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Predictors of retention and mortality among patients on methadone maintenance therapy

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Summary

Background: Methadone maintenance therapy (MMT) was started as a pilot project in Malaysia in 2005, and many individuals have benefited from it. **Aim:** This study aimed to examine the retention rate among patients enrolled in a tertiary hospital MMT programme in Malaysia, as well as factors predicting retention and mortality among these patients. **Methods:** A total of 164 patients were enrolled in a MMT programme implemented at a tertiary centre in Malaysia between 2005 to 2013. During enrolment, sociodemographic data, blood investigations and urine toxicology were recorded, along with Opiate Treatment Index (OTI) and World Health Organisation Quality of Life (WHOQOL)-BREF scores. Data, including the most recent follow-up date of patients and their daily methadone dose, were obtained retrospectively, in 2015. Retention rate was ascertained on the basis of living patients who stayed in the MMT programme up to 2015. Factors predicting retention rate and mortality were ascertained using Cox's proportional hazards regression analysis. **Results:** The retention rate for MMT at its implementation 10 years ago was 70.1%. Methadone dose ≥ 80 mg/day significantly predicted better retention, while HIV risk-taking behaviour significantly predicted poorer retention in MMT. Mortality was found to be significantly lower among patients of Malay ethnicity and higher among patients who had been found to have HIV and other medical illnesses. **Conclusions:** MMT retention rate at a tertiary centre in Malaysia was high, but more effort is required to enhance retention among patients with HIV risk-taking behaviour, while also attempting to improve the health of patients with HIV and other medical illnesses.

Key Words: Methadone; Opioid Use Disorder; retention; mortality; HIV

1. Introduction

Substance use disorder remains a serious global concern, which is why many countries, including Malaysia, attempt to control the rate of illicit drug use. As many as 246 million people were reported to have used an illicit drug in 2013 worldwide, with 27 million people having substance use disorders and almost half of this number injecting drugs [36].

In Malaysia, the cumulative number of people who used drugs from year 1988 to 2015 was 413,754, making up 1.4% of its total population. Opioids remain the most frequently used drug, accounting for 60.5% of all the drugs used [1]. While 76.1% of the people who were identified as drug users in 2015 were new cases, the remaining 23.9% were individu-

als who had undergone some form of treatment provided by the National Anti-Drug Agency of Malaysia. This is not surprising, in view of the neurobiological factors which worsen the vulnerability to relapse of this group of individuals [15].

Methadone maintenance therapy (MMT) was started as a research project centring on narcotic addiction in 1964 by Dole and Nyswander [7], and has been recognized to be an effective treatment for opioid use disorder [39]. Although proven to be effective in improving various outcomes related to opioid use disorder [10, 21], the issue of whether patients remain in methadone treatment or not should always be considered. This is crucial, because treatment dropout is associated with adverse outcomes such as overdose and mortality [5, 8], whereas staying in methadone

treatment is associated with more desirable outcomes [4, 41].

Retention rate at 1 year ranges from 53% to 87% in different countries [13, 28, 40]. Factors found to predict retention include greater age, higher methadone dose, treatment satisfaction and good family support, whereas imprisonment, living in a rural area and having to travel a longer distance from home to the clinic predicted patient drop-out [17, 37, 40].

In Malaysia, MMT started as a pilot project at the University of Malaya Medical Centre in 2005. A pilot trial was conducted then, and the retention rate was found to be 75% after 18 weeks of methadone treatment [12]. At that time it seemed like a heartening achievement, as the pilot trial was done without prior experience in the local setting, in addition to the widespread resistance and criticisms expressed against its use. Since then MMT has been expanded, and in 2011 was being offered in 674 centres nationwide [24].

While patients with opioid use disorder who receive methadone treatment have a higher probability of survival than those not on methadone, studies have found that some factors may increase mortality among patients in methadone treatment, such as HIV infection, polysubstance use, use of medications causing QTc prolongation, and electrolyte abnormalities [8, 25]. On the other hand, higher methadone doses and increased duration of methadone treatment were found to be associated with lower mortality [2, 16].

As MMT was reaching the 10-year mark since its first implementation in Malaysia, this study aimed to examine the retention rate among patients in one of the earliest MMT programmes initiated here, as well as factors predicting retention and mortality in these patients.

2. Methods

2.1. Design of the study

This was a retrospective study carried out in the University of Malaya Medical Centre (UMMC), a tertiary hospital located in Kuala Lumpur, the capital of Malaysia. It offers full psychiatric services, including an addiction psychiatry service.

Ethics approval was obtained from the medical ethics committee of UMMC prior to commencement of the study.

2.2. Sample

Patients were enrolled in the MMT programme at the University of Malaya Medical Centre from 2005 to 2013. Those who were enrolled were aged 18 years and above, fulfilled the criteria for opioid dependence based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) and consented to methadone treatment as well as the programme policies. The MMT programme was strictly regulated by the Malaysian National Methadone Maintenance Therapy Guidelines, which include suitability for treatment, contraindications, assessment and monitoring [23].

A total of 164 patients enrolled in the MMT programme from 2005 to 2013. All patients were male. The patients had a mean age of 40.7 years (SD \pm 10.09) at entry to the programme, and consisted predominantly of Malays (84.8%). A majority of the patients had secondary education (92.1%), were unemployed (75.6%) and did not have a sexual partner (72.0%) at entry to the programme. More than half of the patients (57.9%) had hepatitis C, while a smaller proportion had HIV (6.7%), hepatitis B (4.9%) or and other medical illnesses (4.9%).

2.3. Instruments

OTI is a structured interview used to assess various domains, including drug use, HIV risk-taking behaviour, social functioning, criminal behaviours and health. Each domain comprises a number of questions, ranging between 4 and 12. The drug use domain allows the calculation of a quantity/frequency estimate (Q score) of the drug used in the month prior to interview. The HIV risk-taking behaviour domain is further subdivided into needle use behaviour and sexual behaviour, and is scored on a scale of 0 to 5 for each question. The social functioning and crime domains are scored on a scale of 0 to 4 for each question. The health domain, on the other hand, is a symptom checklist designed to give an indication of the state of the patient's physical health in the month prior to interview, and within it a score of 1 is recorded for each symptom the patient has. In all domains, a higher score indicates a greater degree of dysfunction.

WHOQOL-BREF is a self-administered questionnaire used to assess quality of life in physical health, psychological, social relationships and environmental domains, as well as the overall quality of life and general health. It comprises 26 questions in all, and each question is assessed on a scale of 1 to

5. Higher scores within any domain indicate a higher quality of life in that particular domain.

Induction of methadone treatment and dose titration were carried out according to the national guidelines [23]. Patients were given follow-up appointments during which they would be assessed by doctors, and urine toxicology was performed during the follow-up appointments. All information was kept confidential in individual case notes that were standardized nationwide for all patients then on an MMT programme.

The definition of 'retention' includes living patients who remained in the MMT programme up to June 2015. Patients who were incarcerated were considered to have dropped out. Duration of retention is calculated from the time of entry into the MMT pro-

gramme either until drop-out or June 2015. For patients who had died, the date of death was traced from their records, and that group of patients was analysed separately.

2.4. Procedure

Upon enrolment, sociodemographic data were collected, and blood investigations were carried out, including those on HIV, hepatitis B and hepatitis C besides urine toxicology. Patients were also required to complete the Opiate Treatment Index (OTI) and World Health Organisation Quality of Life (WHOQOL)-BREF questionnaires to allow them to be assessed.

In June 2015, a decade after the initial implementation of the MMT programme in 2005, information regarding the patients who had enrolled in the programme was obtained retrospectively. Data comprising sociodemographic data, blood investigation results, and any documented medical illnesses, as well as OTI and WHOQOL-BREF scores at baseline, were obtained from patients' individual case notes. Frequency of urine positivity for opioids within a year following initiation of methadone treatment was ascertained, too. The last follow-up date for each patient, and his/her daily methadone dose, were traced from the medical records. Further information on patients who had stopped coming to follow-up sessions was traced from the hospital computer-generated system, other case notes or via phone calls.

2.5. Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS, Inc.). Cumulative retention rates of patients on MMT were calculated using life tables method, after excluding patients who had died or transferred to other centres. To determine factors associated with retention in MMT, Cox univariate regression analysis was performed on patients after excluding those who had died or been transferred to other centres. To determine factors associated with mortality, Cox univariate regression analysis was performed on patients after excluding those who were transferred to other centres. Variables in both analyses which were statistically significant at the level of $p < 0.05$ (two-tailed) were included in the Cox multivariate regression analyses.

Table 1. Sociodemographic characteristics of the patients

Variable	M±sd or N (%)
Mean age at entry to MMT (years)	40.7±10.09
Ethnicity	
Malay	139 (84.8)
Chinese	14 (8.5)
Indian	10 (6.1)
Others	1 (0.6)
Education level	
No formal education	1 (0.6)
Primary education	8 (4.9)
Secondary education	151 (92.1)
Tertiary education	4 (2.4)
Employment	
Yes	40 (24.4)
No	124 (75.6)
Sexual partner	
Yes	46 (28.0)
No	118 (72.0)
Comorbid medical illness	
HIV positive	11 (6.7)
Hepatitis B positive	8 (4.9)
Hepatitis C positive	95 (57.9)
Other medical illness	8 (4.9)
Status of patients at end of follow-up	
Retained	96 (58.5)
Transferred to other centres	10 (6.1)
Died	17 (10.4)
Dropped out	41 (25.0)
Mean dose of methadone (mg/day)	
Retained	90.68±30.80
Dropped out	64.39±25.70
Mean duration of MMT (years)	
Retained	7.56±1.41
Dropped out	3.22±1.92

3. Results

3.1. Study Population Characteristics

At the time of data collection in June 2015, 96 patients were still participating in the MMT programme (58.5%), 10 patients had transferred to other centres (6.1%), 17 patients had died (10.4%), while 41 patients (25.0%) had dropped out of treatment. Patients who remained in the MMT programme were on a higher mean dose of methadone (90.68 mg/day) compared with those who had dropped out (64.39 mg/day). The mean duration of MMT for patients who remained in the programme was 7.56 years, while the mean duration for those who had dropped out was 3.22 years (Table 1).

3.2. Retention Rate

After excluding patients who had died or transferred to other centres, the retention rate was 70.1%.

Using the life tables method, the cumulative retention rates were 94% at 1 year, 82% at 3 years and 74% at 5 years. The largest number of patients who dropped out was found at 3 years, and subsequently there was no further drop-out of patients from 8 years onwards. Figure 1 shows the survival curve for MMT retention rate.

3.3. Cox's Proportional Hazards Regression Analysis on Factors Predicting MMT Retention

In the univariate Cox's proportional hazards regression analysis on factors predicting MMT retention, methadone dose ≥ 80 mg/day ($p < 0.001$), other substance use in the month prior to initiation of methadone treatment ($p = 0.040$), HIV risk-taking behaviour ($p = 0.044$) and quality of health in the psychological ($p = 0.029$) and environmental ($p = 0.022$) domains were significantly associated with retention in MMT.

In the multivariate Cox's proportional hazards

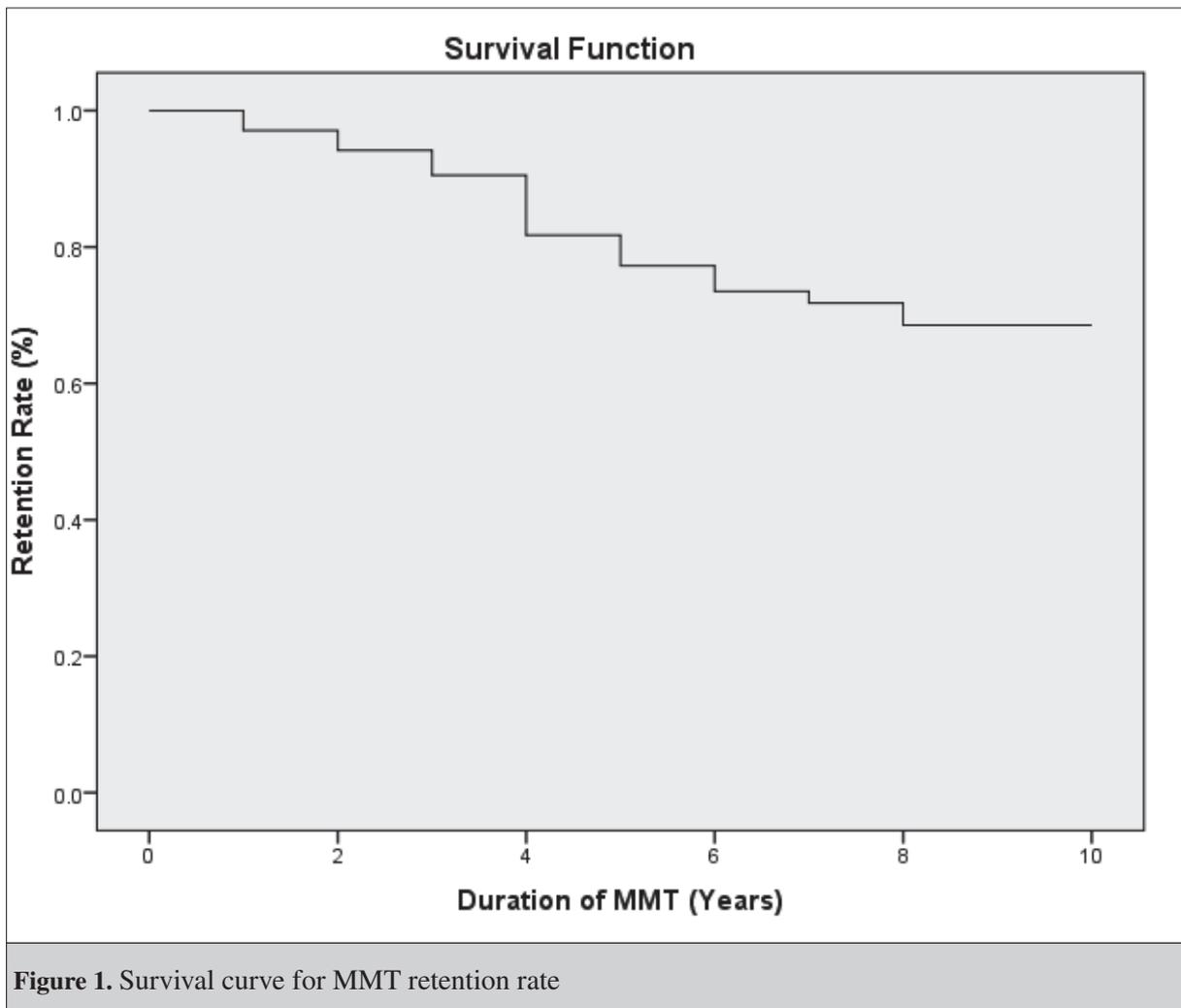


Table 2. Cox proportional hazards regression analysis on factors predicting MMT retention

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age (years)	1.00	0.97 – 1.04	0.816			
Ethnicity						
Malay	1.02	0.40 – 2.60	0.967			
Non-Malay (ref)						
Sexual partner						
Yes	0.99	0.51 – 1.94	0.978			
No (ref)						
Education level						
> 6 years	2.75	0.38 – 20.00	0.318			
≤ 6 years (ref)						
Employment						
Yes	0.99	0.50 – 1.94	0.970			
No (ref)						
Methadone dose						
< 40 mg/day (ref)						
40 – 79 mg/day	0.70	0.31 – 1.59	0.393	0.79	0.33 – 1.89	0.600
≥ 80 mg/day	0.20	0.08 – 0.47	< 0.001*	0.23	0.09 – 0.55	0.001*
HIV						
Positive	0.05	0.00 – 117.12	0.444			
Negative (ref)						
Hepatitis B						
Positive	0.66	0.09 – 4.78	0.677			
Negative (ref)						
Hepatitis C						
Positive	1.46	0.77 – 2.75	0.247			
Negative (ref)						
Other medical illnesses						
Positive	0.84	0.12 – 6.08	0.859			
Negative (ref)						
Other substance use in the month prior to MMT						
Yes	1.93	1.03 – 3.63	0.040*	1.90	0.97 – 3.73	0.062
No (ref)						
Frequency of urine positivity within a year after initiation of MMT	0.95	0.82 – 1.11	0.501			
OTI score at baseline						
Quantity/frequency of heroin use in the month prior to MMT	0.99	0.98 – 1.00	0.196			
HIV risk-taking behaviour	1.06	1.01 – 1.12	0.044*	1.06	1.01 – 1.12	0.054*
Social functioning	1.03	0.98 – 1.09	0.267			
Crime	0.76	0.44 – 1.31	0.320			
Health	1.02	0.96 – 1.09	0.569			
WHOQOL-BREF at baseline						
Physical health	0.96	0.89 – 1.03	0.222			
Psychological	0.91	0.84 – 0.99	0.029*	0.97	0.86 – 1.08	0.549
Social relationships	0.90	0.78 – 1.04	0.163			
Environment	0.92	0.85 – 0.99	0.022*	0.97	0.88 – 1.08	0.580
Overall QOL and general health	0.84	0.68 – 1.04	0.107			

Notes: ref = Reference group; HR = Hazard ratio; *Significant when $p < 0.05$

regression analysis, methadone dose ≥ 80 mg/day was significantly associated with better retention in MMT (HR = 0.23; 95% CI = 0.09 – 0.55; $p = 0.001$). HIV risk-taking behaviour at baseline (HR = 1.06; 95% CI = 1.01 – 1.12; $p = 0.054$) was significantly associated with poorer retention in MMT (Table 2).

3.4. Cox's Proportional Hazards Regression Analysis on Factors Predicting Mortality Among Patients on MMT

In the univariate Cox's proportional hazards regression analysis on factors predicting mortality among patients on MMT, ethnicity ($p = 0.004$), HIV

Table 3. Cox proportional hazards regression analysis on factors predicting mortality among patients on MMT

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age (years)	1.04	0.99 – 1.10	0.108			
Ethnicity						
Malay	0.24	0.09 – 0.63	0.004*	0.21	0.07 – 0.60	0.004*
Non-Malay (ref)						
Sexual partner						
Yes	0.76	0.25 – 2.34	0.636			
No (ref)						
Education level						
> 6 years	1.04	0.14 – 7.84	0.970			
≤ 6 years (ref)						
Employment						
Yes	0.40	0.16 – 1.04	0.060			
No (ref)						
Methadone dose						
< 40mg (ref)						
40 – 79mg	1.41	0.31 – 6.45	0.655			
≥ 80mg	0.33	0.06 – 1.68	0.181			
HIV						
Positive	9.10	3.35 – 24.74	< 0.001*	11.05	3.67 – 33.31	< 0.001*
Negative (ref)						
Hepatitis B						
Positive	3.08	0.70 – 13.46	0.136			
Negative (ref)						
Hepatitis C						
Positive	1.81	0.64 – 5.15	0.264			
Negative (ref)						
Other medical illnesses						
Positive	6.79	2.21 – 20.91	0.001*	5.35	1.61 – 17.82	0.006*
Negative (ref)						
Other substance use in the month prior to MMT						
Yes	0.60	0.17 – 2.10	0.428			
No (ref)						
Frequency of urine positivity within a year after initiation of MMT	0.94	0.73 – 1.20	0.613			
OTI score at baseline						
Quantity/frequency of heroin use in the month prior to MMT	0.99	0.97 – 1.01	0.175			
HIV risk-taking behaviour	1.06	0.98 – 1.14	0.161			
Social functioning	1.08	1.00 – 1.16	0.047*			
Crime	1.00	0.57 – 1.76	0.996	1.06	0.98 – 1.15	0.154
Health	1.05	0.96 – 1.14	0.138			
WHOQOL-BREF at baseline						
Physical health	0.96	0.85 – 1.08	0.474			
Psychological	0.91	0.80 – 1.03	0.144			
Social relationships	0.84	0.68 – 1.04	0.109			
Environment	0.98	0.88 – 1.10	0.777			
Overall QOL and general health	0.93	0.66 – 1.32	0.694			

Notes: ref = Reference group; HR = Hazard ratio; *significant when $p < 0.05$

status ($p < 0.001$), other medical illnesses ($p = 0.001$) and social functioning at baseline ($p = 0.047$) were significantly associated with mortality.

In the multivariate Cox's proportional hazards regression analysis, Malay ethnicity (HR = 0.21;

95% CI = 0.07 – 0.60; $p = 0.004$) was significantly associated with lower mortality. Being HIV-positive (HR = 11.05; 95% CI = 3.67 – 33.31; $p < 0.001$) and having other medical illnesses, such as tuberculosis, renal failure and cancer (HR = 5.35; 95% CI = 1.61

– 17.82; $p = 0.006$), were associated with higher mortality (Table 3).

4. Discussion

Findings from this study showed that the retention rate for MMT in a tertiary hospital located in the main city of Malaysia was 70.1% during the 10 years following its implementation. Methadone dose ≥ 80 mg/day was significantly associated with better retention, whereas HIV risk-taking behaviour in the month prior to methadone treatment was associated with poorer retention in MMT. Patients in MMT who were of Malay ethnicity were found to have significantly lower mortality, whereas being HIV-positive and having other medical illnesses corresponded to significantly increased mortality.

The retention rate of 70.1% found in our study in the decade following the initial implementation of MMT was a heartening figure, considering that the retention rate at 18 weeks was 75% during the pilot study conducted in the same centre when MMT was first introduced in Malaysia [12]. Other studies carried out here showed various retention rates, ranging from 63% to 95% after 2 years [27, 31]. The cumulative retention rates of 94% at 1 year, 82% at 3 years and 74% at 5 years found in our centre seem relatively high compared with other Asian countries. One study conducted in Indonesia reported a 6-month retention rate of 61.3% [33], while the 1-year retention rate in China showed a wide range, from as low as 13% to as high as 87% [13, 40].

The high retention rate in our centre may be attributable to the location of our centre, which is in the middle of an urban area in the capital city of Malaysia, making it easily accessible to individuals staying in the city or in other nearby cities. A study carried out in China found that patients living in rural areas were more likely to drop out from MMT compared with those living in urban areas, possibly due to poor socioeconomic status or to differences in the skills of medical staff working in methadone clinics [40]. An inconvenient methadone clinic location is similarly found to be associated with a higher risk of failing to appear at follow-up appointments, while direct observation treatment requires daily travel to a clinic, which creates serious issues in terms of time and money [3]. Besides being in a central location, our centre provides takeaway doses for patients who fulfil the criteria laid down by the Malaysian National Methadone Maintenance Therapy Guidelines, so they do not have to travel to the clinic daily for metha-

done treatment [23]. Studies have concluded that take-home doses result in enhanced treatment retention [29, 32]. In addition to saving money and time, patients do not need to frequently take leave off from work to attend the clinic once they find employment, thus enhancing retention in methadone treatment.

In our study, being on a methadone dose ≥ 80 mg/day was significantly associated with better retention in methadone treatment. This finding was in line with other local studies which demonstrated a similar result. A study conducted in the same centre found that higher doses of methadone were correlated with the retention rate, with 80% of those retained being on a methadone dose of 80mg or more [26]. Considering now those released from prison, methadone dose ≥ 80 mg/day at the time of release was associated with retention in treatment 12 months post-release from prison [38]. In fact, a higher methadone dose proved to be one of the strongest predictors of retention in methadone treatment, surpassing both buprenorphine < 8 mg/day and levo-acetylmethadol (LAAM) in retention rates [9, 33, 37]. Higher doses of methadone may result in lower opioid use and opioid craving, thus enhancing retention in methadone treatment [18, 34].

Our study found that HIV-risk taking behaviour in the month prior to MMT initiation, which includes needle use and sexual behaviour, was a predictor of poor retention in methadone treatment. This was similar in trend to another study which showed that sharing needles was a risk factor for MMT retention [40]. Similarly, syringe lending, heroin injection and sex trade involvement were demonstrated to be negatively correlated with MMT use in another study [14]. It remains true that the knowledge and attitude of individuals with HIV-risk taking behaviour towards MMT needs to be further investigated, but it is worrying that this group of individuals is at higher risk of drop-out from MMT, given the effectiveness of MMT in reducing HIV risk behaviour and HIV seroconversion [11].

In terms of mortality among MMT patients, our study found that those of Malay ethnicity had lower mortality compared with other races in Malaysia. This finding reflects the differences in mortality rate among the different ethnic groups in Malaysia, as can be observed in the national statistics for 2014, which demonstrated that Indians had the highest crude death rate (6.3 per 1,000 population), followed by the Chinese (5.9 per 1,000 population) and then by the Bumiputera – a group that includes Malays (4.8 per 1,000 population) [6]. While the exact reason for this

difference remains unclear, some studies have demonstrated ethnic differences in non-communicable diseases, in which diabetes and coronary heart disease were more prevalent among Indians, whereas Chinese people had the highest rate for hypertension and hyperlipidaemia [19, 35]. These illnesses may not have been detected during follow-up, given the asymptomatic nature of some of these illnesses.

On the other hand, being HIV-positive and having other medical illnesses, such as tuberculosis, renal failure and cancer, were associated with increased mortality among patients in MMT. This finding was parallel with other studies which likewise demonstrated the association between HIV and increased mortality among patients on MMT [8, 16]. In any case, the mortality rate among those not on antiretroviral therapy seemed to be twice the rate recorded for those on antiretroviral therapy [2]. This highlights the importance of antiretroviral therapy among this group of individuals; given that patients on MMT attend a methadone clinic regularly to obtain methadone, a logical proposal would be to have a combined clinic providing methadone services alongside medical services such as treatment for HIV, which would improve their compliance with both treatments. It has, indeed, been shown that patients who received directly administered antiretroviral therapy in methadone clinics were more likely to achieve viral suppression than those who were on self-administered antiretroviral therapy [20, 22]. In addition, having clinics that combine methadone treatment with medical services may be beneficial for patients with illnesses that are known to be at high risk among drug users, such as tuberculosis, in detecting, treating and improving compliance with treatment.

Limitations

One of the main limitations of this study is that it was conducted in one centre located in an urban area, so prompting the reflection that the retention rate found in our centre may not accurately reflect the retention rates that might be found in other geographical locations, such as rural or more inaccessible areas. In addition, our sample consisted entirely of male patients, which implies that our result may not be representative of all opioid patients, as gender has been demonstrated to influence retention rates and mortality [2, 30]. Thirdly, our study did not take into account the possibility that patients may have dropped out of and then reinitiated methadone treatment within the full duration of treatment. It is known that opioid use

disorder is a chronic condition in which relapses are not uncommon; this study, however, aimed to examine the long-term retention rate over 10 years rather than the short-term rate. Having said that, this is the only study in Malaysia, to the best of our knowledge, to have investigated the retention rate in MMT since MMT was inaugurated a decade ago in Malaysia.

5. Conclusions

The retention rate for MMT at a tertiary centre in Malaysia since its first implementation just over 10 years ago was 70.1%. Methadone dose ≥ 80 mg/day predicted better retention, whereas HIV-risk taking behaviour predicted poorer retention in MMT. Mortality was lower among Malays and higher among patients who had HIV and other medical illnesses. Although the MMT programme was only initiated in Malaysia just over a decade ago, the retention rate found in our study can be considered fairly high, and is an achievable target. Thus the MMT programme should be more widely implemented and made available in more health centres, with adequate attention given to methadone dosing, while also attempting to meet the needs of groups of individuals with HIV risk-taking behaviour, HIV and other medical illnesses.

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Contributors

JT and AY designed the study and conducted the research. MD was involved in statistical analysis. JT and AY prepared the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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