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Research Article

Association of Quality of Life with Symptomatic and Cognitive Functional Changes in Patients with Schizophrenia Treated with Electroconvulsive Therapy

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Abstract

Aim: To examine associations between changes in quality of life (QoL) and psychiatric symptom and cognitive changes amongst patients with schizophrenia treated with acute ECT.

Methods: This is a retrospective cohort study of 132 patients who received ECT treatment from July 2017 till December 2019. Sociodemographic and clinical characteristics were obtained from medical records. Changes of QoL, psychiatric symptoms and cognition function were examined after 6 sessions of ECT treatment. Generalized linear regression was used to examine the associations of changes in Brief Psychiatric Rating Scale (BPRS) scores and the changes in Montreal Cognitive Assessment (MoCA) scores with the changes of QoL score.

Results: There was significant improvement in overall EQ-5D score and subdomain scores after ECT treatment. Both improvement in BPRS symptoms and improvement of MoCA function score were significantly associated with improvement in the EQ-5D utility score after adjustment for sociodemographic and clinical characteristics. Improvement of BPRS symptoms was significantly associated with improvement of the EQ-5D pain subdomain and anxiety while compared to patients without MoCA change, patients with MoCA improvement were significantly associated with improvement in the usual activity subdomain.

Conclusions: ECT was associated with an overall improvement of QoL among patients with schizophrenia. Improvement in psychiatric symptoms was significantly associated with improvement of mental health QoL scores while improvement of cognitive function was associated with improvement of physical activity QoL scores.

Keywords: Electroconvulsive therapy; Schizophrenia; Quality of life; Psychiatric symptoms; Cognitive function

Abbreviations

ECT: Electroconvulsive Therapy; QoL: Quality of Life; QLS: Quality of Life Scale; WHO QOL-Brief: World Health Organization Quality of Life Scale - Brief Version; EQ-5D-5L: 5-level EQ-5D Version; SF-36: 36-Item Short Form Survey; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10: International Statistical Classification of Diseases, 10th Revision; TI: Anaesthesia-ECT Time Interval; EEG: Electroencephalogram; PIS: Postictal Suppression; VAS: Visual Analogue Scale; BF: Bifrontal; BT: Bitemporal; RUL: Right Unilateral; CI: Confidence Interval

Introduction

Schizophrenia is a severe mental disorder with profound impact on patients, their families, caregivers and society. The global prevalence of lifetime schizophrenia is 0.2%-0.4% without significant difference between gender, ethnicity, nor between urban/rural environment [1]. The health and economic burden of schizophrenia is significant, given the resources required to provide services to patients and indirect costs from loss of productivity of patients and their caregivers [2]. Unfortunately, the current long-term treatment strategies remain suboptimal for patients with schizophrenia. A sub-group of patients may not respond satisfactorily to current treatment modalities and experience symptom relapses over a prolonged period of their life [3]. Therefore, the goal of clinicians and healthcare workers has increasingly shifted over time from focusing on the psychiatric symptoms alone towards functional improvement and quality of life (QoL) [4].

A large amount of effort has been expended to investigate the factors affecting the QoL among patients with schizophrenia. Younger age, female gender, being married and lower education level are important sociodemographic factors associated with better QoL in patients with schizophrenia [5]. Psychiatric symptoms are consistently and negatively associated with QoL domains such as mental health and social relationships [6,7]. For patients with schizophrenia, positive symptoms such as hallucinations and delusions can cause patients to lose touch with reality and impair their daily functioning. Negative symptoms tend to persist longer

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than positive symptoms and patients who exhibit significant negative symptoms have particularly poorer functioning in both mental and physical activities [8-10]. Comorbid depressive symptoms in patients with schizophrenia have often been associated with impaired mental functioning, suicidal ideation and poorer subjective QoL [11-13]. In addition, cognitive functioning has been identified as an important determinant of QoL in patients with schizophrenia [14,15].

Electroconvulsive therapy (ECT) is arguably the first among the effective biological methods of treatment for schizophrenia with the potential of augmenting treatment response when used with antipsychotics [16-19]. Even in patients resistant to the gold standard antipsychotic (clozapine), ECT augmentation can result in up to a 50% response rate in both clinical trial [20,21] and real-world settings [22]. Additionally, although there are reports of cognitive side effects induced by ECT among patients with schizophrenia [23-27], some studies demonstrated cognitive improvement [28-32]. Despite the large amount of research into the symptomatic and cognitive effects of ECT and the ECT associated improvement of QoL among patients with depression [33-35], the impact of ECT treatment on QoL among patients with schizophrenia remains largely unexplored. In three studies with relative small samples (n=46, 30 and 15 respectively) [36-38], participants reported a global improvement of overall and subdomain scores of QoL which was assess by the Quality of Life Scale (QLS) [36] or World Health Organization Quality of Life Scale - brief version (WHO QOL - Brief) [37] at immediately after acute ECT or with 36-item short form survey (SF-36) at 3 or 6 months after acute ECT [38]. However, the question of whether these improvements are associated with symptomatic and/or cognitive changes with treatment remains unclear.

Hence, this study aimed to examine the changes in QoL with an acute ECT treatment course and potential associations with changes in psychiatric symptoms and cognition in patients with schizophrenia. We hypothesized that both symptom and cognitive improvements would be associated with QoL improvement.

Materials and Methods

Study population

This is a retrospective cohort study. We included the medical records of all patients in the Institute of Mental Health in Singapore who were initiated on ECT treatment from July 2017 to Dec 2019. The subgroup of patients with diagnosis of schizophrenia or schizophrenic spectrum disorder and with completed Montreal Cognitive Assessment (MoCA) assessment before and after 6 ECT sessions were included for this analysis. Patients' sociodemographic and clinical characteristics including ECT treatment information and outcome assessment were extracted using the CARE Network data collection system as described in our previous studies [39-41]. Ethical approval to conduct the study was obtained from the National Healthcare Group Domain Specific Review Board (2015/01283) with waiver of consent for use of the registry data. Patients were referred to the ECT service by psychiatrists who had made clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition (DSM-IV/DSM-5) or the International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria. The ECT treatment algorithm at the service placed Bifrontal ECT at 1.5x seizure threshold as the initial treatment modality. All patients received individual empirically derived seizure titration dosing for ECT treatment.

Anaesthesia-ECT time interval (TI), propofol dosage, succinylcholine dosage, ECT dosage and electroencephalogram (EEG) postictal suppression (PIS) score was averaged across ECT treatments 2 to 6 (as treatment 1 was a seizure threshold titration session). We used the Brief Psychiatric Rating Scale (BPRS) to assess changes in psychiatric symptoms. The BPRS is a Likert rating scale ranging from score 1 to 7 in each item which a clinician or researcher may use to measure psychiatric symptoms such as depression, anxiety, hallucinations, psychosis and unusual behaviour [42]. A lower BPRS score indicates a better mental condition. We used Montreal Cognitive Assessment (MoCA) to assess cognitive functioning in the language patients were most comfortable with (English, Chinese, Malay, or Tamil). The MoCA is a cognitive screening test designed to assist health professionals in the detection of mild cognitive impairment with lower score indicating worse cognitive function [43]. Patients also reported their QoL using the 3-level version of EQ-5D questionnaire. EQ-5D contains 5 subdomains including mobility, self-care, usual activity, pain and anxiety ranging from 1 to 3 levels, with lower scores indicating better conditions [44]. EQ-5D utility score was calculated according to formular provided by Luo N et al. which reflects the local population norms of QoL [45]. For both EQ-5D utility score and visual analogue scale (VAS) score, a lower score indicated worse QoL. All assessment scales including BPRS, MoCA and EQ-5D were administered to patients 1-2 days pre-ECT and 1-2 days after the 6th session of ECT treatment.

Statistical analysis

For statistical analysis, all changes in scores were calculated as the post 6 ECT scores minus pre-ECT scores. We recoded the change of MoCA scores into three categories. Change of MOCA ≥2 was recoded into "improvement"; Change of MOCA ≤ (-2) was recoded into "deterioration"; other values were recoded into "no change" [46]. EQ-5D utility score, VAS score, EQ-5D subdomain scores and BPRS at pre-ECT and after ECT 6 were compared using repetitive analysis of variance.

Generalized linear regression was conducted to examine the associations of changes of BPRS score and MoCA changes with the changes in the EQ-5D scales. EQ-5D utility scores were multiplied by 100 for ease of interpretation. Covariates included in the regression model were patients' age, gender, number of previous episodes, medication class prescribed, number of failed medication trials, past ECT treatment, mean propofol dosage, mean ECT dosage and mean electroencephalogram (EEG) score [47]. These covariates were selected based on prior studies [48-50].

Statistical analyses were conducted using IBM SPSS Statistics, Version 22.0 (Armonk, NY: IBM Corp). Statistical significance was set at $p < 0.05$.

Results and Discussion

A total of 132 patients diagnosed with schizophrenia or schizophrenia spectrum disorder were included in the analysis. Patients' characteristics are shown in Table 1. The average age was 38.9±13.8 (mean±SD) years and 43.9% were female. The main ECT treatment type was Bifrontal (BF) ECT (N=117 (90.2%)), they

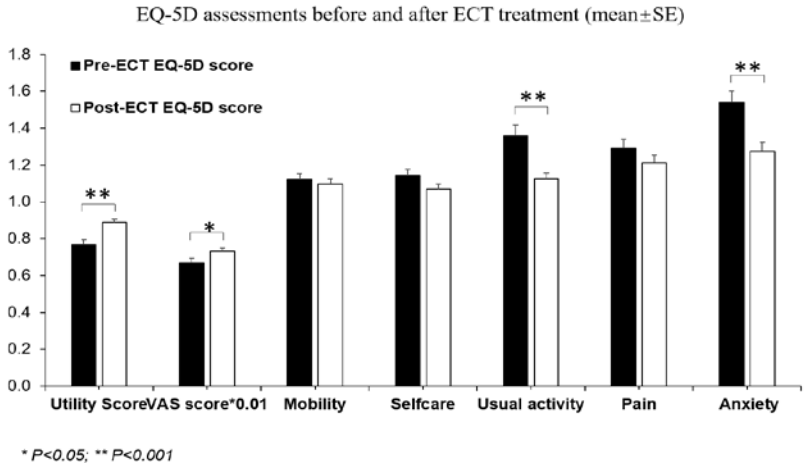

Figure 1: EQ-5D assessments before and after ECT treatment (mean±SE).

received 8.5 (SD 3.8) sessions of ECT on average and the main reason for ECT was due to failure of medicine (N=93 (70.5%)).

In this study, we demonstrated that ECT treatment was associated with a significant improvement of psychiatric symptoms, cognitive function and a global improvement of QoL after 6 sessions of ECT treatment (2-3 weeks) among patients with schizophrenia or schizophrenia spectrum disorder. There was a global improvement of pre-ECT to post-ECT EQ-5D, BPRS and MoCA scores. Among those assessments, the improvements (Mean±SE) were statistically significant for assessment scales of EQ-5D utility score (0.77±0.02 to 0.89±0.02, p<0.001), EQ-5D VAS score (66.82±2.61 to 73.05±1.93, p=0.012), EQ-5D subdomain scores of usual activity (1.36±0.06 to 1.12±0.03, p<0.001) and anxiety (1.54±0.06 to 1.27±0.05, p<0.001, Figure 1). Thus, while evidence remains scarce regarding the QoL effect of ECT in patients with schizophrenia, our data demonstrated a global improvement of QoL assessed by EQ-5D after ECT 6. This is in agreement with one of the few papers documenting quick improvement in QoL in schizophrenia patients treated by ECT [37]. As our patients were mostly severely ill patients who were typically referred for ECT due to treatment resistance to several courses of pharmacotherapy (65.2% with previous relapses of episodes and 91.7% resistant to antipsychotics) and in need of rapid relief of symptoms, ECT has the potential to be a significant rapid acting treatment option if it can be efficiently delivered to patients and improve QoL quickly.

ECT induced significant improvement of BPRS score (from 51.73±1.05 to 36.41±0.76, p<0.001). More patients demonstrated an improvement of MoCA score (n=57, 43%) than the patients without change of MoCA (n=41, 31%) and with MoCA deterioration (n=34, 26%). Moreover, Improvements of BPRS score was significantly associated with improvements of EQ-5D utility score after adjustment for sociodemographic and clinical characteristics (adjusted β: (-0.446), 95% Confidence Interval (CI): (-0.840) - (-0.052), p=0.027, Table 2) but not significantly associated with changes of VAS score. Compared to patients without MoCA change, patients with improvement of MoCA scores displayed significant association with improvement of EQ-5D utility score (adjusted β: 12.068, 95% CI: 0.865-12.271, p=0.035 Table 3). Similar with BPRS, improvement of MoCA score was not associated with change of VAS score.

In our study population, both improvement of BPRS score and MoCA improvement were significantly associated with an improvement of overall utility score, but not VAS score. The possible reason of this discrepancy is that utility score is a validated composite score calculated from EQ-5D subdomain scores and normalized to local population's general perception of QoL whereas VAS score is a subject self-reported score. Evidence has shown that factors such as political structure, social culture and economic condition may affect the utility values of EQ-5D health states [51,52], so people's evaluation on same health problems varied from different counties/social status. For example, affective mood problems such as anxiety/depression had different effects on people from countries with different economic levels [53]. Therefore utility score could be more accurately and objectively reflected the overall improvement of QoL among local population induced by ECT while VAS score is more self-biased due to lacking of insight in patients with schizophrenia. In a comparison study of self-reported QoL among patients with schizophrenia with objective QoL assessed by their primary clinicians, it was found that there was moderate agreement on symptoms and function, less agreement on physical health, and little to no agreement on social relations and occupational aspects of QoL [54]. In our early study of QoL among patient with mental disorders [55], we also recognized that patients with psychosis lacked self-awareness of their illness and social environment. Consequently, they may develop self-protective strategies and assign meaning to their lives, leading to reporting of better subjective QoL than patients with depression. Thus, although schizophrenia patients reported a general improvement of both utility score and VAS score after ECT treatment, VAS may not be a valid measurement of change of QoL in this population.

We observed that improvement of psychiatric symptoms was significantly associated with patients' mental health which were assessed by EQ-5D subdomain score of pain (adjusted β: 0.012, 95% CI: 0.004-0.021, p=0.005) and anxiety (adjusted β: 0.013, 95% CI: 0.002-0.024, p=0.024) while improvement of cognitive function was significantly associated with patients' physical health which were assessed by EQ-5D subdomain score of usual activity (adjusted β: (-0.349), 95% CI: (-0.607)-(-0.09), p=0.008). MoCA scale was also

Table 1: Patient sociodemographic and clinical characteristics.

Patient Characteristics	Mean	SD
Age (years)	38.9	13.8
Averaged propofol dosage (mg/kg)	62.6	13.8
Averaged succinylcholine dosage (mg/kg)	26	4.6
Averaged ECT dosage (mc)	213.9	156.3
Averaged EEG PIS score	2.5	0.3
Averaged number of ECT sessions	8.5	3.8
	N	**%**
Gender		
Female	58	43.9
Male	74	56.1
Consent†		
Consent by others	102	77.3
Own consent	27	20.5
Number of previous episodes		
>3	86	65.2
0	6	4.5
1-3	38	28.8
Duration of current episode†		
Acute (≤12 months)	125	94.7
Chronic (>24 months)	3	2.3
Sub-acute (13-24 months)	2	1.5
Antidepressants†		
NO	91	68.9
YES	39	29.5
Antipsychotics other than clozapine†		
NO	9	6.8
YES	120	90.9
Benzodiazepines†		
NO	56	42.4
YES	73	55.3
Lithium†		
NO	123	93.2
YES	6	4.5
Anticonvulsants†		
NO	99	75
YES	30	22.7
Stimulants†		
NO	127	96.2
YES	1	0.8
Clozapine†		
NO	89	67.4
YES - with no/minimal response	19	14.4
YES - with partial/good response	19	14.4
Failed antipsychotics		
>=3	85	64.4
1-2	36	27.3
None	7	5.3
ECT modalities		
BF	117	90.2
BT	9	6.8
RUL	4	3.1
Past ECT treatment†		
NO	80	60.6
YES - with no/minimal response	3	2.3
YES - with partial/good response	46	34.8
Main reason for ECT†		
Failure of medication	93	70.5
High suicide risk	1	0.8
Inadequate oral intake	1	0.8
Intolerable medication side effects	1	0.8
Patient preference	2	1.5
Previous good ECT response	24	18.2
Severe aggression/agitation	4	3

†Data may not sum to total due to missing value.

Abbreviations: ECT; Electroconvulsive therapy; EEG: Electroencephalogram; PIS: Post_Ictal Suppression; BF: Bifrontal; BT: Bitemporal; RUL: Right Unilateral.

displayed a trend of association with improvement of physical health assessed by EQ-5D subdomain of self-care after adjustment for socio-demographics and other clinical characteristics. This discrepancy may be explained by the structure of BPRS questionnaire which was designed to assess psychiatric mood including positive, negative, depression symptoms etc. and MoCA is a screening test for mild and severe cognitive impairment, which is more relevant to physical activities [56].

In addition, we found that ECT associated symptomatic and cognitive improvement had no association of EQ-5D mobility function. One possibility is that ECT treatment had limited effect on mobility. This is in agreement with our data that schizophrenia patients demonstrated a trend but statistically non-significant improvement of mobility function after 6 sessions of ECT treatment. Another explanation is possibly due to the insensitivity of 3 level versions EQ-5D to assess the changes of mobility function. The insensitivity of EQ-5D-3L subdomain assessment may also partially explain the observed relatively small effect size and model-fit testing value in the regression analysis for both BPRS score and MoCA change to predict EQ-5D change. Indeed, the 5-level EQ-5D version (EQ-5D-5L) was recently introduced by the EuroQol Group to improve the instrument's sensitivity and to reduce ceiling effects [57]. However, this version has not been validated in local population in Singapore.

In western countries, ECT is a primarily used in the treatment of treatment resistant depression [58] while in Asia, ECT is primarily prescribed for patients with treatment resistant schizophrenia as an augmentation of antipsychotic medicine to alleviate psychotic symptoms [18,59]. Despite clear evidence of the symptomatic effectiveness of ECT in patients with schizophrenia, there remains

Table 2: Association of ECT induced psychiatric symptomatic change with changes in quality of life (EQ-5D) scores.

Dependent variable	Independent variable	Crude				After adjustment†			
		β	lower 95% CI	upper 95% CI	p value	β	lower 95% CI	upper 95% CI	p value
Change of Utility Score	Change of BPRS score	-0.615	-1.005	-0.226	0.002*	-0.446	-0.84	-0.052	0.027*
Change of VAS score		0.037	-0.367	0.441	0.858	-0.095	-0.555	0.365	0.685
Change of Mobility		0.004	-0.002	0.01	0.172	0.001	-0.005	0.006	0.836
Change of Self-care		0.002	-0.005	0.008	0.592	-0.001	-0.008	0.005	0.679
Change of Usual activity		0.006	-0.004	0.015	0.231	0	-0.009	0.009	0.965
Change of Pain		0.01	0.002	0.018	0.015*	0.012	0.004	0.021	0.005*
Change of Anxiety		0.015	0.004	0.026	0.006*	0.013	0.002	0.024	0.024*

*P<0.05.

†Adjusted for age, gender, antidepressant, antipsychotics, clozapine, anticonvulsant, previous episodes, past-ECT treatment, number of failed antipsychotics, ECT-anaesthesia time interval, averaged ECT dosing, averaged EEG score and averaged propofol dosage.

Abbreviations: BPRS: Brief Psychiatric Rating Scale; VAS: Visual Analogue Scale; CI: Confidence Interval.

Table 3: Association of ECT induced cognitive change with changes of in quality of life (EQ-5D) scores.

Dependent variable	Independent variable	Crude				After adjustment*			
		β	lower 95% CI	upper 95% CI	p value	β	lower 95% CI	upper 95% CI	p value
Change of Utility Score	MoCA improvement *vs.* no change	15.029	3.567	26.491	0.010*	12.068	0.865	23.271	0.035*
	MoCA deterioration *vs.* no change	7.345	-5.844	20.534	0.275	5.396	-7.804	18.597	0.423
Change of VAS score	MoCA improvement *vs.* no change	-4.003	-15.363	7.357	0.49	-5.003	-17.775	7.768	0.443
	MoCA deterioration *vs.* no change	5.023	-7.67	17.717	0.438	3.136	-11.238	17.511	0.669
Change of Mobility	MoCA improvement *vs.* no change	-0.028	-0.187	0.131	0.734	-0.039	-0.199	0.121	0.631
	MoCA deterioration *vs.* no change	0.064	-0.114	0.241	0.484	-0.02	-0.201	0.162	0.83
Change of Self-care	MoCA improvement *vs.* no change	-0.125	-0.306	0.057	0.178	-0.163	-0.345	0.019	0.079
	MoCA deterioration *vs.* no change	0.065	-0.138	0.267	0.532	0.144	-0.061	0.349	0.169
Change of Usual activity	MoCA improvement *vs.* no change	-0.328	-0.59	-0.066	0.014*	-0.349	-0.607	-0.09	0.008*
	MoCA deterioration *vs.* no change	-0.204	-0.503	0.094	0.18	-0.115	-0.417	0.187	0.454
Change of Pain	MoCA improvement *vs.* no change	-0.053	-0.284	0.177	0.651	0.073	-0.17	0.315	0.558
	MoCA deterioration *vs.* no change	0.032	-0.225	0.289	0.806	0.057	-0.217	0.331	0.684
Change of Anxiety	MoCA improvement *vs.* no change	-0.24	-0.558	0.079	0.141	-0.143	-0.461	0.175	0.378
	MoCA deterioration *vs.* no change	-0.24	-0.599	0.119	0.191	-0.157	-0.519	0.205	0.396

*P<0.05.

†Adjusted for age, gender, antidepressant, antipsychotics, clozapine, anticonvulsant, past-ECT treatment, number of failed antipsychotics, ECT-anaesthesia time interval, averaged ECT dosing, averaged EEG score and averaged propofol dosage.

Abbreviations: MoCA: Montreal Cognitive Assessment; VAS: Visual analogue scale; CI: Confidence Interval.

controversy about ECT cognitive side effects. Studies examining these effects seem to suggest findings like those in patients with depression with respect to transient cognitive change after ECT. Although randomized controlled trials have suggested greater transient memory impairment in ECT treatment combined with antipsychotics compared with antipsychotic monotherapy for Chinese patients with schizophrenia [26,27], these ECT-induced acute cognitive impairments would typically resolve within several weeks after the last ECT session [23,24]. However, our results is in agreement with some recent studies demonstrating cognitive improvement after ECT treatment in schizophrenia patients [30,32]. Future work with multiple cognition assessment tools and longer term follow up are needed to validate this. The ECT induced cognitive improvement could possibly be a new treatment indication of ECT and benefit more patients suffering with schizophrenia.

The number of research that has investigated predictors of ECT treatment efficacy in patients with schizophrenia is limited. The influence of common socio-demographics including age and gender on efficacy of ECT remains unclear. Summarized by Stenmark et al., so far no studies have found age to be a predictor of treatment response to ECT in patients with schizophrenia [50]. ECT was reported to be significantly more effective in female patients than in male patients suffering from schizophrenia [60] while contrary evidence does exist that gender does not influence the ECT dose requirement to achieve response among group of patients with schizophrenia [61]. In our study, we did not find evidence of the correlation of age and gender with ECT induced changes of QoL (Supplementary Table 1 and 2).

The relevance of this finding is unclear. Individual variations in ECT treatment parameters may limit the generalizability of this result.

Several limitations of our study need to be noted. Our assessment data was captured after a short course (i. e. 2-3 weeks) of ECT treatment without following up. Patients could have been even more benefit by the end of their ECT course. The longer-term impact of ECT on QoL and the long-term associations between symptomatic/cognition function and subjective QoL remains unclear although prior evidence does exist regarding the diminished benefit of ECT on patients subjective QoL after one year treatment [36]. Further interventions, such as maintenance ECT or other ECT augmentation aiming to improve symptoms and cognition function could probably help to maintain QoL improvements. Additionally, other subjective or objective QoL instruments which have a better sensitivity and clearer differentiation assessment of patients' mental health and physical health may be needed to replicate our results. Finally, similar to other retrospective studies with medical records, we cannot rule out the confounding effect of other important factors that were not included in our analysis model, such as the education of participants and dosage of concurrent medicine etc.

Conclusion

In summary, we have found ECT induced an overall and quick improvement of QoL among patients with schizophrenia. The improvement of psychiatric symptoms was found significantly associated with better mental health while the improvement of cognitive function was associated with better physical health. Meanwhile, several issues remain a concern including the utilization of EQ-5D VAS score to assess treatment outcome and the sensitivity of EQ-5D subdomain scales. To our knowledge, this is the first study to examine associations between ECT induced symptomatic improvement and cognition function with QoL among patients with schizophrenia which warrants a future prospective and blinded trial to validate our observations. The information gained is valuable for identifying patient-reported needs for and benefits of ECT treatment.

Declaration

Contributors: TPC, DM, TXW formulated the research questions; TPC, DM designed the study; KL, TPC collected the data; TXW, TPC, DM, KL analyzed the data; TXW, TPC wrote first draft of the article and all authors reviewed and agreed the submission of the manuscript in current version.

Availability of data and materials: The data that support the findings of this study is not publicly available and only accessible from the corresponding author (Dr Phern Chern Tor, phernchern_tor@imh.com.sg) on reasonable request *via* approval by the Institutional Research Review Committee and the National Healthcare Group Domain Specific Review Board.

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