statistical significance at the $p < 0.1$ level in univariate analysis to select the confounding variable. Sex was judged as a clinically meaningful variable and included in the confounding variable to be corrected. Asterisk (*) denotes statistical significance at the $p < 0.05$ level.

the association of suicidality with chronic fatigue. Depression is widely known to be one of the most common risk factors for suicide in patients experiencing physical illness (Webb et al., 2012). A study of suicide risk in patients with chronic renal failure showed higher levels of fatigue, anxiety, and suicide risk in depressed patients, and reported a significant correlation between fatigue and depression (Chen et al., 2010). A study of people with multiple sclerosis also demonstrated an association between fatigue and suicidal ideation, but after controlling for depression, the correlations disappeared (Mikula et al., 2020). Fatigue is defined as a subjective sense of weakness, loss of energy, and tiredness; these symptoms are shared with depression. Therefore, we used the PHQ-2 scale, which assesses core symptoms of depression. Our results demonstrated that chronic fatigue in MERS survivors was associated with suicidality, independent of core symptoms of depression. In addition, the problem-focused coping strategy was a confounding factor in this study. Previous research has shown that adoption of problem-focused coping strategies reduces the risk of suicide (Knafo et al., 2015). Problem-focused coping strategies adopted during EID outbreaks in the general population include seeking alternative measures (e.g., qigong and complementary medicine), and engagement in behaviors that aim to

protect oneself or others (Chew et al., 2020). This coping strategy allows us to take active steps towards self-empowerment and reduces feelings of uncertainty by providing us with a sense of control over our health (Siu et al., 2007). However, we found that chronic fatigue in MERS survivors was associated with suicidality, independently of any coping strategies. The association between chronic fatigue and suicide risk may be related to impairment of functioning and disruption of daily life (Kapur and Webb, 2016). We suggest that survivors of EIDs who report chronic fatigue should be assessed in terms of suicide risk, so that appropriate treatment strategies can be applied.

The limitations of the present study were as follows. First, sampling bias may have been present, as only around 43% of the MERS survivors participated in the study. Moreover, given the 5–15% dropout rate, it is possible that someone who thought that they had a mental health problem continued to participate in the study. However, our data are meaningful in that we monitored survivors of EID in terms of the suicide rate over 2 years. Second, we could not assess other variables, such as other anxiety problems or mental stress, as dependent variables because those could be related with suicidality in the post-infection period. Future studies evaluating many other psychological problems would be needed to reveal risk factors of long-term suicidality in survivors of EIDs. Third, it should also be noted that we evaluated chronic fatigue and suicidality using self-report measures only; despite these limitations, this is the first study to report on the suicidality of MERS survivors and its association with chronic fatigue.

In conclusion, our follow-up study of MERS survivors showed that around 10–20% experienced suicidality after recovering from MERS infection. Chronic fatigue at 12 months after MERS may influence long-term suicidality among MERS survivors. Thus, EID survivors should be assessed for chronic fatigue; effective treatments to alleviate this s are needed.

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Credit

So-Hyun Ahn: Investigation; Writing – original draft. Jeong Lan Kim: Data curation; Investigation. Jang Rae Kim: Investigation; Writing – original draft. So Hee Lee: Data curation; Funding acquisition; Investigation; Supervision; Writing – review & editing. Hyeon Woo Yim: Methodology; Formal analysis; Writing – original draft. Hyunsuk Jeong: Methodology; Formal analysis; Writing – original draft. Jeong-Ho Chae: Funding acquisition; Investigation; Supervision; Writing – review & editing. Hye Yoon Park: Data curation; Investigation. Jung Jae Lee: Data curation; Investigation. Hae Woo Lee: Data curation; Investigation.

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