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Epidemiology of fatal/non-fatal suicide among patients with chronic osteomyelitis (COM): a nationwide population-based study

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Abstract

Objective: Chronic osteomyelitis (COM) can induce systemic inflammation, and systemic inflammation may be associated with suicide tendency. However, no studies have investigated the correlation between COM and suicide tendency.

Methods: The aim of this population-based study was to determine the epidemiology of fatal/non-fatal suicide among COM patients. Subjects with at least two outpatient visits or one course of inpatient care diagnosed with COM were recruited into a COM cohort. The control/COM subject ratio was approximately 4:1 matched by age, sex, major depression coding and index year (COM patients). Subjects with suicide attempts before COM diagnosis and subjects aged <20 years were excluded.

Results: COM patients had 1.93 (95% confidence interval [CI]: 1.11–3.36) times the risk of fatal/non-fatal suicide as control subjects. Considering death as the competing event of fatal/non-fatal

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suicide, COM patients had 1.76 (95% CI: 1.03–3.01) times the risk of fatal/non-fatal suicide (competing risk regression model). The effect of COM on fatal/non-fatal suicide was more prominent among diabetic patients. COM severity also correlated with the risk of fatal/non-fatal suicide.

Conclusions: More attention must be paid to suicide tendency among COM patients.

Keywords

Chronic osteomyelitis, suicide, systemic inflammation, depression, diabetes, schizophrenia

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Introduction

Osteomyelitis is a bone infection that can arise from contiguous spread, penetrating injury or hematogenous seeding.[1] The disease frequently becomes a chronic infection after the acute stage owing to inadequate treatment or relapse.[2] Chronic osteomyelitis (COM) can last for weeks, months, years or even be permanent, and involves pathological processes that induce intense inflammation in the foci because of the formation of abscesses, bone debris and sinus tracts.[3] Patients with COM are usually male and most are older.[4,5] COM can lead to chronic systemic inflammation, which is associated with multisystem disorders, including coronary artery disease, stroke, and head and neck cancer.[6–8]

Suicide attempt is defined as an intentional act of taking one's life by engaging in self-directed injurious behaviors.[9,10] Suicide is the 10th leading cause of death in the United States, and its incidence has grown over the past 15 years.[11] The World Health Organization has predicted that there will be almost 1 million suicide deaths by 2030, contributing to a projected 1.4% of all deaths worldwide.[9] A previous study has suggested a correlation between neuroinflammation, as assessed by microglia activity in the brain, and suicidal ideation.[12] In one prospective study, subjects with higher levels of serum C-reactive protein had a higher risk of suicide death after 9 years of follow-up.[13]

Despite that COM can lead to chronic systemic inflammation, and systemic inflammation is associated with suicide tendency, no studies have examined the correlation between COM and suicide tendency. We thus performed a nationwide population-based study to determine the epidemiology of health care service use for suicide, including suicide attempt or suicide death, among COM patients. Suicide deaths/attempts are here expressed as fatal/non-fatal suicide throughout.

Materials and methods

Data source

Since 1995, the Taiwanese government has been developing the National Health Insurance Research Database (NHIRD). The database includes data for more than 99% of Taiwanese citizens and their medical records. The Longitudinal Health Insurance Database (LHID), which randomly selects 1 million subjects from the NHIRD, was used in this study. To protect the privacy of the beneficiaries, original identification numbers were encrypted before the data were released. The ICD-9-CM (International Classification of Diseases, 9th Revision,

Clinical Modification) system was used for disease coding in the NHIRD and LHID.

The research ethics committee of China Medical University Hospital in Taiwan approved the study (CMUH-104-REC2-115-R3).[14] The committee confirmed that informed consent was not required, as the identity of the participants could not be determined. All the data analyzed were encrypted in terms of participant identity when released from the NHIRD.

Study population

We used a population-based cohort study to determine the epidemiology of fatal/non-fatal suicide, including suicide attempt or suicide death, among COM patients. Subjects with at least two outpatient visits or one course of inpatient care (or both) diagnosed with COM (ICD-9-CM: 730.1–730.9, 909.3) from January 2000 to December 2012 were recruited into a COM cohort. The index date was defined as the date when the COM diagnosis was initially coded. The control/COM subject ratio was approximately 4:1 matched by age, sex, a coding of major depression and index year (COM patients). Subjects with a history of at least two outpatient visits or one course of inpatient care with a coding of major depression (ICD-9-CM: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) before the index date were diagnosed with major depression. Subjects with previous suicide coding (ICD-9-CM: E950–E959) and subjects <20 years old before the index date were excluded. All subjects were followed up from the index date until the date of initial suicide coding (ICD-9-CM: E950–E959), until they were withdrawn from the database or until 31 December 2013. Suicide death, or fatal suicide, was defined as death within 30 days of the suicide-coded (ICD-9-CM: E950–E959) date. Suicide attempt, or non-fatal suicide, was defined as the absence of death within 30 days of suicide coding (ICD-9-CM: E950–E959). Fatal/non-fatal suicides, including suicide attempts or suicide deaths, were defined as events in a Cox regression model. The mean (±standard deviation) follow-up period was 6.3 ± 4.1 years.

The baseline comorbidities analyzed in our model were hypertension (ICD-9-CM: 401–405), diabetes (ICD-9-CM: 250), epilepsy (ICD-9-CM: 345), ischemic heart disease (ICD-9-CM: 410–414), chronic obstructive pulmonary disease (ICD-9-CM: 491, 492, 493, 496), stroke (ICD-9-CM: 430–438), liver cirrhosis (ICD-9-CM: 571.2, 571.5), osteoporosis (ICD-9-CM: 733), end-stage renal disease (ICD-9-CM: 585), bipolar disorders (ICD-9-CM: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80 and 296.89) and schizophrenia (ICD-9-CM: 295 and A211). Subjects with at least two outpatient visits or one course of inpatient care under the aforementioned coding before the index date were diagnosed with the specific comorbidity.

Statistical analysis

We described the sex, age group, level of urbanization and comorbidities in both cohorts using number of subjects and percentages. The mean age was expressed as mean ± standard deviation. Chi-square tests and t-tests were used to estimate differences in categorical and continuous variables between the two cohorts. To estimate the risk of fatal/non-fatal suicide in the COM cohort relative to the comparison cohort, hazard ratios (HR) and adjusted hazard ratios (aHR) were calculated using crude and adjusted Cox proportional hazard models, respectively. The incidence density of fatal/non-fatal suicide was expressed as event number per 100,000 person-years. The Kaplan–Meier method was used to determine the cumulative incidence of fatal/non-fatal suicide, and the log-rank test was used to determine the

significance of between-group differences. SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for data analysis and R software (www.r-project.org) was used to plot the incidence curves.[14]

Results

There were 5,762 patients in the COM cohort and 23,039 subjects in the control cohort (Table 1). The study design and the flow diagram of the recruitment process are shown in Figure 1. Sex and age were homogenous between the two groups. The urbanization level was substantially different between the two cohorts, and COM patients had significantly more baseline comorbidities (all P values < 0.001) except depression and bipolar disorder (Table 1).

The incidence of fatal/non-fatal suicide in the COM group and the control group was 55.30 and 24.68 per 100,000

Table 1. Demographic characteristics and baseline comorbidities of the chronic osteomyelitis and control cohorts.

		Chronic osteomyelitis		
Characteristics	Total	No N = 23,039	Yes N = 5,762	*P*-value
Sex				0.99
Female	12,244	9,795 (42.5)	2,449 (42.5)	
Male	16,557	13,244 (57.5)	3,313 (57.5)	
Age (years)				1.00
<45	6,675	5,340 (23.2)	1,335 (23.2)	
45–64	11,295	9,036 (39.2)	2,259 (39.2)	
≥65	10,831	8,663 (37.6)	2,168 (37.6)	
Mean ± SD[a]		57.97 ± 16.85	58.05 ± 16.88	
Urbanization level[†]				<0.001
1 (highest)	8,157	6,854 (29.8)	1,303 (22.6)	
2	8,337	6,668 (29)	1,669 (29)	
3	4,789	3,822 (16.6)	967 (16.8)	
4	7,479	5,664 (24.6)	1,815 (31.5)	
Baseline comorbidity				
Depression	2,814	2,250 (9.8)	564 (9.8)	0.96
Hypertension	12,849	9,795 (42.5)	3,054 (53)	<0.001
Diabetes	6,827	4,807 (20.9)	2,020 (35.1)	<0.001
Epilepsy	458	303 (1.3)	155 (2.7)	<0.001
IHD	7,473	5,636 (24.5)	1,837 (31.9)	<0.001
COPD	7,101	5,439 (23.6)	1,662 (28.8)	<0.001
Stroke	5,533	4,066 (17.6)	1,467 (25.5)	<0.001
Liver cirrhosis	715	431 (1.9)	284 (4.9)	<0.001
Osteoporosis	4,130	2,762 (12)	1,368 (23.7)	<0.001
ESRD	328	141 (0.6)	187 (3.2)	<0.001
Bipolar disorder	225	179 (0.8)	46 (0.8)	0.87
Schizophrenia	317	225 (1.0)	92 (1.6)	<0.001

IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; SD: standard deviation.

Chi-square test, [a]t-test. Data are N (%) unless otherwise stated.

[†]Urbanization level was obtained by classifying the population density of the residential area in terms of four levels (level 1 = highest urbanization; level 4 = lowest urbanization).

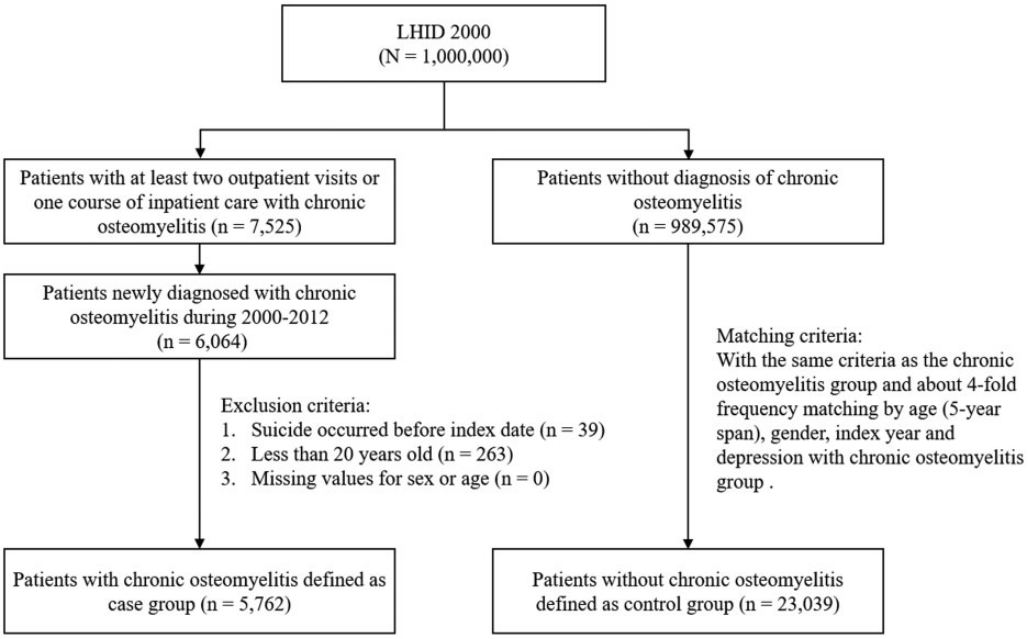

Figure 1. Flow diagram of the recruitment process.
LHID: Longitudinal Health Insurance Database.

person-years, respectively. COM patients had 1.93 times the risk of fatal/non-fatal suicide (aHR = 1.93, 95% confidence interval [CI]: 1.11–3.36; $P = 0.02$) than control subjects (Table 2). Considering death as the competing event for fatal/non-fatal suicide, COM patients had 1.76 times the risk of fatal/non-fatal suicide (aHR = 1.76, 95% CI: 1.03–3.01; $P = 0.04$) than control subjects in the competing risks regression model (Table 3). The cumulative incidence of fatal/non-fatal suicide was higher in the COM group than in the control group ($P = 0.003$ for log-rank test) (Figure 2). Other risk factors for fatal/non-fatal suicide were urbanization level, depression (aHR = 3.82, 95% CI: 2.06–7.07; $P < 0.001$), IHD (aHR = 2.25, 95% CI: 1.17–4.34; $P = 0.02$), liver cirrhosis (aHR = 3.12, 95% CI: 1.19–8.16; $P = 0.02$) and bipolar disorder (aHR = 3.29, 95% CI: 1.09–9.94; $P = 0.03$) (Table 2). The effect of COM on the increased risk of fatal/non-fatal suicide was more prominent among diabetic patients (aHR = 3.79, 95% CI: 1.42–10.16; $P < 0.01$) (Table 4).

Compared with the control cohort, we observed a severity-dependent risk of fatal/non-fatal suicide associated with COM after controlling for age, sex, urbanization level and medical comorbidities (outpatients only: aHR = 1.81, 95% CI: 1.02–3.22; outpatients and inpatients: aHR = 4.79; 95% CI: 1.08–21.34; P for trend = 0.0006) (Table 5).

Discussion

COM is a disease that can contribute to chronic systemic inflammation, and its fluctuating and relentless course can present substantial psychological burden to patients. Chronic systemic inflammation has been recently shown to be correlated with suicide tendency,[9] indicating that long-term illness is a potential proximal

Table 2. Incidence of fatal/non-fatal suicide stratified by presence of chronic osteomyelitis, sex, age, urbanization and baseline comorbidities.

Characteristics	E (n = 60)	PY	IR	Crude		Adjusted[#]	
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
COM							
No	40	16,2074	24.68	Ref.		Ref.	
Yes	20	3,6169	55.30	2.23 (1.30–3.82)	0.003	1.93 (1.11–3.36)	0.02
Sex							
Female	25	8,5508	29.24	Ref.		Ref.	
Male	35	11,2735	31.05	1.06 (0.63–1.76)	0.84	1.09 (0.64–1.87)	0.75
Age at baseline (years)							
<45	18	53,947	33.37	Ref.		Ref.	
45–64	21	81,884	25.65	0.76 (0.40–1.42)	0.39	0.61 (0.31–1.20)	0.15
≥65	21	62,412	33.65	0.96 (0.51–1.81)	0.91	0.57 (0.25–1.30)	0.18
Urbanization							
1 (highest)	11	56,261	19.55	Ref.		Ref.	
2	12	57,941	20.71	1.06 (0.47–2.40)	0.89	1.01 (0.44–2.29)	0.98
3	10	33,526	29.83	1.53 (0.65–3.60)	0.33	1.48 (0.63–3.50)	0.37
4	27	50,275	53.70	2.74 (1.36–5.52)	0.005	2.47 (1.22–5.03)	0.01
Comorbidities							
Depression	19	15,431	123.13	5.29 (3.06–9.13)	<0.001	3.82 (2.06–7.07)	<0.001
Hypertension	27	77,013	35.06	1.25 (0.75–2.08)	0.40	0.66 (0.33–1.31)	0.23
Diabetes	18	38,911	46.26	1.70 (0.98–2.96)	0.06	1.21 (0.64–2.28)	0.56
Epilepsy	2	2,417	82.75	2.69 (0.66–11.04)	0.17	0.97 (0.22–4.24)	0.97
IHD	25	43,754	57.14	2.46 (1.47–4.11)	<0.001	2.25 (1.17–4.34)	0.02
COPD	19	40,268	47.18	1.74 (1.01–3.01)	0.05	1.28 (0.69–2.35)	0.43
Stroke	18	30,398	59.21	2.30 (1.32–3.99)	0.003	1.52 (0.78–2.99)	0.22
Liver cirrhosis	5	3,239	154.39	5.24 (2.09–13.13)	<0.001	3.12 (1.19–8.16)	0.02
Osteoporosis	8	23,789	33.63	1.09 (0.52–2.30)	0.82	0.64 (0.29–1.44)	0.28
ESRD	1		92.60	2.91 (0.40–21.05)	0.29	1.62 (0.21–12.22)	0.64
Bipolar disorder	4	1,256	318.46	10.82 (3.92–29.84)	<0.001	3.29 (1.09–9.94)	0.03
Schizophrenia	2	1,836	108.94	3.59 (0.88–14.69)	0.08	1.20 (0.27–5.22)	0.81

E: number of suicide attempts or suicide deaths; PY: person-years; IR: incidence rate per 100,000 person-years; HR: hazard ratio; CI: confidence interval; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; COM: chronic osteomyelitis.

[#]Adjusted for sex, age, urbanization and all comorbidities.

risk factor for suicide. It is therefore likely that COM patients have a greater suicide tendency. In this study, we demonstrated that COM patients had 1.93 times the risk of fatal/non-fatal suicide than control subjects. Considering death as the competing event, COM patients had 1.76 times the risk of fatal/non-fatal suicide than control subjects using a competing risk regression model. The effect of COM on fatal/non-fatal suicide was more prominent among diabetic patients. We also showed that higher COM severity was associated with greater risk of fatal/non-fatal suicide. This is the first report of such a link, so these results merit attention.

Infections can induce systemic inflammation and subsequent neuroinflammatory processes, which may lead to the onset of suicide symptoms.[9] The prevalence of suicidal ideation and attempted suicide among human immunodeficiency virus patients is 31% and 32.7%, respectively.[15] Before medical treatment, 36% of chronic hepatitis C patients experience major depression and 18% have a moderate-to-severe

Table 3. Subhazard ratios for fatal/non-fatal suicide estimated using a competing risks regression model.

	Chronic osteomyelitis		
Variable	No	Yes	*P*-value
Suicide			
Crude SHR (95% CI)	1.00 (Ref.)	2.14 (1.25–3.64)	0.005**
Adjusted SHR† (95% CI)	1.00 (Ref.)	1.76 (1.03–3.01)	0.040*

Crude SHR: relative subhazard ratio; CI: confidence interval.
Adjusted SHR†: multivariable analysis including all factors in the univariable Cox model.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

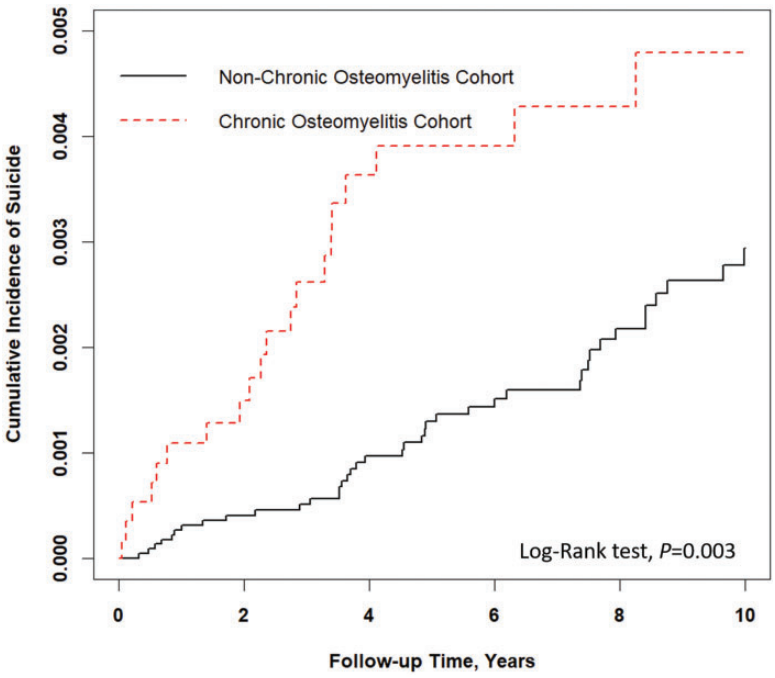

Figure 2. Incidence of suicide attempts and suicide deaths among chronic osteomyelitis (COM) and control cohorts. The dashed line indicates the COM cohort and the solid line indicates the matched control cohort. The log-rank test was used to assess the significance of the difference between the curves ($P = 0.003$).

suicide risk.[16] Latent Toxoplasma gondii infection has been recognized as a risk factor for suicide attempt.[17,18] Despite the known correlation between suicide tendency and the various infections mentioned above, no studies have examined the correlation between COM and suicide tendency. To our knowledge, this is the first study to demonstrate a correlation between COM and increased risk of fatal/non-fatal suicide. The incidence of fatal/non-fatal suicide, including suicide attempt or suicide death, was higher in the COM group than in the control group. The cumulative

Table 4. Crude and adjusted hazard ratios for fatal/non-fatal suicide stratified by sex, age, urbanization and baseline comorbidities.

	Control group			COM group			COM group vs. control group	
	n = 23039			n = 5762				
Variables	E	PYs	IR	E	PYs	IR	Crude HR (95% CI)	#Adjusted HR (95% CI)
Overall	40	162,074	24.68	20	36,169	55.30	2.23 (1.30–3.82)**	1.93 (1.11–3.36)*
Suicide attempt	35	162,074	21.60	16	36,169	44.24	2.04 (1.13–3.68)*	1.58 (0.86–2.92)
Suicide death	5	162,074	3.09	4	36,169	11.06	3.62 (0.97–13.48)	3.72 (0.95–14.58)
Sex								
Female	17	69,528	24.45	8	15,980	50.06	2.05 (0.88–4.75)	1.56 (0.66–3.73)
Male	23	92,546	24.85	12	20,189	59.44	2.37 (1.18–4.76)*	2.02 (0.98–4.18)
Age (years)								
<45	12	43,484	27.60	6	10,463	57.34	2.07 (0.78–5.52)	1.60 (0.54–4.69)
45–64	13	66,896	19.43	8	14,988	53.38	2.73 (1.13–6.6)*	2.04 (0.79–5.21)
≥65	15	51,694	29.02	6	10,718	55.98	1.92 (0.75–4.96)	1.88 (0.72–4.92)
Urbanization								
1 (highest)	7	48,482	14.44	4	7,779	51.42	3.51 (1.03–12.01)*	2.47 (0.70–8.71)
2	6	47,283	12.69	6	10,657	56.30	4.39 (1.42–13.62)*	3.07 (0.87–10.74)
3	6	27,092	22.15	4	6,433	62.18	2.82 (0.8–10.00)	2.69 (0.69–10.54)
4	21	39,003	53.84	6	11,272	53.23	0.99 (0.40–2.45)	1.02 (0.41–2.59)
Comorbidities								
Depression	13	12,677	102.54	6	2,754	217.89	2.13 (0.81–5.61)	2.25 (0.86–6.15)
Hypertension	17	60,812	27.95	10	16,201	61.72	2.21 (1.01–4.82)*	1.89 (0.84–4.26)
Diabetes	7	28,793	24.31	11	10,118	108.71	4.31 (1.67–11.11)**	3.79 (1.42–10.16)**
Epilepsy	1	17,03.3	58.71	1	714	140.10	–	7.6 (0.14–422.92)
IHD	19	34,444	55.16	6	9,310	64.45	1.17 (0.47–2.92)	1.11 (0.43–2.87)
COPD	13	31,876	40.78	6	8,391	71.50	1.73 (0.66–4.56)	1.58 (0.57–4.38)
Stroke	14	23,345	59.97	4	7,054	56.71	0.95 (0.31–2.89)	0.90 (0.29–2.84)
Liver cirrhosis	1	21,04.8	47.51	4	1,134	352.81	6.89 (0.77–61.69)	17.46 (1.27–240.21)*
Osteoporosis	4	16,270	24.58	4	7,519	53.20	2.11 (0.53–8.44)	1.14 (0.25–5.22)
ESRD	0	569,27	0.00	1	511	195.85	–	–
Bipolar disorder	3	97,7.92	306.77	1	278	359.56	1.28 (0.13–12.32)	0.99 (0.04–24.16)
Schizophrenia	2	13,23.1	151.17	0	513	0.00	–	–

E: number of suicide attempts or suicide deaths; PY: person-years; IR: incidence rate per 100,000 person-years; HR: hazard ratio; CI: confidence interval; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; COM: chronic osteomyelitis.

#Adjusted for sex, age, urbanization and all comorbidities in the Cox proportional hazards regression model.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

incidence of suicide attempt or suicide death was higher in the COM group than in the control group. We also demonstrated that among COM patients receiving both inpatient and outpatient care, the incidence of suicide attempt or suicide death was as high as 318.32 per 100,000 person-years. In other words, COM patients receiving both outpatient and inpatient care had 4.79 times the risk of fatal/non-fatal suicide (aHR = 4.79, 95% CI: 1.08–21.34) than control subjects. These results highlight the effect of COM on suicide occurrence.

Table 5. Incidence rate and adjusted hazard ratios for fatal/non-fatal suicide stratified by chronic osteomyelitis severity.

COM severity	Event	PY	IR	Adjusted HR (95% CI)
Control group	40	162,074	24.68	Ref.
Outpatients only	18	35,541	50.65	1.81 (1.02–3.22)*
Outpatients and inpatients	2	628	318.32	4.79 (1.08–21.34)*
P for trend				$P = 0.0006$

PY: person-years; IR: incidence rate per 100,000 person-years; HR: hazard ratio; CI: confidence interval; COM: chronic osteomyelitis.
Models adjusted by demographic factors and comorbidities.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

There are some study limitations. The definition of diseases was based only upon ICD-9-CM coding, so the severity, frequency and duration of treatment for respective diseases could not be fully investigated. We could not obtain data for all suicide risk factors (e.g. family history) from the LHID database. Only data for subjects seeking medical services owing to suicide attempt or subsequent suicide death could be obtained from the LHID database, so subjects with suicidal ideation or suicide plans could not be identified. The relatively low incidence rate of coded suicide events meant that some subgroup analyses, such as the fatal or non-fatal comparison, may have been underpowered. Finally, we could only obtain 23,039 matching subjects from the LHID instead of 23,048.

Conclusions

These findings demonstrate that COM is a risk factor for fatal/non-fatal suicide, including suicide attempts and suicide death. The relative importance of COM as a risk factor for fatal/non-fatal suicide was greater among diabetic patients. These data indicate that COM is not merely a local musculoskeletal disease and its association with suicide tendency justifies preventive measures for suicide attempts or suicide deaths among COM patients.

Data availability

The data used to support the findings of this study are restricted by the research ethics committee of China Medical University Hospital in Taiwan to protect patient privacy. Data are available from the corresponding author (Shu-Jui Kuo) for researchers who meet the criteria for access to confidential data.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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