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# Cost-effectiveness and cost-utility analysis of outpatient follow-up frequency in relation to three-year mortality in discharged patients with bipolar disorder

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ABSTRACT

There is a lack of clarity in terms of cost-effectiveness and cost-utility comparisons across different outpatient (OPD) follow-up patterns in discharged patients with bipolar disorder (BD). In this study, adult patients hospitalised for BD treatment ($n$ = 1,591) were identified from the National Health Insurance Research Database in Taiwan. With survival as the effectiveness measure and quality-adjusted life years (QALYs) as the utility measure, a cost-effectiveness and cost-utility analysis was conducted over the 3-year follow-up period by post-discharge frequency of OPD visits. Compared to those making 1–7, 8–12 and 18 or more OPD visits, BD patients making 13–17 OPD visits within the first year after discharge had the lowest psychiatric and total healthcare costs over the follow-up period. With survival status as the effectiveness outcome, making 13–17 OPD visits was more likely to be the cost-effective option, as revealed by incremental cost-effectiveness ratios. Cost-utility analysis demonstrated that having 13–17 OPD visits was probably the more cost-effective option when considering QALYs; for instance, if society was willing to pay NTD1.5 million for one additional QALY, there was a 75.2% (psychiatric costs) to 77.4% (total costs) likelihood that 13–17 OPD visits was the most cost-effective option. In conclusion, post-discharge OPD appointments with a frequency of 13–17 visits within the first year were associated with lower psychiatric and total healthcare costs in the subsequent 3 years. Having an adequate outpatient follow-up frequency was likely to be cost-effective in the management of discharged patients with BD in this real-world setting.

## 1. Introduction

Bipolar disorder (BD) is associated with premature death. Women and men with BD die on average 9.0 and 8.5 years earlier than the rest of the population, respectively (Crump et al., 2013). Compared with the general population, all-cause mortality is elevated approximately two- to threefold among individuals with BD (Chang et al., 2010; Chesney et al., 2014; Pan et al., 2017) and they have been reported to have higher risk of mortality from various causes including cardiovascular disease, diabetes mellitus, unintentional injuries, and suicide (Chesney et al., 2014; Crump et al., 2013). BD strongly affects an individual's ability to maintain quality of life owing to its early onset, severity, and chronicity. In terms of years lived with disability (YLDs), BD accounts for 1.3% of the total YLDs among all diseases globally (Ferrari et al., 2016). Prior data have consistently shown that BD represents a substantial economic burden for patients, caregivers, healthcare providers, and society in terms of costs associated with the healthcare, social, and justice systems. Although individuals with BD may have wide-ranging needs, in simple cost terms, health services still constitute the single largest share. The annual societal costs per capita of BD are reported to vary from US$1,904 to US$33,090 (Jin and McCrone, 2015) while the reported cost per capita of total direct healthcare of BD ranges from approximately US$8,000 to US$14,000 (Kleine-Budde et al., 2014).

Given the huge impacts of BD on the individual and society, efforts to improve healthcare services should ideally address both outcomes, including mortality, and the need for cost savings. Pan et al. (2016)

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**Table 1**
Demographic and clinical characteristics.

| | Full sample of patients with BD ($n$ = 1,591) Whole group ($n$ = 1,591) | OPD 1–7 ($n$ = 483) | OPD 8–12 ($n$ = 431) | OPD 13–17 ($n$ = 369) | OPD ≧18 ($n$ = 308) | Statistics |
|---|---|---|---|---|---|---|
| **Age [mean (SD)]** | 41.60(13.90) | 40.65(13.83) | 42.75(14.77) | 42.78(14.17) | 40.07(12.14) | $F = 3.888$, $p = 0.009$* |
| **Male [n (%)]** | 763(48.0) | 269(55.7) | 186(43.2) | 183(49.6) | 125(40.6) | $\chi^2 = 22.668$, $p < 0.001$* |
| **Newly-diagnosed patients with BD [n (%)]** | 820(51.5) | 279(57.8) | 205(47.6) | 193(52.3) | 143(46.4) | $\chi^2 = 13.528$, $p = 0.004$* |
| **Low Income household [n (%)]** | 73(4.6) | 26(5.4) | 16(3.7) | 10(2.7) | 21(6.8) | $\chi^2 = 7.924$, $p = 0.048$* |
| **Insurance premium [n (%)]** | | | | | | $\chi^2 = 7.200$, $p = 0.616$ |
| **Level (1)** | 1018(64.0) | 328(67.9) | 278(64.5) | 223(60.4) | 189(61.4) | |
| **Level (2)** | 511(32.1) | 137(28.4) | 138(32.0) | 130(35.2) | 106(34.4) | |
| **Level (3)** | 57(3.6) | 17(3.5) | 13(3.0) | 15(4.1) | 12(3.9) | |
| **Level (4)** | 5(0.3) | 1(0.2) | 2(0.5) | 1(0.3) | 1(0.3) | |
| **Catastrophic illness card [n (%)]** | 978(61.5) | 253(52.4) | 299(69.4) | 234(63.4) | 192(62.3) | $\chi^2 = 28.902$, $p < 0.001$* |
| **Comorbid physical illness** | | | | | | |
| **Cancer [n (%)]** | 29(1.8) | 10(2.1) | 7(1.6) | 8(2.2) | 4(1.3) | $\chi^2 = 0.979$, $p = 0.806$ |
| **Cardiovascular disease [n (%)]** | 254(16.0) | 63(13.0) | 71(16.5) | 59(16.0) | 61(19.8) | $\chi^2 = 6.542$, $p = 0.088$ |
| **Chronic obstructive pulmonary disease [n (%)]** | 156(9.8) | 38(7.9) | 41(9.5) | 37(10.0) | 40(13.0) | $\chi^2 = 5.639$, $p = 0.131$ |
| **Diabetes mellitus [n (%)]** | 157(9.9) | 44(9.1) | 50(11.6) | 36(9.8) | 27(8.8) | $\chi^2 = 2.193$, $p = 0.533$ |
| **Hyperlipidemia [n (%)]** | 151(9.5) | 35(7.2) | 41(9.5) | 36(9.8) | 39(12.7) | $\chi^2 = 6.469$, $p = 0.091$ |
| **Hypertension [n (%)]** | 257(16.2) | 70(14.5) | 67(15.5) | 68(18.4) | 52(16.9) | $\chi^2 = 2.632$, $p = 0.452$ |
| **Renal disease [n (%)]** | 46(2.9) | 11(2.3) | 10(2.3) | 14(3.8) | 11(3.6) | $\chi^2 = 2.727$, $p = 0.436$ |
| **Stroke [n (%)]** | 34(2.1) | 10(2.1) | 6(1.4) | 10(2.7) | 8(2.6) | $\chi^2 = 2.045$, $p = 0.563$ |
| **Comorbid mental illness** | | | | | | |
| **Other psychotic disorder [n(%)]** | 182(11.4) | 48(9.9) | 46(10.7) | 50(13.6) | 38(12.3) | $\chi^2 = 3.193$, $p = 0.363$ |
| **Substance-related disorder [n (%)]** | 211(13.3) | 62(12.8) | 49(11.4) | 46(12.5) | 54(17.5) | $\chi^2 = 6.505$, $p = 0.089$ |
| **Alcohol-related disorder [n (%)]** | 94(5.9) | 46(9.5) | 18(4.2) | 18(4.9) | 12(3.9) | $\chi^2 = 16.631$, $p = 0.001$* |
| **Baseline total healthcare costs [mean (SD)]** | 113,982 (136,871) | 111,141 (142,854) | 112,428 (143,867) | 99,813 (117,194) | 137,590 (136,800) | $F = 4.490$, $p = 0.004$* |

BD = bipolar disorder; SD = standard deviation; OPD = outpatient department.
Baseline total healthcare costs were expressed in New Taiwan Dollar (NTD); the implied purchasing power parity conversion rate between 2008–2009 NTD and the international dollar was 16.99:1.
Insurance premium was classified into four different levels: Level(1): Under 17,280 NTD. Level(2): Between 17,281 NTD to 36300NTD. Level(3): Between 36,301 NTD to 72800NTD. Level(4): Above 72,801 NTD.
Catastrophic illness cared: People diagnosed by a physician as having a condition classified as a catastrophic illness by the Ministry of Health and Welfare can apply for a catastrophic card with which they do not need to pay a co-payment for getting care for the illness.
Comorbid physical and mental illnesses, as well as baseline total healthcare costs, were measured during the 12-month pre-index period.
Chi-squared test was used for comparing categorical variables between groups and ANOVA was used for continuous variables.
*$p < 0.05$, **$p < 0.001$

reported an inverse relationship between the frequency of visit to outpatient department (OPD) within the first year of BD diagnosis and three-year mortality in a real-world setting in Taiwan, which suggested that strategies to enhance adherence to the scheduled outpatient visits might reduce mortality in patients with BD (Pan et al., 2016). Although adherence to treatment could be a complex concept and influenced by multiple factors, it was reported to be related to the likelihood of achieving remission, risk of relapse, suicide attempts, and cost of managing BD (Hong et al., 2011). However, it would be difficult to fully evaluate a management recommendation regarding an adequate frequency of outpatient follow-up visit without simultaneously comparing cost and outcome across different choices. Consequently, a full economic evaluation—in the form of a cost-effectiveness and cost-utility analysis—conducted in a real-world setting may be warranted to provide further evidence.

As revealed in the previous cost-of-illness studies, inpatient care is likely to be the main cost driver in the management of patients with BD (Kleine-Budde et al., 2014). Particularly, patients with BD requiring hospitalisation do not have optimistic outcomes considering their poor adherence to the prescribed treatment, high recurrence rates, and low rates of recovery (Li et al., 2014). Therefore, with a target population of BD patients receiving psychiatric inpatient treatments in this study, a cost-effectiveness and cost-utility analysis was conducted from the perspectives of healthcare providers to compare cost and effectiveness outcomes across different outpatient follow-up patterns in terms of frequency of OPD visits following the index hospitalisation.

## 2. Method

### 2.1. Setting

Taiwan is a country with population of approximately 23 million. The National Health Insurance (NHI) programme in Taiwan is a single-payer compulsory social insurance system that centralises the disbursement of healthcare funds and guarantees all enrolees equal access to healthcare. In 2008, a total of 22.92 million individuals were enrolled in Taiwan's NHI programme, a coverage rate of 99.48% (National Health Insurance Administration, 2017). The National Health Insurance Research Database (NHIRD) consists of data characterising healthcare utilisation by enrolees, including expenses, medical procedures and treatments, and basic demographic characteristics. Diagnoses in the NHIRD are coded based on the International Classification of Diseases, ninth revision, clinical modification diagnoses (ICD-9-CM). The study protocol was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital (No. 102,178-F). All subjects in this study were first identified from the NHIRD, and the index date was defined as the earliest date on which a subject was first diagnosed with BD (ICD-9-CM codes: 296.0, 296.1, 296.4–296.7) in 2008. Only those who were diagnosed during hospitalisation for BD treatment were subsequently included in this study. NHI data of each subject were extracted for 1 year preceding and 3 years following the index date, and all data were de-identified before analysis.

### 2.2. Participants

All subjects in the NHIRD that met the following criteria were considered to have qualified for inclusion in the study:

i Subject was first diagnosed with BD in a psychiatric inpatient setting in 2008.
ii Age of subject was 18 years or more on the index date.
iii Subject was alive until the end of the first year.
iv Subject had at least one psychiatric OPD visit after discharge within the first year of diagnosis.

### 2.3. Sociodemographic data and comorbidities of mental and physical illness during the preceding year

Demographic and clinical data of the study subjects were extracted, including age, sex, type of mood episode on the index date, and whether the individual held a catastrophic illness card. Socioeconomic variables included belonging to a low-income household (as recognised by the government), insurance premium (defined as the monthly salary-based income of the insured, categorised into four levels: higher than New Taiwan Dollar (NTD) 72,801; NTD36,301–72,800; NTD17,281–36,300; and less than NTD 17,280; the implied purchasing power parity conversion rate between the NTD and the international dollar in 2008–2009 is 16.99:1) (World Economic Outlook (WEO) Data IMF, 2017), and urbanisation level of residence (Liu et al., 2006). Comorbidities were traced back over the 12 months prior to the index date, including comorbid mental disorders (other psychotic disorder, alcohol-related disorder, substance-related disorder) and comorbid physical illnesses (cardiovascular disease, chronic obstructive pulmonary disease, renal diseases, cancer, diabetes mellitus, hypertension, hyperlipidemia, stroke), which were described in Table 1. Beyond the above-mentioned comorbidities, data regarding diagnoses of bipolar disorder and depressive episode in the preceding year were also extracted.

### 2.4. Service use and cost

Service use components extracted from the NHIRD included outpatient services, emergency attendances, and inpatient stays across the year preceding the diagnosis and the 3 years following the index hospitalisation. All costs were calculated from the actual claims data, categorised based on type of service (i.e., psychiatric costs, nonpsychiatric costs, and total healthcare costs), and expressed in NTD. For instance, costs incurred in the settings of psychiatric outpatient clinic including therapies, medications and all the other cost items were included as psychiatric outpatient costs. Similarly, costs incurred in the settings of non-psychiatric hospitalisations including therapies, medications and all the others were included as non-psychiatric hospitalisation costs. Total healthcare costs included psychiatric and non-psychiatric costs from all clinical settings from emergency services, outpatient clinics, and hospitalisation services. Because the available willingness-to-pay data in Taiwan are expressed in NTD (Shiroiwa et al., 2010), the national currency was used instead of international dollars in the interpretation of the results in this study.

### 2.5. Frequency of OPD follow-up visit within the first year

Given our aim of identifying the adequate frequency of post-discharge OPD visit and exploring the relationship between the first-year outpatient visit frequency and subsequent mortality, we categorised all study subjects into four mutually exclusive groups based on OPD visit frequency within the first year: those with 1) 1–7; 2) 8–12; 3) 13–17; and 4) 18 or more OPD visits. The four levels of frequency of OPD visits were arbitrarily defined aiming to approximately equal the size of each group.

### 2.6. Mortality

Death status was defined as withdrawal of the subject from the NHI programme without any subsequent re-use of healthcare services. Previous studies have used withdrawal from the NHI programme of Taiwan as the definition of death (Pan et al., 2017; Pan et al., 2016; Wu et al., 2012). There are three scenarios in which a person withdraws from the NHI programme of Taiwan: 1) death; 2) missing for more than 6 months; and 3) disqualification as an insurance applicant of the NHI programme, such as because of immigration or expiration of the legal duration of stay of aliens. The second scenario, missing for more than 6 months, is closely related to death, and the occurrence of the third scenario, disqualification as an insurance applicant, is relatively minimal given that foreigners constitute only approximately 2% of all individuals insured under Taiwan's NHI programme (National Health Insurance Administration, 2011).

### 2.7. Utility weights and estimation of quality-adjusted life years (QALYs)

Health state valuations (utilities) are an essential component of cost-utility analyses. 'Utilities' are often used to measure outcomes and are anchored by 0 and 1, where 0 indicates death and 1 indicates full health. In the current study, the utility value for death was set to 0, and the baseline utility value was taken from a naturalistic longitudinal observational study of 176 patients with BD who were recruited from the Bipolar Comprehensive Outcome Study in Australia (Subero et al., 2013). The sample in Subero et al. (2013) was similar to that of the current study: a substantial part of the study subjects in that study had recently been discharged from hospitalisation, and the distributions of age and sex were similar to those in our sample. A generic instrument for obtaining utility values, the EuroQol five-dimensions (EQ-5D) questionnaire, was completed by the patients in Subero et al. (2013) who were comprised of individuals with BD and Clinical Global Impression (CGI)-severity scores of 1–5. The CGI-severity score is a 7-point scale that requires the clinician to rate the severity of the patient's illness relative to the clinician's past experience with patients who have the same diagnosis: 1 denotes normal; 2 denotes borderline mentally ill; 3 denotes mildly ill; 4 denotes moderately ill; 5 denotes markedly ill. The baseline utility value for patients with BD was taken from that study (Subero et al., 2013) and set to 0.7436 assuming the study subjects in the present study were comprised of those with CGI-severity score of 3–5. Using this utility value, the QALY profiles of our subjects over the 36 months after the index date were estimated using area-under-the-curve methods based on the following assumption: the baseline utility value remained the same until a linear decline to 0 began six months prior to death.

Because every evaluation contains some degree of uncertainty, imprecision, or methodological controversy, the uncertainty in the utility values was subsequently tested using sensitivity analyses. The tested scenarios included (1) adjusting the baseline utility weights to a higher value—that is, 0.77—assuming the current study subjects were comprised of a group of patients with BD and CGI-severity scores of 1–5 (Subero et al., 2013), where the utility value remained constant until a linear decline to 0 began six months prior to death; and (2) maintaining the baseline utility weights at their original level—that is, 0.7436—remaining the same until death or the end of the follow-up (Subero et al., 2013).

**Table 2**
Unadjusted costs, death outcomes, and QALYs (3-yr f/u).

| | Full sample ($n$ = 1,591) Whole group ($n$ = 1,591) | OPD 1–7 ($n$ = 483) | OPD 8–12 ($n$ = 431) | OPD 13–17 ($n$ = 369) | OPD ≥18 ($n$ = 308) | Statistics |
|---|---|---|---|---|---|---|
| Psychiatric costs [mean (SD)] | 455,985 (426,147) | 467,680 (513,964) | 460,166 (413,158) | 404,607(338,880) | 493,345 (379,788) | $F = 2.721, p = 0.043$* |
| Psychiatric inpatient care costs [mean (SD)] | 364,888 (416,114) | 427,755 (507,512) | 377,430(396,594) | 297,454(322,105) | 329,539(366,817) | $F = 7.878, p < 0.001$** |
| Total costs [mean (SD)] | 556,444 (460,978) | 561,960(539,851) | 560,735(453,276) | 503,206(385,625) | 605,570(413,608) | $F = 2.852, p = 0.036$* |
| Total inpatient care costs [mean (SD)] | 406,897 (438,128) | 475,472(524,895) | 421,890(421,283) | 333,553(350,570) | 366,249(387,115) | $F = 8.564, p < 0.001$** |
| Total death [$n$ (%)] | 54(3.4) | 20(4.1) | 13(3.0) | 9(2.4) | 12(3.9) | $\chi^2 = 2.272, p = 0.518$ |
| QALY gained [mean (SD)] | 2.02(0.15) | 2.02(0.15) | 2.03(0.13) | 2.02(0.15) | 2.02(0.15) | $F = 0.379, p = 0.768$ |

Unadjusted costs and QALYs gained were compared using ANOVA and death rates were compared via chi-squared test.
Costs were measured over the 3-yr f/u period following the index date and expressed in New Taiwan Dollar (NTD).
The implied purchasing power parity conversion rate between 2008–2009 NTD and the international dollar was 16.99:1.
SD = standard deviation; QALY = quality-adjusted life year; OPD = outpatient department.
*$p < 0.05$, **$p < 0.001$.

## 2.8. Statistical analyses and economic evaluations

Demographic and clinical data, socioeconomic variables, comorbid mental and physical conditions, and healthcare utilisation were compiled for the overall sample of subjects with BD and compared among groups categorised according to frequency of OPD visit within the first year following the index hospitalisation. Comparative analyses were undertaken across OPD frequency groups in terms of both psychiatric and total costs by using analysis of variance. In addition, death rates and QALYs accrued during the 36-month period were compared among the OPD frequency groups. The incremental cost-effectiveness ratio (ICER) was defined as the difference in cost divided by the difference in outcome (survival rate). Adjusted means of costs and QALYs for OPD frequency groups were determined using linear regression analyses, in which all the demographic and clinical covariates described in Table 1 along with affective presentations at diagnosis and urbanisation levels were controlled for. Adjusted survival rates of the OPD frequency groups were determined using logistic regression while simultaneously considering the covariates. ICERs were then calculated based on the adjusted estimates.

The robustness of our results was confirmed using nonparametric bootstrapping techniques to account for any nonnormality in the results' distribution. Cost-effectiveness acceptability curves (CEACs) were constructed using the net benefit approach (Briggs, 2001; Briggs et al., 1997). The net benefit equation is expressed as follows: net benefit = $\lambda \times (\triangle E - \triangle C)$, where $\lambda$ is the threshold value, $\triangle E$ is the difference in effects between study arms, and $\triangle C$ is the difference in costs between study arms. Net benefits to the sample were calculated using $\lambda$ (i.e., willingness to pay for an additional QALY) values ranging from NTD0 to NTD3,000,000 (approximately 0–150,000 international dollars). One and half million NTD (approximately equal to 75,000 international dollars; 50,000 US dollars) was considered as "the threshold value" in this study (Neumann et al., 2014). Regression models were constructed to estimate the difference in net benefit between OPD frequency groups with demographic and clinical covariates being controlled for and bootstrapping was used to produce 1,000 differences for each value of $\lambda$. The proportion of these replications that were greater than zero indicated the probability that the OPD frequency group was more cost-effective than the alternatives for that value of $\lambda$. By plotting these probabilities, we created a CEAC that graphically depicts the probability that the treatment of interest was the most likely treatment to be cost-effective. This approach assumes that a theoretical but unknown value exists that the public would assign to an improvement in QALY; NTD1.5 million was considered the threshold value in this study. Statistical analyses were performed using Stata version 11.1, a statistics and data analysis statistical package (StataCorp LP, College Station, TX, USA), and Microsoft Excel 2003 (Microsoft Corp., Redmond, WA, USA). The significance level was set to 0.05.

## 3. Results

In total, 1,591 discharged patients with BD were included in the analyses. On the index date, the mean age of the study individuals was 41.60 years (standard deviation (SD) = 13.90 years); approximately 48% of the individuals were male; and 4.6% were classified as being from low-income households. Those in the income premium distributions from the lowest to the highest level accounted for 64.0%, 32.1%, 3.6%, and 0.3% of all study participants, respectively. At first diagnosis, the affective presentations were manic (61.1%), mixed (8.9%), depressed (16.2%), and unspecified (13.8%). During the year preceding the index diagnosis, 9.9% of the study participants had diabetes mellitus, 2.9% had kidney disease, and 16% had cardiovascular disease. Additionally, 13.3% of them had substance-related disorders and 5.9% had alcohol-related disorders during the year preceding the index hospitalisation. With regards to baseline healthcare utilisation, the mean number of nonpsychiatric admissions during the year preceding the index diagnosis was 0.31 (SD = 0.88); that for nonpsychiatric emergency room visits was 1.75 (SD = 3.77); and that for non-psychiatric OPD visits was 18.21 (SD = 20.71). The median number of nonpsychiatric OPD visits during the preceding year was 12. Within the first year after index hospitalisation, 30.36% of the BD patients made 1–7 OPD visits after discharge; 27.09% made 8–12 OPD visits; 23.19% made 13–17 OPD visits; and 19.36% made 18 or more OPD visits. The group that made 13–17 OPD visits had the lowest baseline total healthcare costs ($F = 4.490$, $p = 0.004$; post-hoc test with Bonferroni correction further showed that those making 13–17 OPD visits had significantly lower baseline total costs than those making 18 or more OPD visits, $p = 0.002$). They also had the lowest death rates over the 3-year follow-up period despite not reaching statistical significance ($\chi^2 = 2.272$, $p = 0.518$) (Table 1).

### 3.1. Costs

The mean total healthcare cost over the 3-year follow-up period for the study cohort was NTD556,444; of this, psychiatric costs accounted for NTD455,985. Table 2 shows that those who made 13–17 OPD visits following hospitalisation had the lowest psychiatric ($F = 2.721$, $p = 0.043$; post-hoc test with Bonferroni correction further showed that those making 13–17 OPD visits had significantly lower psychiatric costs than those making 18 or more OPD visits, $p = 0.042$) and total costs ($F = 2.852$, $p = 0.036$; those making 13–17 OPD visits had significantly lower total costs than those making 18 or more OPD visits, $p = 0.024$) during the 3-year follow-up period. Besides, those making 13–17 OPD visits had the lowest inpatient costs, either psychiatric ($F = 7.878$, $p < 0.001$; 13–17 OPD vs. 1–7 OPD, $p < 0.001$; 13–17 OPD vs. 8–12 OPD, $p = 0.039$) or total inpatient costs ($F = 8.564$, $p < 0.001$; 13–17 OPD vs. 1–7 OPD, $p < 0.001$; 13–17 OPD vs. 8–12 OPD, $p = 0.026$).

### 3.2. Cost-effectiveness and cost-utility

From the perspective of psychiatric services, the ICERs demonstrated that the OPD 13–17 group dominated the OPD 1–7 and OPD ≥18 groups (i.e., the OPD 13–17 group had lower costs and better outcomes), whereas the ICER for the OPD 8–12 group compared with the OPD 13–17 group was NTD110,400 (psychiatric cost) per percentage point increase in survival rate. From the perspective of total healthcare services, the ICERs revealed that the OPD 13–17 group dominated the OPD 1–7 and ≥18 groups, whereas the ICER for the OPD 8–12 group compared with the OPD 13–17 group was NTD150,400 (total cost) per percentage point increase in survival rate (Table 3).

CEACs were employed to interpret the cost-utility results. There was a 77.3% (psychiatric costs) to 80.2% (total costs) likelihood that having 13–17 OPD visits within the first year was the most cost-effective option compared with 1–7, 8–12, and ≥18 OPD visits, if society was willing to pay nothing for an additional gain in QALY. If society was willing to pay NTD1.5 million for one additional QALY, there was a 75.2% (psychiatric costs) to 77.4% (total costs) likelihood that 13–17 OPD visits was the most cost-effective option. If willingness to pay increased to NTD2 million for one additional QALY, there was a 72.5% (psychiatric costs) to 75% (total costs) likelihood that 13–17 OPD visits was the most cost-effective option (Figs. 1 and 2). In the sensitivity analyses, 13–17 OPD visits remained the more cost-effective option compared with 1–7, 8–12, and ≥18 OPD visits with similar CEAC results.

## 4. Discussion

Based on a national cohort of discharged patients with BD, the current study provided rarely available real-world data regarding the cost-effectiveness and cost-utility comparisons across different post-discharge frequency of outpatient visits. Individuals making 13–17 OPD visits within the first year of their index hospitalisation had the lowest psychiatric and total healthcare costs over a 3-year follow-up period.

**Table 3**
Adjusted psychiatric/total costs, survival outcomes, and ICER.

| | Hospitalised patients<br>OPD 1–7 | OPD 8–12 | OPD 13–17 | OPD ≧18 |
|---|---|---|---|---|
| Psychiatric costs [mean (95%CI)] | 447,600 (395,154, 500,020) | 470,900 (414,681, 527,121) | 415,700 (358,032, 473,359) | 463,700 (400,804, 526,624) |
| Total costs [mean (95%CI)] | 580,000 (524,928, 634,990) | 585,300 (526,257, 644,268) | 510,100 (449,587, 570,628) | 568,700 (502,717, 634,772) |
| Survival rate [mean (95%CI)] | 0.954 (0.928, 0.980) | 0.976 (0.948, 1.003) | 0.971 (0.943, 1.000) | 0.968 (0.937, 0.999) |
| | 1–7 vs. 13–17 | 8–12 vs. 13–17 | > = 18 vs. 13–17 | |
| ICER_total cost | 13–17 dominates | 75,200/0.5% = 150,400 | 13–17 dominates | |
| ICER_psychiatric cost | 13–17 dominates | 55,200/0.5% = 110,400 | 13–17 dominates | |

Costs and outcomes were adjusted for age, gender, physician specialty, baseline total healthcare costs, mental and physical comorbidities and other factors as described earlier in the section of demographic and clinical information.
Costs were measured over the 3-yr f/u period following the index date and expressed in New Taiwan Dollar (NTD).
The implied purchasing power parity conversion rate between 2008–2009 NTD and the international dollar was 16.99:1.
ICER = incremental cost per percentage point of survival; OPD = outpatient department.

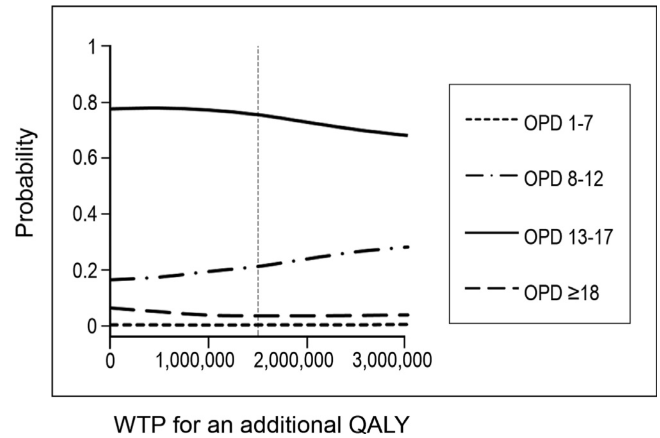


**Fig. 1.** CEAC based on psychiatric costs.

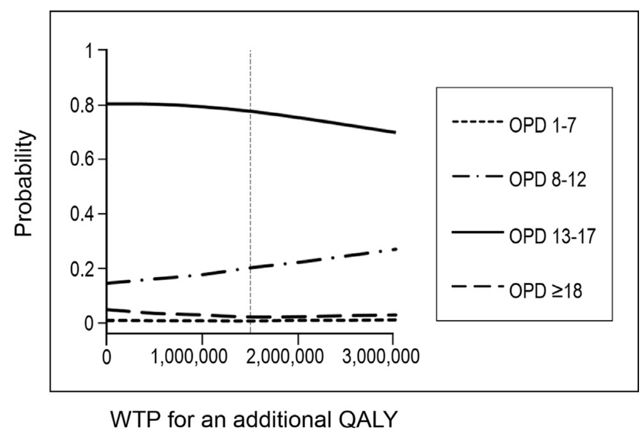


**Fig. 2.** CEAC based on total costs.

With survival status as the effectiveness outcome, 13–17 OPD visits was more likely to be the cost-effective option, as revealed by the ICERs. Moreover, the CEACs demonstrated that in the cost-utility analysis, 13–17 OPD visits was probably the most cost-effective option of follow-up frequency when considering QALYs.

In this study, discharged patients with 13–17 OPD visits within the first year were associated with lower psychiatric and total healthcare costs over the 3-year follow-up period compared to those with 1–7, 8–12, or 18 or more OPD visits (Tables 2 and 3). Prior studies showed that nonadherence to treatment might be predictive of negative outcomes of BD such as relapse, impaired functioning, and suicidality (Gonzalez-Pinto et al., 2006; Hong et al., 2011). Evidence also demonstrated a close relationship between poor adherence to treatment and cognitive impairment in patients with BD (Martinez-Aran et al., 2009). It is understandable that more regular OPD attendances as revealed in the current study might be associated with improved outcomes for discharged patients with BD and, in turn, could be associated with future cost savings, probably through reduced likelihood of relapses and functional impairments. Besides, the current results suggested that strategies to improve OPD follow-up adherence could be particularly relevant in a population of more severe patients with BD, e.g., individuals requiring hospitalisation. In this study, those making 13–17 OPD visits following hospitalisation were associated with the lowest inpatient costs over the follow-up period in terms of both psychiatric and total healthcare services compared with the other groups. Such results suggested that cost savings shown in this study might be at least partly related to the reduced inpatient healthcare costs.

Despite not reaching statistical significance, those making more regular OPD visits within the first year seemed to be associated with lower mortality over the follow-up period (Table 2), raising a question regarding whether strategies to improve adherence to the prescribed treatment might reduce BD patient's risk of relapses and mortality. Similar scenario could be found in literature of schizophrenia research. Many studies have reported that long-acting injectable antipsychotics (LAIs) were associated with lower risk of relapse and all-cause mortality in the real-world settings (Taipale et al., 2017; Tiihonen et al., 2017), possibly through improvement of adherence to treatment. However, in randomised controlled studies (RCTs), pooled data did not show significant differences in the risk of relapse and mortality between LAIs and oral antipsychotics (OAPs) (Kishi et al., 2016; Kishimoto et al., 2014), which may be attributable to the fact that RCTs are less representative of real-world patients who are largely different in their adherence to the prescribed treatment, thus cancelling out the benefits of better adherence of LAIs than OAPs. Aside from the potentially negative effects on mortality due to poorer clinical outcomes resulting from nonadherence to treatment, the existence of the 'healthy adherer effect' could yield a complementary hypothesis behind the association between frequency of outpatient follow-up visit and mortality. 'Healthy adherers' may have superior ability to keep appointments, possibly a surrogate marker of an individual's overall healthy behaviour (Simpson et al., 2006), which in turn can be related to better survival outcome. The fact that the group making 13–17 OPD visits also had the lowest baseline total healthcare costs supported the hypothesis that healthier subjects might take better care of themselves and have better outcomes.

Additionally, the non-adherent patients may be denied of opportunity to receive adequate management of the associated physical conditions such as regular physical checkup, monitoring of cardiovascular morbidities, and management of metabolic syndromes. Considering the increased risk of chronic physical illnesses associated with BD including metabolic syndromes, it would be of great interest to improve BD patients' adherence to OPD follow-up visit as well as to address physicians' "clinical inertia" to further encourage screening and management of comorbid health conditions (Phillips et al., 2001). Previous studies reported that psychoeducation can not only improve level of adherence (D'Souza et al., 2010; Pakpour et al., 2017) but also patients' knowledge of their illness, which can subsequently reduce distress and improve functioning (Batista et al., 2011). Therefore, strategies addressing psychoeducation, motivational interviewing and shared decision-making regarding treatment choices should be emphasised to improve patients' motivation to comply with the scheduled OPD follow-up and management of comorbid physical illnesses.

From the perspective of psychiatric treatment, 13–17 OPD visits was shown in this study to be the more cost-effective follow-up frequency for reducing mortality risk. Although the underlying mechanisms remained to be determined, the results of ICERs demonstrated that compared to other groups of different follow-up frequencies, OPD 13–17 group may be the favourable one. From the perspective of total healthcare treatment, 13–17 OPD visits was also shown to be the more cost-effective option from the viewpoint of reducing subsequent mortality. The ICERs showed that the OPD 13–17 group dominated the OPD 1–7 and OPD ≥18 groups (OPD 13–17 group had lower cost and better outcome), and the ICER for the OPD 8–12 group compared with the OPD 13–17 group was NTD150,400 per percentage point increase in survival rate. Up to date, only a limited number of prospective studies have addressed the relationship between clinical outcome and adherence or frequency of OPD visit in patients with BD (Sylvia et al., 2014). The present study was the first attempt at comparing healthcare costs and mortality outcomes simultaneously in a routine clinical practice setting, evaluating the effects of adequate outpatient follow-up frequency in a specific population of discharged patients with BD.

In this study, the cost-utility analyses further suggested that an adequate outpatient follow-up frequency within the first year of index hospitalisation may be a cost-effective choice to improve the quality of life of discharged patients with BD. The CEACs demonstrated that when society is willing to pay NTD1.5 million for one additional QALY, there is a 75.2% (psychiatric cost) to 77.4% (total cost) likelihood that having 13–17 OPD visits may probably be the cost-effective choice. Very few studies have provided data on quality of life outcome in patients with BD in real-world settings (Subero et al., 2013); none of them have specifically evaluated the relationship between post-discharge OPD follow-up frequency and quality of life in the discharged patients with BD.

The strengths of the current study included coverage of an entire country, inclusion of patients with BD who were diagnosed during hospitalisation, longitudinal follow-up for 3 consecutive years, and provision of rarely available data on cost-effectiveness and cost-utility comparisons across different OPD follow-up patterns, which could be of interest to both clinicians and policymakers. Given the likelihood of confounding or selection bias owing to the nonrandomised study design, patients with different OPD follow-up patterns may vary in terms of other unidentified factors that can affect mortality outcome. Other limitations include use of a proxy definition of death status and the adoption of utility values from other studies. Besides, more frequent OPD visits may not be equal to better adherence. It is also possible that more frequent outpatient contacts may result from poor adherence to the prescribed therapy or medication regimens which leads to relapses. Additionally, the four levels of frequency of OPD visits are arbitrarily defined based on the currents data and may not be directly generalizable to other populations. Although we have included all medication costs and therapy costs in the presented total costs, we did not discuss the relative impacts of these cost items separately in the current study. In conclusion, this study—using data from a national database—suggests that frequency of OPD visit following hospitalisation may be associated with longer-term healthcare cost, quality of life, and mortality in discharged patients with BD in a real-world setting. Special care should be provided to patients with BD following hospitalisation to improve their motivation and adherence to the arranged OPD follow-up schedule.

## Conflicts of interest

No authors report any financial relationships relevant to the subjects of this article.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.067.

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