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Reduced mortality in patients with extended duration of methadone maintenance treatment: a five-year retrospective nationwide study

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Abstract

Background. The retention of patients under methadone maintenance treatment (MMT) is an indication for the effectiveness of the therapy. We aimed to explore the relation between mortality and the cumulative MMT duration.

Methods. A retrospective cohort analysis was performed using Taiwan Illicit Drug Issue Database (TIDID) and National Health Insurance Research Database (NHIRD) during 2012–2016. We included 9149 and 11 112 MMT patients as the short and long groups according to the length of their cumulative MMT duration, 1–364 and ⩾365 days, respectively. The risk of mortality was calculated by Cox proportional hazards regression model with time-dependent exposure to MMT, and the survival probability was plotted with the Kaplan-Meier curve.

Results. The mortality rates were 2.51 and 1.51 per 100 person-years in the short and long cumulative MMT duration groups, respectively. After adjusting for on or off MMT, age, sex, marital status, education level, maximum methadone dose, and comorbidities (human immunodeficiency virus, depression, hepatitis C virus, hepatitis B virus, alcoholic liver disease, and cardiovascular disease), the long group had a lower risk of death (hazard ratio = 0.67; 95% confidence interval 0.60–0.75) than the short group. Increased risk was observed in patients with advanced age, being male, unmarried, infected by HIV, HCV, and HBV, and diagnosed with depression, ALD, and CVD. Causes of death were frequently related to drug and injury.

Conclusions. Longer cumulative MMT duration is associated with lower all-cause and drug-related mortality rate.

Introduction

Opioid use disorder (OUD) is related to a high risk of premature death, while methadone maintenance treatment (MMT) is one of the primary therapies (Ma et al., 2019; McCarty, Priest, & Korthuis, 2018; Volkow, Jones, Einstein, & Wargo, 2019). Mortality rate of patients with OUD is 2.09 per 100 person-years, which is 14.66-fold higher than that of the general population (Degenhardt et al., 2011). Patients with OUD are vulnerable for human immunodeficiency virus (HIV) and viral hepatitis, such as hepatitis C virus (HCV) and hepatitis B virus (HBV), due to injection drug use and risky sexual behaviors (Fanucchi, Springer, & Korthuis, 2019; Kresina, Eldred, Bruce, & Francis, 2005). High prevalence of depressive symptoms has been found in opioid-dependent individuals (Mbaba et al., 2018) and identified as a predictor for suicide (Berg, Malte, Reger, & Hawkins, 2018). Co-use of opioids and alcohol is common (Witkiewitz & Vowles, 2018), and alcoholic liver disease (ALD) is a main cause of liver-associated death (Lucey & Weinrieb, 2009; Seitz et al., 2018). Opioids could influence the electrical activity of the heart and cause prolongation of QT interval and arrhythmogenicity (Behzadi, Joukar, & Beik, 2018), which may lead to sudden cardiac death (Ramakrishna et al., 2015).

Retention in MMT is associated with substantial reductions in the risk for all cause and overdose mortality (Sordo et al., 2017), yet potential confounding factors from the comorbidities of these patients were frequently overlooked. In Taiwan, MMT services expanded into a nationwide program in 2006, and have been remarkably successful in controlling HIV in injecting drug users (Lyu, Su, & Chen, 2012). To evaluate how mortality of OUD patients was influenced by MMT and comorbidities, we compared the death rates in patients with short (1–364 days) and long (⩾365 days) cumulative MMT duration using the Taiwan

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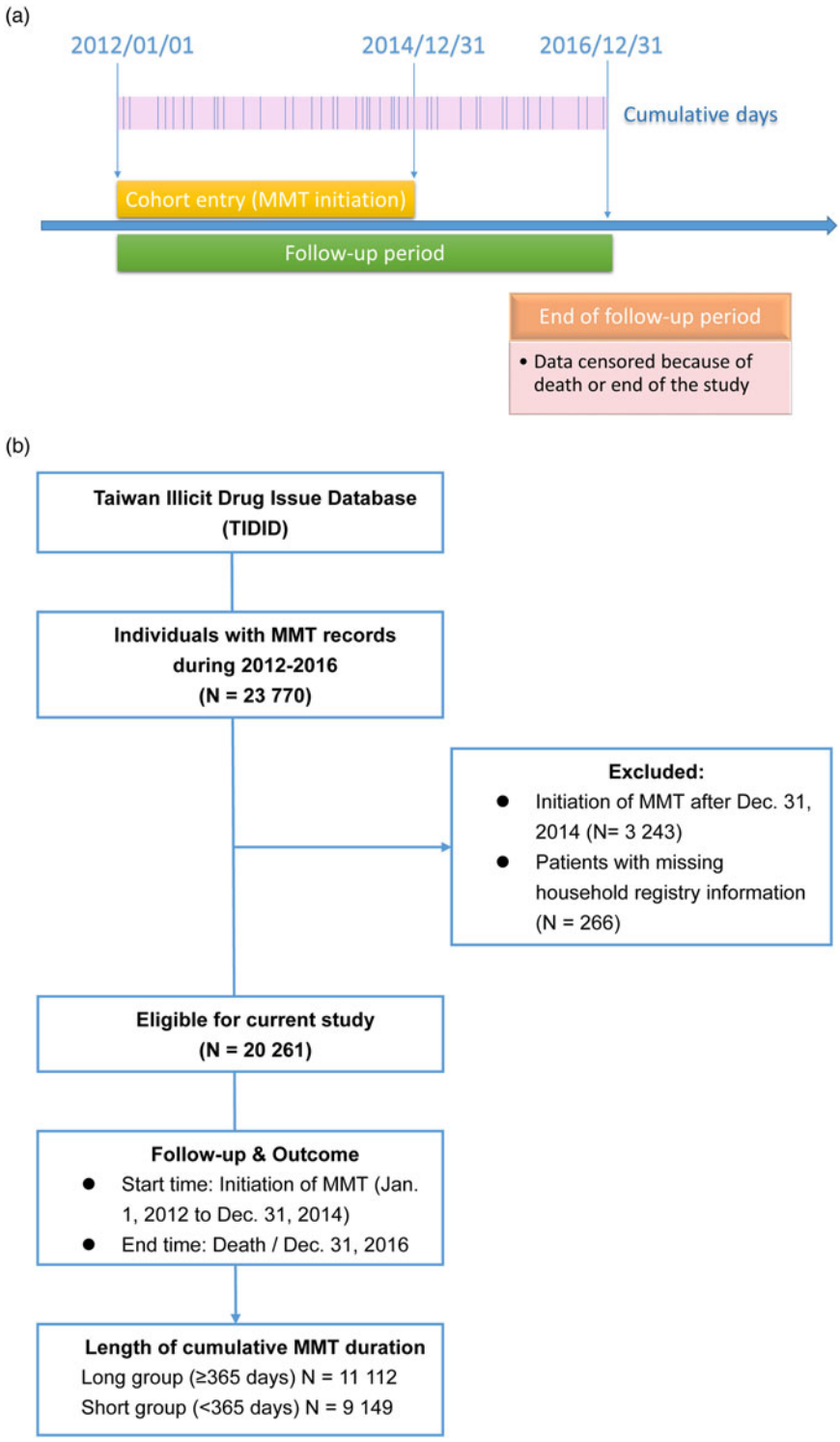

Fig. 1. (a) Overview of the Study Design. Cohort entry is designated as the date of the first prescription for MMT. Cumulative duration is defined as the total number of days attending the MMT clinics during the follow-up period. (b) Flow chart of MMT patients included in this study.

Illicit Drug Issue Database (TIDID) and National Health Insurance Research Database (NHIRD) between 2012 and 2016.

Methods

Data source

Taiwan Illicit Drug Issue Database (TIDID) is an interagency database dedicated to the illicit drug users in Taiwan, including case information of the Drug Abuse Prevention Center, Data of Drug Crime and Penalty from National Police Agency, Database of Substitution Therapy from Department of Mental and Oral Health, Ministry of Health and Welfare (MOHW), etc. Claims data of Taiwan National Health Insurance (NHI), a mandatory single-payer health insurance program covering 99% of the population in Taiwan, constitutes Taiwan's National Health Insurance Research Database (NHIRD) (Hsieh et al., 2019). Both TIDID and NHIRD are maintained by the Health and Welfare

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Table 1. ICD-9-CM codes for comorbidities

Disease	ICD-9-CM codes
Depression	290.21, 296.20-296.24, 296.30-296.34, 296.8, 300.4, 311
Hepatitis C virus	070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V0262
Hepatitis B virus	070.20-070.23, 070.30-070.33, 070.42, 070.52, V0261
Alcoholic liver disease	571.0-571.3
Cardiovascular disease	426-427

Data Science Center (HWDC), providing Taiwanese scientists with access to databases for research purposes.

TIDID contains illicit drug user data on date of birth, sex, marital status, education level, methadone dose, prescription date and taken date. NHIRD holds patient data on death date and diseases diagnosed according to the codes in the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM). The data used in this study were in compliance with the regulations of the HWDC to maintain the privacy of patients. Because of the anonymous property of the TIDID and NHIRD, the informed consent could not be obtained from the participants. The Ethics Review Board of National Health Research Institutes in Taiwan approved this study (EC1060510-E-R1). The analysis was not pre-registered and that the results should be considered exploratory.

Study population

This was a retrospective, population-based cohort study. From the TIDID, patients aged older than 18 years who initiated MMT between 1 January 2012 and 31 December 2014 were designated as the short and long retention groups according to the duration of their cumulative MMT days, 1–364 and ⩾365 days, between the date entering the MMT and 31 December 2016. Both groups with missing information (age, sex, marital status, and education level) were excluded from this study. In total, the short group comprised 9149 patients and the long group comprised 11112 subjects. The main outcome of this study was mortality. All study subjects were followed from the date entering the MMT to the date of endpoint, i.e. until death or to the end of the year 2016 (Fig. 1).

Demographic factors encompassed age (in groups aged 18–35, 35–49, and 50 years and older), sex, marital status, and education level. Comorbidities were assigned if patients were registered in the HIV/AIDS Database, diagnosed with depression, HCV, HBV, ALD, or cardiovascular disease (CVD) during 2012–2016. The ICD-9-CM codes for comorbidities were listed in Table 1.

We grouped 278 causes of deaths of MMT patients into eight categories (Evans et al., 2015; Nordstrom, Yokoi-Shelton, & Zosel, 2013): (1) drug-related; (2) cardiovascular disease-related; (3) suicide-related; (4) injury-related; (5) cancer-related; (6) liver-related; (7) HIV-related; and (8) all other causes. The ICD-10-CM codes for causes of death were itemized in Table 2.

Statistics

The continuous variables were expressed by medians, quartile 1 (Q1) and quartile 3 (Q3), whereas categorical variables were expressed by the numbers and percentages. The χ^2 test was used to determine the differences between the two groups in the distribution of the comorbidities. Wilcoxon two-sample test was used to examine the differences between two continuous variables. The mortality rates were calculated for both groups (per 100 person-years) stratified according to age, sex, marital status, education, maximum methadone dose, and comorbidities. The Kaplan–Meier method was employed to plot the survival curves during the follow-up period, and the log-rank test was used to assess the differences between the two curves. Because MMT patients could be in or out of treatment during the study period, we used multivariate Cox proportional hazards regression with time-dependent MMT exposure for age-, sex-, marital status-, education-, maximum methadone dose-, and comorbidity-stratified analysis to investigate the association between MMT cumulative duration and mortality in order to reduce the immortal time bias. According to the policy of MMT treatment in Taiwan, patients

Table 2. ICD-10-CM codes for causes of death

Category	ICD-10-CM codes
Drug-related	F10.2, F15.0, F16.0-F16.2, F19.0-F19.2, X41, X42, X44, X61, X62, X64, Y11, Y12, Y14
Cardiovascular disease-related	I10, I11.9, I21.9, I25.1, I25.2, I25.9, I27.0, I27.9, I33.0, I33.9, I38, I42.0, I42.2, I46.1, I49.0, I49.9, I50.9, I51.0, I51.4, I51.6, I51.7, I51.9, I60.9, I61.4, I61.9, I62.0, I62.9, I63.9, I64, I69.4, I69.8, I71.0, I71.1, I71.3, I71.4, I71.9, I74.9, I80.3, I85.0, I87.1, R57.0, R57.1, R58
Suicide-related	X67, X68, X70, X71, X74, X76, X78, X80-X82, X84
Injury-related	V02.1, V03.1, V09.2, V22.4, V23.4, V24.4, V27.4, V28.4, V28.5, V29.4, V29.5, V29.9, V47.5, V49.4, V49.5, V49.9, V58.6, V59.4, V69.9, V83.9, V87.0-V87.2, V89.2, V89.9, W10, W13, W17, W19, W20, W26, W34, W67, W74, W79, W80, W87, X09, X45, X47, X49, X59, X95, X97, X99, Y079, Y08, Y18, Y19, Y21, Y26, Y30, Y32, Y86
Cancer-related	C02.9, C06.0, C06.2, C06.9, C08.9, C09.9, C10.9, C11.9, C13.9, C15.9, C16.9, C18.2, C18.9, C20, C22.0, C22.1, C22.9, C25.9, C26.1, C34.9, C37, C43.9, C48.2, C50.9, C53.9, C56, C64, C740, C80, C84.5, C85.9, C92.0, C92.1, C97, D37.6, D38.1, D43.2, D46.9
Liver-related	B16.9, B17.1, B19.9, K70.1, K70.3, K70.4, K72.0, K72.9, K73.9, K74.0, K74.6, K75.9, K76.0, K76.7, K76.9
HIV-related	B20.0, B20.1, B20.3, B20.6-B20.8, B21.2, B22.7, B23.2, B23.8, B24
All other causes	A09, A16.2, A41.9, A49.0, A49.1, A83.0, A90, B34.8, B37.7, B49, D61.9, D68.9, D69.6, D84.9, E11.1, E14.1, E14.2, E14.5, E14.6, E14.9, E15, E23.3, E41, E87.2, F10.0, F29, F32.9, G04.9, G06.0, G06.1, G12.2, G52.9, G58.8, G92, G93.1, G93.4, J04.1, J11.1, J15.9, J18.9, J44.9, J45.0, J45.9, J46, J69.0, J69.8, J84.1, J84.9, J85.2, J93.9, J96.0, J98.4, J98.8, K25.0, K25.5, K25.9, K26.4, K26.9, K27.4, K27.5, K27.9, K55.0, K80.0, K85, K86.0, K92.2, K92.9, L02.1, L02.3, L03.9, L89, M31.1, M46.9, M48.9, M60.0, M72.5, M79.2, M86.9, N15.1, N17.9, N18.0, N19, N39.0, N70.9, O72.0, O88.1, R06.0, R09.2, R99

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Table 3. Baseline demographic factors and comorbidity according to cumulative MMT duration

	Long (⩾365 days) N = 11 112		Short (<365 days) N = 9 149		
Variables	*n*	%	*n*	%	*p*-value
Age, years					
Median (Q1, Q3)	41	(36, 47)	39	(34, 45)	<0.0001
18–34	2228	20.1	2374	25.9	<0.0001
35–49	6968	62.7	5562	60.8	
⩾50	1916	17.2	1213	13.3	
Sex					0.0631
Male	9592	86.3	7814	85.4	
Female	1520	13.7	1335	14.6	
Marital status					<0.0001
Unmarried	8398	75.6	7195	78.6	
Married	2714	24.4	1954	21.4	
Education					0.7793
Junior high school	5756	51.8	4698	51.4	
Senior high school	4890	44.0	4056	44.3	
College	466	4.2	395	4.3	
Treatment duration, days					
Median (Q1, Q3)	968	(620, 1460)	117	(41, 222)	<0.0001
Maximum dose, mg					
Median (Q1, Q3)	80	(60, 100)	50	(35, 70)	<0.0001
<45	1115	10.0	3477	38.0	<0.0001
45–64	2322	20.9	2567	28.1	
65–89	3149	28.3	1738	19.0	
⩾90	4526	40.7	1367	14.9	
Comorbidities					
HIV	1825	16.4	1041	11.4	<0.0001
Depression	2883	25.9	2608	28.5	<0.0001
HCV	3763	33.9	2425	26.5	<0.0001
HBV	834	7.5	557	6.1	<0.0001
ALD	192	1.7	219	2.4	0.0008
CVD	240	2.2	218	2.4	0.2880

MMT, methadone maintenance treatment; Q1, quartile 1; Q3, quartile 3; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; CVD, cardiovascular disease.

failed to receive the MMT treatment for a consecutive 14-days would be designated as 'out of MMT'. In this model, patients would be designated as the out-of-MMT group when they stopped MMT for more than 14 days, and patients in MMT were defined as the exposure group if they received MMT continuously (i.e. no time gap longer than 14 days). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of death.

All data management, statistical analyses, Kaplan–Meier survival curve plot, and the figure of mortality rates by cause of death were performed and generated using SAS 9.4 (SAS Institute, Cary, NC, USA) and Prism (GraphPad Software, La Jolla, CA, USA). A 2-sided p value less than 0.05 was considered significant.

Results

Characteristics of cohort

There were 20 261 drug-addicted patients aged from 18 to 77 years with MMT included in our study. We divided them into two groups by treatment cumulative duration: <365 days (Short; $n = 9149$) and ⩾365 days (Long; $n = 11\,112$). Table 3 showed the characteristics of the study subjects. The median age of long the group [median = 41 years with interquartile range (IQR) = 36–47] was 2 years older than that of the short group (median = 39 years with IQR = 34–45). More than 60% of the patients were 35–49 years old and more than 85% of the patients were

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Table 4. Cox model measured hazard ratios and 95% confidence intervals of mortality associated with time-dependent exposure to MMT

Variables	Deaths	Person-years (PY)	MR	HRs (95% CIs)[a]
Duration, days				
⩾365	755	49 863	1.51	0.67 (0.60–0.75)***
<365	917	36 501	2.51	1 (reference)
Age, years				
18–34	252	19 994	1.26	1 (reference)
35–49	980	53 352	1.84	1.44 (1.25–1.66)***
⩾50	440	13 019	3.38	2.68 (2.28–3.15)***
Sex				
Male	1515	73 945	2.05	1.39 (1.17–1.64)***
Female	157	12 419	1.26	1 (reference)
Marital status				
Unmarried	1315	66 030	1.99	1.14 (1.01–1.28)*
Married	357	20 334	1.76	1 (reference)
Education				
Junior high school	932	44 417	2.10	1.06 (0.83–1.36)
Senior high school	673	38 248	1.76	1.02 (0.80–1.32)
College	67	3699	1.81	1 (reference)
Maximum dose, mg				
<45	432	18 684	2.31	1 (reference)
45–64	476	20 357	2.34	1.21 (1.06–1.38)*
65–89	369	21 099	1.75	1.04 (0.90–1.20)
⩾90	395	26 224	1.51	0.96 (0.82–1.11)
Comorbidities				
HIV	396	12 052	3.29	1.91 (1.69–2.16)***
Depression	598	23 125	2.59	1.44 (1.30–1.60)***
HCV	729	26 242	2.78	1.29 (1.15–1.44)***
HBV	180	5840	3.08	1.18 (1.00–1.39)*
ALD	116	1602	7.24	2.92 (2.40–3.54)***
CVD	103	1830	5.63	2.53 (2.06–3.09)***

MMT, methadone maintenance treatment; MR, mortality rate, per 100 person-years; HRs, hazard ratios; CIs, confidence intervals; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; CVD, cardiovascular disease.
[a]Adjusting for in or out of MMT, duration, age, sex, marital status, education, maximum dose, and comorbidities.
***$p < 0.001$. *$p < 0.05$.

men in both groups. The median cumulative durations were 117 days (IQR = 41–222) in the short group and 968 days (IQR = 620–1460) in the long group. The median maximum dose of methadone was higher in the long group (median = 80 mg with IQR = 60–100) than in the short group (median = 50 mg with IQR = 35–70). Approximately two-thirds of the patients in the short group had maximum dose below 65 mg, while roughly two-fifths of the patients in the long group had maximum dose more than 90 mg. The proportion of unmarried patients in short group was 3% higher than that in the long group (78.6% *v.* 75.6%, $p < 0.0001$). The distributions of educational attainment were similar in both groups. There were about 50% of the patients having junior high school degrees, and another 50% having senior high school or higher degrees. Among the comorbidities, the proportions of having HIV (16.4% *v.* 11.4%), HCV (33.9% *v.* 26.5%) or HBV (7.5% *v.* 6.1%) in the long group were significantly higher than those in the short group. On the contrary, the proportions of patients having depression (25.9% *v.* 28.5%) or alcoholic liver disease (1.7% *v.* 2.4%) in the long group were significantly lower than those in the short group.

All-cause mortality

Table 4 demonstrated the all-cause mortality rates in both groups and HRs of mortality stratified by potential risk factors. Applying 'not showing up at the MMT clinics for more than 14 days' as the cut-off point, we divided the treatment episodes into 43 106 and 30 912 on- and off-MMT periods, and observed 736 and 935

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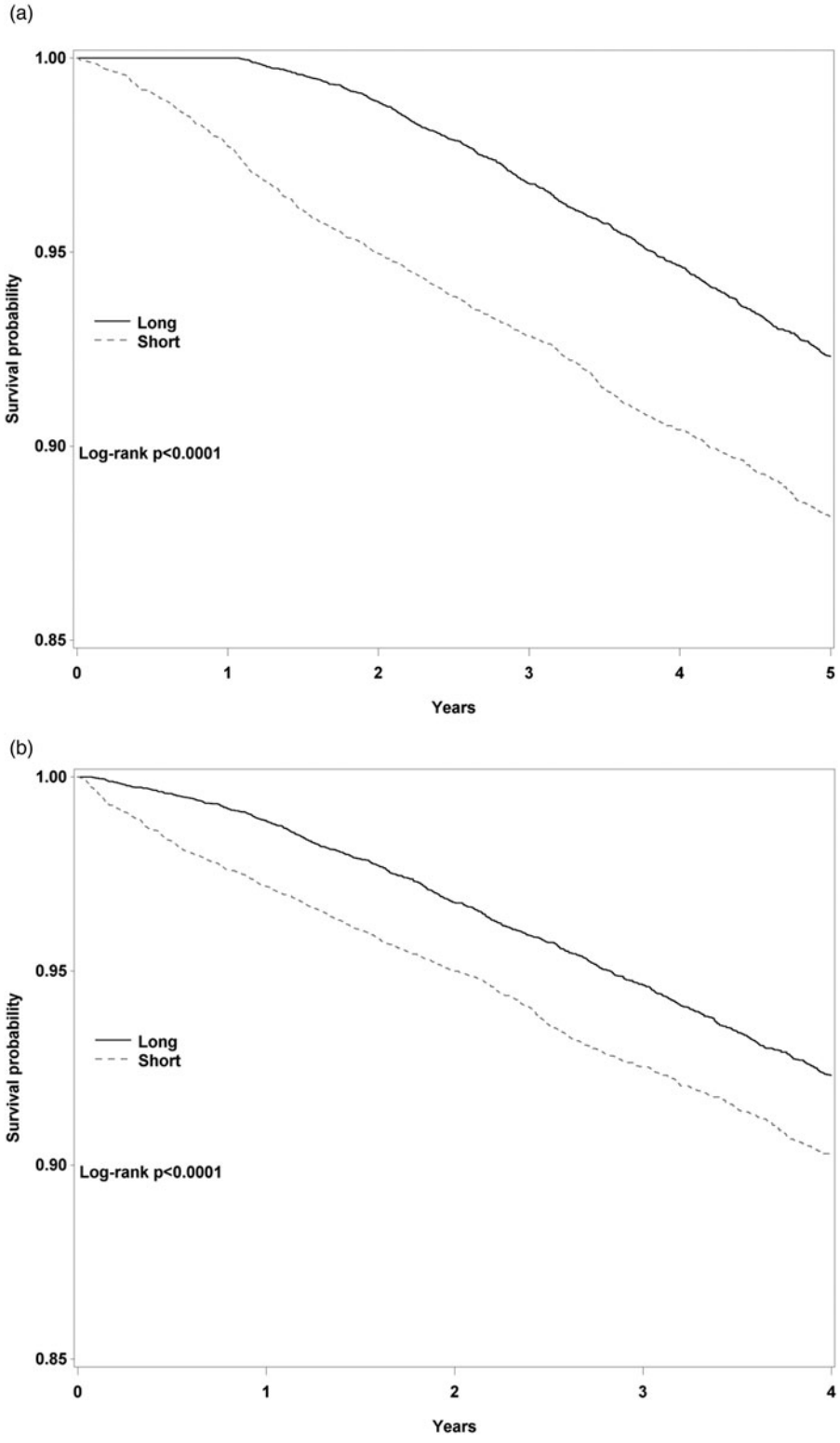

Fig. 2. Survival curves for the short (1–364 days) and long (⩾365 days) cumulative duration groups (a) immediately and (b) one year after the beginning of the follow-up period.

deaths, respectively. The mortality rate was 1.66-fold greater in the short group than in the long group (2.51 *v.* 1.51 per 100 person-years). It also increased with age, from 1.26 for patients aged 18–34 years to 3.38 for those aged more than 50 years, with an HR of 2.68 (95% CI 2.28–3.15) for the oldest group compared to the youngest group. In addition, males had a higher mortality rate than females (HR = 1.39 with 95% CI 1.17–1.64), and unmarried patients had higher mortality rate than married ones (HR = 1.14 with 95% CI 1.01–1.28). Among the comorbidities, the risk of mortality had strong association with HIV (HR = 1.91 with 95% CI 1.69–2.16), depression (HR = 1.44 with 95% CI 1.30–1.60), HCV (HR = 1.29 with 95% CI 1.15–1.44), HBV (HR = 1.18 with 95% CI 1.00–1.39), ALD (HR = 2.92 with 95% CI 2.40–3.54), and CVD (HR = 2.53 with 95% CI 2.06–3.09).

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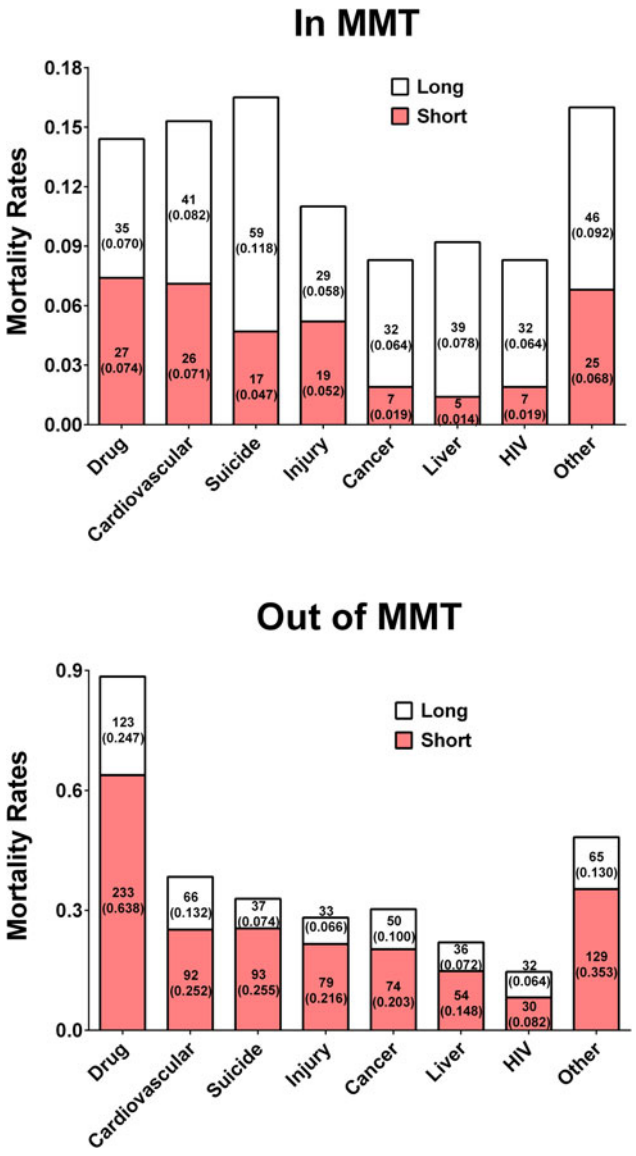

Fig. 3. Mortality rates by cause of death for the short (1–364 days) and long (⩾365 days) cumulative duration groups in or out of MMT. Numbers in bars represent number of deaths (mortality rates per 100 person-years).

Figure 2 illustrated the Kaplan-Meier plot for the survival probability over time between the two groups. The risk of mortality is lower for patients with longer duration (Log-rank $p <$ 0.0001).

Cause-specific mortality

Figure 3 showed the distributions of the cause-specific mortality rates (per 100 person-years) in the two groups in or out of MMT. Overall, patients in MMT had lower mortality rates than those out of MMT (0.992 *v.* 3.034). For patients in MMT, the short group had a higher mortality rate from drug (0.074 *v.* 0.070), but lower mortality rates from cardiovascular disease (0.071 *v.* 0.082), suicide (0.047 *v.* 0.118), injury (0.052 *v.* 0.058), cancer (0.019 *v.* 0.064), liver (0.014 *v.* 0.078), HIV (0.019 *v.* 0.064), and other causes (0.068 *v.* 0.092) compared to the long group. For patients out of MMT, however, the short group had higher mortality rates from all categories than the long group: drug (0.638 *v.* 0.247), cardiovascular disease (0.252 *v.* 0.132), suicide (0.255 *v.* 0.074), injury (0.216 *v.* 0.066), cancer (0.203 *v.* 0.100), liver (0.148 *v.* 0.072), HIV (0.082 *v.* 0.064), and other causes (0.353 *v.* 0.130). Combining the mortality rates both in and out of MMT, the short group had higher mortality rates due to drug (0.71 *v.* 0.32), cardiovascular disease (0.32 *v.* 0.21), suicide (0.30 *v.* 0.19), injury (0.27 *v.* 0.12), cancer (0.22 *v.* 0.16), liver (0.16 *v.* 0.15), and other causes (0.42 *v.* 0.22) than the long group. However, the short group had a lower mortality rate from HIV (0.10 *v.* 0.13). Age-stratified analysis further revealed that patients older than 50 years were more likely to die from cancer than other age groups.

Discussion

Our investigation of 20 261 MMT patients in Taiwan during 2012–2016 demonstrated that the cumulative MMT duration is associated with mortality rates. Compared to patients of short duration (<1 year), MMT patients of long duration (⩾1 year) were at a lower risk of death. Higher mortality rates were observed in MMT patients above 35 years old, being male, single, with HIV, depression, HCV, HBV, ALD, and CVD. On the other hand, education level and maximum dose of methadone did not affect the mortality significantly.

Greater drug service intensity and quality were related to longer treatment retention, which in turn was linked to better follow-up outcomes (Hser, Evans, Huang, & Anglin, 2004). According to the observations in our study, longer duration in MMT treatment is indeed associated with lower all-cause and drug-related mortality. Our finding corresponds to a previous nationwide study which showed that higher methadone doses were associated with longer treatment duration and lower mortality in patients with OUD in Taiwan during 2006–2008 (Liao et al., 2013), a study using 1616 patients from four general hospitals in central Taiwan between October 2006 and December 2008 that demonstrated remaining on MMT was protective for survival (Huang & Lee, 2013), as well as a study in individuals with OUD accessing pharmacological treatment in California, 2006–2010, indicating that MMT reduced the instantaneous hazard of all-cause and drug-related mortality (Evans et al., 2015). Diagnostic overshadowing (Shefer, Henderson, Howard, Murray, & Thornicroft, 2014), a patient with a mental illness receives inadequate or delayed treatment due to the misattribution of his physical symptoms to his mental illness, is a form of discrimination by healthcare professionals, and the often siloed nature of substance use disorder might make the situation even worse in patients with OUD. Besides HIV, we also identified depression, HCV, HBV, ALD, and CVD as the risk factors associated with mortality, indicating that healthcare for mental problems, viral liver diseases, co-existing alcoholism, and cardiovascular problems warrants more attention. Sofosbuvir and velpatasvir for hepatitis C virus infection should be offered to people who inject drugs (Grebely et al., 2018). Collaborative care for opioid and alcohol use disorders in primary care (Watkins et al., 2017) could be one solution to assist the MMT patient with alcohol use disorder.

Our study has several limitations. First, compared to mortality rates for U.S. residents in the age group between 15 and 64, the overall mortality rate of State prisoners was 19% lower during 2001 to 2004 (Mumola, 2007), indicating that imprisonment might be a protection factor for mortality. Additionally, the transition from prison back into the community is especially hazardous for OUD patients, with a boosted risk of drug-related death

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right after release from prison (Merrall et al., 2010). Unfortunately, we did not have complete access of data on imprisonment due to privacy concerns from the Ministry of Justice and hence could not correct the confounding factors concerning incarceration. Second, OUD may influence comorbidities, so we used HIV, depression, HCV, HBV, ALD, and CVD to eliminate the confounding factors caused by OUD. Yet, a bias attributable to the presence of unknown confounders may still exist. Plus, many people do not seek treatment immediately when they get sick, and therefore comorbidities may be under-ascertained when using health records. Third, the absence of complete data on poly-drug use limited our ability to associate patients with OUD using other illicit drugs with a higher risk of mortality. Fourth, there are no data on the genotypes to predict retention and associate potential risk for death. Fifth, a cumulative count of days of MMT use over a five year period is an imperfect marker of treatment retention/duration, so we need to be careful when comparing the results in this study to the results of other studies since other studies may have different definitions of treatment retention. All of these warrant future research to identify the risk factors and propose prevention strategies of mortality in MMT patients.

In conclusion, patients with cumulative MMT duration more than 365 days were with lower all-cause and drug-related mortality. Male patients above 35 years old, single, with HIV, depression, HCV, HBV, ALD, and CVD are of higher risk for death. Besides increasing the treatment duration of MMT patients via improving the service quality and intensity, concomitant medical care on comorbidities may be worthy for better outcome of patients with OUD.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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