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Mortality and Morbidity of Patients with Treated and Untreated Epilepsy in New Zealand

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Ethics statement

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUMMARY

Objective

To investigate whether delayed or no treatment was associated with increased mortality and morbidity risks in people with newly-diagnosed epilepsy.

Methods

We examined New Zealand hospitalisation and antiseizure medication prescription data from 2007-2015. Mortality and hospital-diagnosed morbidities were compared between patients immediately treated after epilepsy diagnosis, treated after a delay, or untreated for the duration of follow-up, adjusted for age, sex and ethnicity.

Results

3,366 patients (54.7% male; median age 37.5 years) were included and followed up for a median of 3.39 years. 3,123 (92.8%) patients were treated immediately, 125 (3.7%) had delayed treatment and 118 (3.5%) were untreated. Compared to the general New Zealand population, the cohort had a standardized mortality ratio of 4.60 (95% confidence interval [CI]: 4.24-4.99). Maori patients were less likely to be treated (Holm-Bonferroni-adjusted p=0.024) and had higher mortality (hazards ratio [HR]=1.41, 95% CI: 1.08-1.83). There was a trend of increased mortality in the untreated or delayed treatment group compared to the immediate treatment group (HR=1.36, 95% CI: 0.99-1.87). Hospitalisation risk was similar between untreated and immediately treated periods (p=0.83). Untreated or delayed treatment patients had higher risk of acute myocardial infarction (HR=9.64, 95% CI: 1.83-50.8). Maori patients were more likely to develop liver disease (HR=4.67, 95% CI: 1.32-16.4) and alcohol or drug dependence (HR=2.55, 95% CI: 1.44-4.51).

Significance

Most epilepsy patients were treated at diagnosis in New Zealand, but Maori patients had lower treatment rates and worse health outcomes. The apparent increased risk of acute myocardial infarction among the untreated or delayed treatment patients warrants further research.

Key words

Seizures; Antiseizure medications; Treatment gap; Maori; Comorbidities.

INTRODUCTION

Epilepsy affects 70 million people worldwide[1]. People with epilepsy have increased mortality[2, 3] and more physical and psychological comorbidities[4-7]. In high-income countries their mortality rates are 1.6-3.0 times higher than the general population,[2] and up to 7.2 times higher in low- and middle-income countries[3]. A substantial proportion of people with epilepsy are either not treated or have delayed antiseizure medication (ASM) treatment[8, 9]. In low- and middle-income countries this 'treatment gap' has been reported to range from 46.8 to 73.3%[8]. A recent large study using a health insurance claims database in the United States found that 36.7% of people with newly-diagnosed epilepsy were untreated three years after diagnosis[9]. Few studies have investigated the effect of no treatment on morbidity and mortality of people with epilepsy. In the US study, untreated patients had significantly more hospitalisations and seizure-related injuries[9]. Another study showed that delayed treatment was associated with increased seizure frequency but had no effect on mortality[10]. Few studies have specifically compared the incidence of comorbidities in treated and untreated patients.

This study aimed to investigate whether delayed treatment or no ASM treatment in people with newly-diagnosed epilepsy was associated with increased mortality, hospitalisations and incidence of comorbidities compared to patients treated immediately in New Zealand.

METHODS

Setting

This was a population-based study of hospitalised patients with newly-diagnosed epilepsy. Hospital discharge data from January 1, 2007 until December 31, 2015 recorded in the National Minimum Dataset (Hospital Events) were analysed. This dataset contains information on all inpatient and day case discharges from New Zealand public hospitals and many private hospitals. Discharge diagnoses were coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM). Clinical audits validated the diagnoses after initial coding according to ICD-10-AM, including checking that the principal diagnosis was appropriate[11]. Data on the use of ASMs were obtained from the Pharmaceutical Collection, the national pharmaceutical claims database of all subsidised medicines dispensed from New Zealand community pharmacies. Death data relating to study patients was obtained from the national Mortality Register.

Patients newly-diagnosed with epilepsy between 2009 and 2014 were identified and followed until December 31, 2015, or their date of death if this occurred prior. Each patient alive for the duration the study had at least 12 months follow-up. In line with a recent similar study in the United States[9], a two-year baseline period from 2007-2008 was used to exclude patients with a potential prior epilepsy diagnosis (defined as having a previous epileptic seizure related hospitalisation or a prescription for ASMs), and to record baseline comorbidities.

Ethics

This study was exempt from ethics committee review according to Section 11.5 of New Zealand's latest Ethical Guidelines for Observational Studies (2012)[12] as all data used were primarily collected for clinical care and de-identified prior to analysis.

Inclusion and Exclusion Criteria

The patient inclusion and exclusion criteria were similar to those adopted and validated in recent studies[6, 9]. Two inclusion criteria were used. In the first, patients must have had an epileptic seizure (ICD-10-AM code G40xx) in two or more separate hospitalisations at least 24 hours apart, and not have status epilepticus (code G41xx) in at least one of the hospitalisations. If both epileptic seizure and status epilepticus were recorded in two sequential hospitalisations, the hospitalisations needed to be at least 30 days apart. Under the second inclusion criterion, patients were included if they had been prescribed an ASM on or after their first epileptic seizure related hospitalisation (code G40xx). ASMs included all drugs listed under the Anatomical Therapeutic Chemical (ATC) Classification therapeutic group for the 'control of epilepsy'. Patients were excluded if there was a G40xx code during a hospitalisation in the baseline period from 2007-2008 or an ASM had been prescribed prior to their first G40xx hospitalisation. Follow-up for each patient started on the date when the inclusion criteria were met.

We identified patients who had common potential causes of acute symptomatic seizures (CNS inflammatory diseases [G00-G09], stroke [G45, I60, I61, I63, I64, H34.1], traumatic brain injury [S02.0, S02.1, S06.0, S06.2, S06.3], anoxic brain damage [G93.1], alcohol abuse disorder [F10], drug abuse disorder [F11, F12, F14],

metabolic disorders [E53.1, E72.9, E80, F02.0, I68.8, G63.8, G99.8, I32.8, I68.8, N18.5], hyperglycaemia [R73.9], or hypoglycaemia [E16.2]), newly recorded at or within 7 days (and not before) prior to the first seizure[13]. Potential remote aetiologies of seizure that were recorded more than 7 days prior to the first seizure were also identified by using the above diagnosis while adding malformation of cortical development (MCD, Q04) and excluding anoxic brain damage, alcohol and drug abuse disorders, hyperglycaemia and hypoglycaemia[14].

Definitions

Patients were defined as immediate, delayed or untreated if an ASM was prescribed within 30 days of the inclusion criteria being met, after 30 days, or not prescribed by the end of follow-up, respectively. A 30-day period was applied to allow for a reasonable time for physicians to form treatment plans.

Other patient conditions recorded before or within 30 days of the epilepsy diagnosis were considered to be pre-existing. Comorbidities recorded more than 30 days following the epilepsy diagnosis were considered to be newly developed. Physical comorbidities were classified according to the Charlson Comorbidity Index[15, 16] and psychiatric comorbidities according to Fazel and colleagues' framework[17].

As well as analysing by treatment group, this study also separated untreated and treated periods (Figure 1) in order to more precisely investigate the impact of no and delayed treatment, especially whether treatment delay had prolonged effects. The ‘immediately treated period’ was defined as the time period in the immediately treated group from 30 days after epilepsy diagnosis until end-of follow-up. The ‘post-

delay treated period' was defined as the time period in the delayed treatment group from commencement of ASM treatment to the end of follow-up. The 'untreated period' was defined as the time period from 30 days after diagnosis until ASM treatment commencement (in the case of the delayed treatment group) or end of follow-up (for the untreated group).

Statistical Analysis

The non-parametric Kruskal-Wallis rank test was used to compare continuous variables across the three treatment groups. The Mann-Whitney test was used for pairwise comparisons of continuous variables between treatment groups. Fisher's exact test was performed to compare categorical variables between treatment groups. The standardised mortality ratio (SMR) was calculated by dividing the number of observed deaths in the patient cohort by the expected number of deaths to the relevant number of person-years followed. The latter was estimated from the New Zealand population mortality rates from 2009-2015[18], matched by age, sex and year of death.

To avoid confounding effects from pre-existing conditions, the analysis of new comorbidities only included patients who did not have any physical or psychiatric comorbidity recorded at baseline. To investigate the impact of no treatment, mortality, hospitalisations and the incidence of comorbidities in the untreated and delayed treatment periods were compared with the immediately treated period. These outcomes were also compared between a combined untreated and delayed group and the immediately treated group.

Cox proportional hazards models were used to compare the rates of mortality and the development of individual new comorbidities between treatment periods and groups. An Andersen-Gill model for repeated events was performed to compare rates of seizure-related (seizure or status epilepticus) hospitalisations, overall hospitalisations and overall comorbidity between treatment periods and groups. All multivariable analyses were adjusted for age, sex and Maori ethnicity, where applicable. The statistical significance level was set at $p<0.05$. The Holm-Bonferroni (HB) method was applied for multiple comparisons. All statistical tests were performed using Stata 15 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 3,366 patients (54.7% male) with newly-diagnosed epilepsy were included for analysis (Figure 2). Their median age at diagnosis was 37.5 years (interquartile range [IQR] 15.0-64.0, range 0-99 years) and median follow-up duration was 3.4 years (IQR 1.8-5.1) (Table 1). The majority of patients were of European descent (2,170/3,366, 64.5%) with Maori the next most common ethnic group (686/3,366, 20.4%), which is an indigenous people group of New Zealand.

At the time of epilepsy diagnosis, 45.0% (1,514/3,366) of the cohort had baseline Charlson or psychiatric comorbidities (Table e-1a). Potentially acute symptomatic seizures were identified in 229 patients (229/3366, 6.8%) who had relevant aetiologies newly recorded at or within 7 days prior to the first seizure (Table e-1b). Additionally, 308 (9.2%) patients had remote aetiologies of seizure recorded in admission more than 7 days prior to the first seizure (Table e-1c). During the study

period, 57.9% (1,949/3,366) of the cohort were prescribed one ASM, 23.7% (796/3,366) had two and 14.9% (504/3,366) had three or more different ASMs. This was similar to a seminal Scottish study in which 67% of participants were treated with a single ASM[19].

Treatment Groups

3,123 patients (92.8%) commenced ASM treatment immediately (within 30 days of epilepsy diagnosis), 125 patients (3.7%) began treatment after 30 days (median delay 127 days, IQR 63-387 days), and 118 patients (3.5%) remained untreated at the end of follow-up. Compared to patients of other ethnicity, Maori patients were significantly less likely to be treated immediately (93.4% vs. 90.4%, p=0.008, HB-adjusted p=0.024) and more likely to remain untreated (3.1% vs. 5.0%, p=0.026, HB-adjusted p=0.052). Patients in the immediate treatment group were older (median 37.5 years) than those untreated (median 26.0 years, p=0.002, HB-adjusted p=0.004) and those who received delayed treatment (median 29.0 years, p=0.026, HB-adjusted p=0.026).

Mortality

In total, 575 (17.1%) of the 3,366 newly-diagnosed patients died during the study period. Most of these had baseline comorbidities (489/575, 85.0%). The SMR was 4.60 (95% confidence interval [CI] 4.24-4.99). The observed number of deaths was higher than expected across all age strata for both sexes, especially among patients aged less than 60 years (Table e-2). The SMR for Maori patients, compared to the New Zealand Maori population, was 6.47 (95% CI: 5.21-8.03).

Multivariable analysis showed that mortality rates during the untreated and immediately treated periods were similar (hazard ratio [HR]=1.00, 95% CI: 0.62-1.60, p=0.98). The mortality rate in the post-delay treated period trended higher than the immediately treated period, although the difference did not reach statistical significance (HR=1.50, 95% CI: 0.99-2.28, p=0.056). The rates of mortality between the untreated or delayed and immediate treatment groups were not significantly different (Table 2), but Maori patients had a significantly higher rate of mortality than non-Maori patients (HR=1.40, 95% CI: 1.09-1.78, p=0.008).

Morbidity

Hospitalisations

Of the 1,852 patients without baseline comorbidities (Table e-3), 1,146 patients had 4,828 subsequent hospitalisations following diagnosis of epilepsy. These were comprised of 1,727 (35.8%) seizure-related hospitalisations and 3,101 (64.2%) hospitalisations due to other conditions. After adjustment for age, sex and Maori ethnicity, patients were less likely to have subsequent seizure-related hospitalisations during the untreated period compared to the immediate treatment period (HR=0.54, 95% CI: 0.36-0.83, p=0.004). The subsequent hospitalisation rates were similar, however, between post-delay and immediate treatment periods and between the untreated or delayed and immediate treatment groups (Table 2). Maori patients did not have a significantly higher subsequent hospitalisation rate than non-Maori patients (HR=1.26, 95% CI: 0.98-1.61, p=0.074).

New Comorbidities

Of the 1,852 patients without baseline comorbidities, 286 (15.4%) developed at least one new comorbidity during follow-up: 126 [6.8%] only had new psychiatric comorbidity, 111 [6.0%] only had new Charlson physical comorbidity, and 49 [2.6%] developed both new Charlson physical and psychiatric comorbidities). Cerebrovascular disease (33/1,852, 1.8%) was the most common newly-developed Charlson physical comorbidity, followed by chronic obstructive pulmonary disease (COPD, 30/1,852, 1.6%) and hemiplegia or paraplegia (24/1,852, 1.3%). In terms of psychiatric comorbidity, alcohol or drug dependence was newly- developed in 57 (3.1%) patients and depression or related mood disorders in 20 patients (1.1%, Table e-4).

Compared to patients in the immediate treatment group, no treatment or delayed treatment were associated with higher risk of developing acute myocardial infarction during follow-up (HR=9.64, 95% CI: 1.83-50.8, p=0.008, Table e-4). Rates of developing individual comorbidities were similar between the untreated and immediate treatment periods (Table e-5). Acute myocardial infarction was more likely to develop during the post-delay treated period than the immediate treatment period (HR=15.0, 95% CI: 1.57-144, p=0.019, Table e-6).

Compared to patients of other ethnicity, Maori patients had significantly higher rates of developing mild liver disease (HR=4.67, 95% CI: 1.32-16.4, p=0.017) and alcohol or drug dependence (HR=2.55, 95% CI: 1.44-4.51, p=0.001, Table e-7).

The rates of developing any new comorbidities overall were similar during the untreated and immediate treatment periods (HR=1.09, 95% CI: 0.59-2.02, p=0.78), post-delay and immediate treatment periods (HR=0.92, 95% CI: 0.46-1.83, p=0.81), and untreated or delayed and immediate treatment groups (HR=1.15, 95% CI: 0.73-1.81, p=0.55) after adjusting for age, sex and Maori ethnicity. There was no significant difference in the rate of developing new comorbidities overall between Maori and other ethnic groups (HR=1.27, 95% CI: 0.92-1.74, p=0.15).

DISCUSSION

Using national population data, we found that 7.2% of the people newly-diagnosed with epilepsy did not commence ASM therapy within 30 days of epilepsy diagnosis, and 3.5% remained untreated at the end of follow-up. Maori patients were significantly less likely to commence treatment immediately compared to non-Maori patients, although the absolute difference was small. The overall mortality, comorbidity and hospitalisation rates were similar between the untreated and immediate treatment periods, post-delay and immediate treatment periods, and untreated or delayed and immediate treatment groups. Compared to patients treated immediately, untreated patients were less likely to have subsequent seizure-related hospitalisation. However, untreated and delayed treatment groups appeared to have a higher risk of developing acute myocardial infarction. Maori patients had higher rates of developing mild liver disease and alcohol and drug dependence than non-Maori patients during follow-up.

The proportion of New Zealand patients with delayed treatment (3.7%) or no treatment (3.5%) appeared to be less than that observed in recent studies from other

high-income countries. A recent study in the United States using data from health insurance claims databases found that 36.7% of patients were untreated three years after diagnosis[9]. This difference may in part be due to the US study only including outpatients and therefore patients with milder epilepsy who might be less likely to be treated. A Swedish study, also including outpatients only, found that 28.4% were untreated one year after the index seizure[20]. The finding in our study is more comparable to a review of six hospital-based prevalence studies in high-income countries which reported an untreated rate of 2-10%[21].

Our cohort of patients with newly-diagnosed epilepsy had a mortality rate 4.6 times that of the general New Zealand population. This is higher than the SMR of 1.6-3.0 reported in a systematic review of studies from high-income countries,[2] but comparable to that reported for Hong Kong (SMR=5.09)[6]. It is likely that the higher SMRs in our study and the Hong Kong study are due to the inclusion of patients only diagnosed during hospitalisation who likely had more severe epilepsy than patients with epilepsy in the general population.

Maoris, an indigenous people group comprising one sixth of New Zealand's population, are known to have higher rates of disease, with the disparities widespread across life stages.[22] They often have delayed treatment, worse outcomes and a lower life expectancy than non-Maori people, with increased poverty as a potential contributing factor.[22] Our study demonstrated a similar situation in the epilepsy population, where Maori people were less likely to commence treatment immediately and also had a higher risk of mortality compared to patients of other ethnicities. While these differences were significant, they were small, suggesting that further research

including aetiology and attitude towards medications is needed to elucidate this phenomenon.

Further, once treated, Maori people were more likely to develop mild liver disease and alcohol or drug dependence. These comorbidities are highly correlated and may be due to life-style factors. This is consistent with findings in the general population that Maori, compared to non-Maoris, were more than five times more likely to have health loss from viral hepatitis, and more than four times more likely to have health loss from drug use disorders.[23] Alcohol use disorders also accounted for 4% of absolute inequality in health loss between Maori and non-Maori people.[23] Therefore, our findings might reflect a generalised increased risk of these conditions amongst Maori people, rather than a specific phenomenon of the epilepsy cohort. These observations highlight the ongoing need to further investigate indigenous health in New Zealand.

We found that the mortality rate in the untreated period was not significantly higher than the immediate treatment period ($p = 0.056$), similar to the findings of previous studies. A previous randomised controlled trial demonstrated no significant difference in mortality between deferred and immediately treated epilepsy patients[10]. A South African prospective population-based cohort study also showed no significant difference in mortality between treated and untreated groups[24].

Overall, patients had a lower risk of seizure-related hospitalisations during the untreated period compared to the treated period, but there were no other differences in hospitalisations. This is surprising, since untreated patients had increased seizure-

related and overall hospitalisations compared to treated groups in previous studies[9, 25]. Given that it is unlikely that no treatment is actually protective of epilepsy-related hospitalisations, this observation is more likely to be due to indication bias where untreated and delayed treatment patients have milder epilepsy and therefore fewer seizure-related hospitalisations.

Untreated or delayed treatment patients were more likely to develop acute myocardial infarction, mainly during the post-delay treated period. However, only two individuals developed acute myocardial infarction in the untreated and delayed treatment groups. The corresponding uncertainty from low incidence is reflected in the wide confidence intervals. Previous studies have suggested that the increased incidence of acute myocardial infarction in epilepsy[26, 27] may be attributed to the use of enzyme inducing ASMs[27], which accelerate atherosclerosis[28]. Further investigation is needed to test this hypothesis.

Our study has limitations. Firstly, the study only included patients with seizures that required hospitalised care. There was a potential selection bias toward including patients with generalised motor seizures but not those with only non-motor or focal aware seizures, as the latter tends to be managed in the outpatient setting. The proportion of 'missed' patients could not be reliably estimated from outpatient prescription data since ASMs are used for several other common indications (e.g. neuropathic pain, migraine), and there is no published population incidence data for epilepsy in New Zealand. As patients with milder and infrequent seizures may be less likely to commence treatment, the proportion of untreated patients in New Zealand might have been underestimated. Secondly, similar to other studies that relied on

hospitalisation databases[6], detailed information on factors known to be associated with mortality[29], such as seizure types and aetiology of the epilepsy, was lacking. Nonetheless, the study findings still reflected the elevated mortality rate in epilepsy at the population level. Like other population database studies, an inherent limitation was that coding and prescriptions were used to infer epilepsy diagnosis. Recent studies have validated the definitions of epilepsy used in this study, however.[6,9] In this method, patients with a single recorded seizure and subsequent ASM prescription were included as well as those with two recorded seizures. The former group would likely have a higher baseline risk of ongoing seizures than single seizure alone, and might be more likely to have an underlying condition that would increase morbidity and mortality. We believe that this would balance the risk of seizure recurrence, morbidity and mortality amongst the two definitions of epilepsy used. Owing to the conservative method used to identify newly-diagnosed epilepsy patients, it is possible that there was an underestimation in the number of delayed and untreated patients, thereby limiting the statistical power to detect differences in outcomes between treatment groups. However, this conservative method enhanced the validity of the hospital diagnosis. On the other hand, patients treated after potentially acute symptomatic seizure might have been mis-categorized as having epilepsy although they were estimated to be less than 7% of the cohort and would unlikely have affected the overall results.

In conclusion, although few hospitalised patients with new onset epilepsy in New Zealand were untreated or had delayed treatment, Maori patients were less likely to receive immediate treatment. People with newly-diagnosed epilepsy had a higher rate of mortality than the general population, particularly among Maori patients. The

apparent increased incidence of acute myocardial infarction among untreated or delayed treatment patients warrants further research.

KEY POINTS

- Most people with epilepsy in New Zealand commenced antiseizure medication treatment immediately after diagnosis.
- People with newly-diagnosed epilepsy had elevated mortality rate compared to the general population.
- An apparent increased risk of acute myocardial infarction among untreated or delayed treatment patients was observed and warrants further investigation.
- The overall mortality, comorbidity and hospitalisation rates were similar between the untreated or delayed and immediate treatment groups.
- Maori people were less likely to commence treatment immediately and had higher mortality rate compared to non-Maori people.

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FIGURE LEGENDS

Figure 1: Definition of treatment groups and treatment periods

The dotted blue line indicates the untreated period and solid black line indicates the treated period. Treated and untreated periods were measured from 30 days after epilepsy diagnosis to end of follow-up.

Figure 2: Flowchart for cohort selection according to inclusion and exclusion criteria

Vertical arrows indicate inclusion and horizontal arrows indicate exclusion. ASM, anti-epileptic drug; G40xx, ICD-10-AM code for epileptic seizure, G41xx, ICD-10-AM code for status epilepticus.

TABLES

Table 1. Baseline characteristics

	Immediate Treatment n=3,123	**Delayed Treatment n=125**	**Untreated n=118**	**Total n=3,366**
Male, n (%)	1,708 (54.7%)	65 (52.0%)	68 (57.6%)	1,841 (54.7%)
Median age at diagnosis (IQR)	32.0 (6.0-63.0)	29.0 (12.0-56.0)	26.0 (6.0-52.0)	37.5 (15.0-64.0)
Median follow-up, years (IQR)	3.40 (1.82-5.14)	3.67 (2.04-5.33)	3.28 (1.53-4.67)	3.39 (1.82-5.14)
Ethnicity, n (%)				
European	2,036 (65.2%)	65 (52.0%)	69 (58.5%)	2,170 (64.7%)
Maori	620 (19.9%)	32 (25.6%)	34 (28.8%)	686 (20.4%)
Pacific Islander	264 (8.45%)	15 (12.0%)	5 (4.24%)	284 (8.44%)
Asian	133 (4.26%)	10 (8.00%)	6 (5.08%)	149 (4.43%)
MELAA	32 (1.02%)	2 (1.60%)	1 (0.85%)	35 (1.04%)
Other	25 (0.80%)	1 (0.80%)	2 (1.69%)	28 (0.83%)
Unspecified	13 (0.42%)	0 (0%)	1 (0.85%)	14 (0.42%)

IQR, interquartile range; MELAA, Middle Eastern, Latin American or African

Table 2. Mortality and hospitalisations between treatment periods and groups

	Mortality		Hospitalisations			
			Overall		Seizure-related	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Untreated vs Immediate treated periods	1.00 (0.62-1.60)	0.98	0.96 (0.65-1.41)	0.83	0.54 (0.36-0.83)	0.004
Post-delay vs Immediate treated periods	1.50 (0.99-2.28)	0.056	1.09 (0.68-1.75)	0.72	1.11 (0.65-1.88)	0.70
Untreated/delayed vs Immediate treatment groups	1.36 (0.99-1.87)	0.058	1.11 (0.80-1.53)	0.54	0.87 (0.58-1.30)	0.49

CI, confidence interval; HR, hazard ratio.

Appendix 1: Author Contributions

Name	Location	Role	Contributions
Kristen Joy Hamilton	The University of Melbourne, Melbourne, Australia	Author	Design and conceptualisation of the study; interpretation of the data; drafting of the manuscript for intellectual content.
Zhibin Chen	Monash University, Melbourne, Australia	Author	Statistical analysis and interpretation of the data; design and conceptualisation of the study; revision of the manuscript for intellectual content.
Andrew Tomlin	Best Practice Advocacy Centre, Dunedin, New Zealand	Author	Data analysis and revision of the manuscript.
Patrick Kwan	Monash University, Melbourne, Australia	Author	Design and conceptualisation of the study; revision of the manuscript for intellectual content.