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Risk factors for early circulatory mortality in patients with schizophrenia

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ABSTRACT

Patients with schizophrenia have higher mortality and shortened life expectancy than the general population, and cardiovascular disease (CVD) accounts for up to 50% cases of early mortality in schizophrenia. We determined risk factors, particularly pathophysiological changes, for early circulatory mortality in schizophrenia. In this multi-institutional, nested, case–control study, we enrolled consecutive inpatients with schizophrenia admitted to three psychiatric hospitals in the northern Taiwan. Seventy-nine patients who died of CVD before 65 years of age were identified as cases through record linkage, and 158 controls were randomly selected in a 2:1 ratio through risk-set density sampling, after matching for age (± 2 years), sex, and index admission (± 3 years). Data were obtained through medical record reviews. At the time of death, the mean age of the patients was 47.5 years (standard deviation = 10.3). Conditional logistic regression revealed that the duration of antipsychotic treatment was significantly associated with a lower risk of early circulatory mortality, and leukocyte counts at index hospitalization were significantly associated with a higher risk. Systemic inflammation may be a risk factor for early circulatory mortality in schizophrenia, but antipsychotic treatment, in particular typical antipsychotic treatment, could be a protective factor.

1. Introduction

Schizophrenia typically has a debilitating course and is associated with 2–4 times higher mortality and 10–25 years of shortened life expectancy in early adults than in the general population worldwide (Crump et al., 2013; Laursen et al., 2012; McGrath et al., 2008; Saha et al., 2007; Wildgust and Beary, 2010). Cardiovascular disease (CVD) is the principal cause of death among natural and unnatural deaths, accounting for up to 50% cases of early mortality in schizophrenia (Hennekens et al., 2005; Laursen et al., 2014; Lemogne et al., 2013; Sweeting et al., 2013), with a 10-fold higher risk than that of suicide (Kisely et al., 2013).

Studies have identified many risk factors for circulatory mortality, including smoking, hypertension, physical inactivity, unhealthy lifestyle, obesity, dyslipidemia, hyperglycemia, psychotropic agents, suboptimal medical treatment, and social disadvantages (Brown and Mitchell, 2012; Correll et al., 2015; Laursen et al., 2012). However, it remains unclear whether the increased mortality is mediated by traditional risk factors for CVD or is associated with an unidentified and inherent mental illness pathophysiology. Growing evidence shows that systemic inflammation may play an important role in the pathophysiology of schizophrenia (Muller et al., 2015). Neuroinflammation-related immune alterations may influence dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission (Muller et al., 2015), resulting in an increased risk of CVD and early death in schizophrenia. Systemic inflammation may involve the cardiovascular and cerebrovascular systems, which should be considered while investigating the association between schizophrenia and early mortality due to circulatory system diseases (Hsu et al., 2016; Wang et al., 2006).

The effects of psychotropic agents on the risk of CVD are controversial. Some studies have suggested that antipsychotics increase the risk of cardiovascular mortality because of the tendency of metabolic syndrome, orthostatic hypotension, corrected QT segment (QTc) changes, sudden death, and myocarditis (Acharya et al., 2013; Hsieh et al., 2013; Shulman et al., 2014), whereas other studies have highlighted the benefits of reduced cardiovascular risk because of adequate treatment responses with improved self-care ability (Crump et al., 2013; Suvisaari et al., 2013; Tiihonen et al., 2009) and the anti-inflammatory properties of antipsychotics (Al-Amin et al., 2013; Kato et al., 2011).

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The risk of CVD and early circulatory mortality in patients with schizophrenia has increased, but risk factors in addition to traditional CVD risk factors are unclear. An association linked by systemic inflammation is hypothesized among psychopathological conditions, psychopharmacological treatment, and circulatory mortality in schizophrenia. The present study attempted to identify additional clinical characteristics as risk or protective factors for early circulatory morality in schizophrenia.

2. Methods

2.1. Study population and design

In this multi-institutional, nested, case–control study, all patients were enrolled from Taipei Medical University Hospital, Taipei City Psychiatric Center, and Bali Psychiatric Center, accounting for a total of 560 and 604 beds for acute and chronic patients, respectively, in the northern Taiwan. This study was approved by the institutional review board of each hospital. Because the methodology has been extensively described elsewhere and successfully used in research on mortality in bipolar disorder (Tsai et al., 2002; Tsai et al., 2005), it is only briefly summarized in this study.

This nested case–control methodology was designed to select deceased schizophrenic patients due to circulatory causes and living control patients in the community, and to identify the risk factors from the data of their previous hospitalizations. There are two phases of patient selection in this study. First, we identified the deceased (potential experimental) patients through record linkage. The national identity (ID) number is unique for each resident in Taiwan. Multiple identifiers were used (e.g., national IDs, sex, and birth date) in the matching process to search for the deceased patients. A record linkage, in which the roster of inpatients with schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 295.xx) excluding schizoaffective disorder (ICD-9-CM 295.7x), was electronically matched against data files from the Department of Health Death Certification System in Taiwan issued from January 1, 1985, to December 31, 2008. As it is mandatory for all deaths throughout Taiwan to be registered, this register provides comprehensive information on the gender, age, marital and employment status of all deaths, along with the date and place of death, and the diagnoses referring to the cause of death based on ICD-9-CM codes. The cause of death was mainly determined and confirmed based on death certificates, although some additional deaths were recorded by reviewing charts with familial confirmation made available to clinicians during the study period.

Patients who died of circulatory diseases (CVD: ICD-9-CM 401–429, cerebrovascular diseases: ICD-9-CM 430–438, and vascular diseases: ICD-9-CM 440–443) were enrolled as potential experimental patients in the study. Information for each patient, particularly that regarding psychiatric diagnoses, was carefully and independently reviewed by two board-certified psychiatrists in the research group. Moreover, the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, was strictly reapplied to each patient to reconfirm the diagnoses and exclude the possibility of psychotic disorders because of general medical conditions or substance-induced. Patients with either unclear chart documentation or early discharge of index hospitalization were excluded. The cutoff age for early death was 65 years because it is established as the geriatric age and is economically relevant as the usual retirement age in developed countries. During the study period, 79 patients with schizophrenia who died of circulatory diseases before 65 years of age were enrolled as final experimental patients (deceased patients).

The second phase of patient selection was selection of control patients. Each patient was matched with two living patients with schizophrenia in one of the three hospitals as control patients in a 2:1 ratio based on age (± 2 years), sex, and date of index admission (± 3 years).

2.2. Data collection

The sources of data regarding patient hospitalization included standard interviews, serial clinical assessments, and direct observation by residents, the nursing staff, and social workers.

If the deceased patients had undergone several hospitalizations during the study period, the most recent event was considered the index admission. The closest hospitalization to the index admission of the deceased patient was considered the index admission for the control patients. Subsequently, the initial study findings were reviewed by a consensus panel of investigators with many years of experience in major psychiatric disorder research to verify the apparent accuracy and completeness of data for each examined patient. The following variables were examined: present psychiatric illness, family history, medication history, physical and laboratory examination results at index admission, electrocardiography (ECG), and chest X-ray. The four main vital signs were routinely monitored by the nursing staff every morning after admission. Based on the hospitals' standard procedure, the heart rate was routinely monitored according to the radial pulse measured during a 1-min recording at rest, and blood pressure was recorded every morning.

Resting ECG was performed using a simultaneously recorded 12-lead machine with automatic measurements of parameters. The instrument calculates the QTc interval (Bazett's correction). The prolonged QTc interval was defined as >440 ms in men and >450 ms in women (Sharp et al., 1998).

2.3. Statistical analyses

Predictive Analytics Software Statistics 18.0 for Windows was used to analyze all identified variables. We conducted two-group comparisons, between the deceased and control patients, by using the chi-squared test with Yates' correction or Fisher's exact test for categorical explanatory variables and two-tailed Student's t test for continuous explanatory variables. Multivariate conditional logistic regression models were subsequently used to determine risk factors for circulatory mortality. In this study, two-tailed $P < 0.05$ was considered statistically significant. Considering the exploratory design of this study, univariate analyses are presented without Bonferroni corrections.

3. Results

In this study, we recruited 79 deceased and 158 living patients with schizophrenia. At the time of death, the mean age of the deceased patients was 47.5 ± 10.3 years. The deceased and control patients had a similar distribution of sociodemographic characteristics, namely age, the marital status, the educational level, living with family, family history of schizophrenia, employment, and the socioeconomic status (Table 1).

Regarding clinical characteristics, the deceased patients were significantly younger at illness onset and at the first psychiatric admission and had a shorter duration of antipsychotic use than did the control patients. Medications used in both deceased and control patients included 1) a variety of high potency and low potency typical antipsychotics, with haloperidol accounting for over half of them, and 2) atypical antipsychotics (risperidone, quetiapine, olanzapine, and clozapine), with risperidone accounting for over half of them. The mean values for blood urea nitrogen, creatinine, uric acid, thyroxine, leukocyte count, body mass index (BMI), and diastolic pressure on day 1 of the index hospitalization were significantly higher in the deceased patients than in the control patients (Tables 2 and 3). In terms of cardiovascular assessment, no significant difference was observed in blood pressure, heart rate, and ECG measurements (Table 3). No significant difference was observed in age at index admission, total number of

Table 1
Characteristics of deceased and control patients, as compared by categorical variables.

Characteristics	Deceased patients (N = 79) N (%)	Control patients (N = 158) N (%)	χ^2	P
Men	47 (59.5)	94 (59.5)	–	–
Education > 12 years	19 (24.1)	43 (27.2)	0.35	0.18
Married	20 (25.3)	52 (32.9)	0.07	0.10
Living with family	58 (73.4)	91 (57.6)	0.36	0.44
Family history of schizophrenia	31 (39.2)	45 (28.5)	0.29	0.30
Employment at index admission	12 (15.2)	26 (16.5)	0.53	0.58
Hollingshead socioeconomic status, class V	71 (89.9)	138 (87.3)	0.57	0.67
Prolonged QTc on ECG	13 (16.5)	18 (11.4)	0.80	0.42
Abnormal ECG finding at index admission	21 (26.6)	46 (29.1)	0.55	0.53
Comorbid substance use disorders during lifetime				
Alcohol consumption	15 (19.0)	30 (19.0)	0.00	1.00
Cigarette smoking	30 (38.0)	59 (37.3)	0.28	0.67
Other substances use	1 (1.0)	3 (1.7)	0.63	1.00
Significant concurrent medical morbidity				
Brain and cerebrovascular diseases	7 (12.1)	16 (10.1)	0.35	0.65
Cardiovascular diseases	28 (35.4)	51 (32.3)	3.83	0.06
Respiratory diseases	13 (16.5)	22 (13.9)	0.02	1.00
Endocrine diseases	19 (24.1)	34 (21.5)	0.00	1.00
Gastrointestinal diseases	26 (32.9)	45 (28.5)	0.01	1.00
Urogenital diseases	11 (13.9)	29 (18.4)	1.56	0.28
Infectious diseases	22 (20.2)	16 (13.9)	0.39	0.46

ms: millisecond, ECG: electrocardiography, QTc: corrected QT segment.

Table 2
Characteristics of deceased and control patients, as compared by continuous variables.

Characteristics	Deceased patients (N = 79) Mean (SD)	Control patients (N = 158) Mean (SD)	t	P
Illness variables				
Age at onset, years	25.6 (8.0)	28.3 (9.3)	−2.23	0.03*
Age at first psychiatric admission, years	31.6 (11.2)	35.1 (11.8)	−2.08	0.04*
Age at index admission, years	42.7 (10.6)	45.1 (11.7)	−2.69	0.14
Total hospitalizations, times	4.0 (3.0)	3.4 (3.1)	1.35	0.18
Interval between discharge and death, years	4.8 (5.2)	–	–	–
Duration of medication before last visit, years				
All antipsychotics	8.1 (8.4)	14.2 (9.9)	−4.78	0.00***
Typical antipsychotics	7.5 (7.9)	10.8 (9.5)	−2.69	0.008**
Atypical antipsychotics	0.8 (1.7)	3.4 (5.1)	−5.63	0.00***
Laboratory data				
Fasting blood sugar, mg/dL	108.7 (56.3)	103.7 (45.1)	0.70	0.49
Blood urea nitrogen, mg/dL	14.6 (9.5)	12.1 (4.1)	2.24	0.03*
Creatinine, mg/dL	1.0 (0.5)	0.9 (0.2)	2.90	0.00***
Uric acid, mg/dL	6.3 (2.6)	5.5 (2.0)	2.09	0.04*
AST, U/L	26.0 (16.5)	24.7 (19.6)	0.47	0.64
ALT, U/L	26.1 (22.5)	25.0 (25.0)	0.32	0.75
Cholesterol, mg/dL	180.6 (48.7)	184.0 (36.6)	−0.50	0.62
Triglyceride, mg/dL	140.0 (131.1)	113.8 (73.3)	1.38	0.17
Sodium, mg/dL	141.4 (7.4)	141.0 (3.8)	0.49	0.63
Potassium, mg/dL	4.5 (0.4)	4.0 (0.5)	1.49	0.14
Thyroxine, mg/dL	8.8 (8.4)	6.8 (3.1)	2.29	0.02*
Leukocytes, × 10^3/μL	7.7 (3.1)	6.5 (2.1)	2.94	0.00***
Erythrocytes, × 10^6/μL	4.6 (0.5)	4.6 (0.7)	−0.08	0.94
Haemoglobin, g/dL	15.7 (1.6)	13.6 (1.6)	1.40	0.16
Platelets, × 10^3/μL	252.1 (85.9)	242.6 (67.5)	0.76	0.45
Body mass index of index hospitalization, mean (SD), kg/m^2				
Day 1	24.2 (5.4)	22.6 (3.8)	2.37	0.02*
Discharge day	24.8 (5.5)	23.2 (3.5)	2.06	0.04*

AST: aspartate aminotransferase, formerly serum glutamic–oxaloacetic transaminase; ALT: alanine aminotransferase, formerly serum glutamic–pyruvic transaminase; SD: standard deviation.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.005$.

hospitalizations, alcohol consumption, smoking, or concurrent medical morbidities (Tables 1 and 2).

To assess the simultaneous effects of risk factors for circulatory mortality, potential variables were evaluated using multivariate conditional logistic regression models (Table 4). The variables with significant difference in univariate analysis, including age at onset, age at first psychiatric admission, duration of all antipsychotic treatments, blood urea nitrogen, creatinine, uric acid, thyroxine, leukocytes, body mass index at index hospitalization at Day 1, and diastolic pressure of index hospitalization at Day 1, were further analyzed in multivariate models. In these models, the duration of all antipsychotic treatment was significantly associated with a lower risk of circulatory mortality (adjusted odds ratio [OR] = 0.95, 95% confidence interval [CI]: 0.91–0.99, $P < 0.05$), whereas the counts of leukocytes were significantly associated with a higher risk of circulatory mortality (adjusted OR = 1.04, 95% CI: 1.01–1.40, $P < 0.05$).

4. Discussion

In this multi-institutional, nested, case–control study, we investigated risk factors for early circulatory mortality in patients with schizophrenia. A previous study measuring the 25-year mortality of schizophrenia reported there was an apparent increase in circulatory mortality relative to the general population, and cigarette smoking, one of traditional CVD risk factors, may account for majority of the excess natural mortality in the cohort (Brown et al., 2010). However, the cohort study failed to identify other non-traditional risk factors. The present study yielded two major findings; compared with the living patients with schizophrenia, the deceased ones had 1) a higher count of leukocytes and 2) a shorter duration of all antipsychotic treatments, after adjustment for clinical illness variables, cardiovascular variables, and laboratory data at the index admission.

First, the elevated leukocyte counts in the patients with schizophrenia were more associated with circulatory mortality than with traditional cardiovascular risk factors, including smoking, BMI, hyperlipidemia, and ECG measurements. Elevated leukocyte counts, as an indicator of systemic inflammation, was reported to predict coronary heart disease progression in patients with preexisting vascular diseases (Danesh et al., 1998). Moreover, the leukocyte count may serve as an independent predictor of adverse events following intervention for myocardial infarction (Kojima et al., 2004). Therefore, systemic inflammation may be strongly associated with early circulatory mortality in patients with schizophrenia as repeatedly observed in patients with bipolar disorder (Tsai et al., 2005). Our results are consistent with a previous study reporting that an unbalanced immune response may be associated with the inflammatory process of the central nervous system, in which dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission is influenced by immune alternations in schizophrenia (Muller et al., 2015). In addition, some evidence regarding novel biomarkers in psychiatry to predict mortality supports our findings. For example, reduced arterial compliance (change in volume divided by change in pressure in an artery during the cardiac cycle) is associated with cytokine abnormalities, and is an early marker of CVD

Table 3
Clinical characteristics and measurements of deceased and control patients.

Characteristics	Deceased patients (*N* = 79) Mean (SD)	Control patients (*N* = 158) Mean (SD)	*t*	*P*
Systolic pressure of index hospitalization, mmHg				
Day 1	124.0 (21.4)	121.4 (18.4)	1.01,	0.31
Day 2	120.8 (20.6)	117.6 (12.3)	1.19	0.24
Day 3	119.9 (20.7)	118.1 (16.6)	0.62	0.53
Discharge day	118.1 (17.9)	115.1 (16.5)	1.15	0.58
Diastolic pressure of index hospitalization, mmHg				
Day 1	81.2 (12.9)	77.1 (11.8)	2.32	0.02*
Day 2	79.0 (12.9)	76.1 (10.1)	1.06	0.09
Day 3	78.5 (14.1)	75.8 (11.9)	1.41	0.16
Discharge day	76.5 (11.1)	74.1 (10.3)	1.50	0.25
Heart rate at rest, bpm				
Day 1	86.7 (15.5)	87.4 (14.0)	−0.31	0.76
Day 2	86.8 (14.9)	87.8 (13.6)	−0.47	0.64
Day 3	84.2 (14.6)	85.5 (12.6)	−0.64	0.52
Discharge day	82.9 (14.2)	85.7 (12.6)	−1.44	0.15
ECG measurements				
Heart rate, bpm	80.3 (19.5)	78.2 (15.5)	0.81	0.42
QRS duration, ms	91.5 (14.9)	92.8 (15.0)	−0.55	0.58
QT interval, ms	362.1 (44.9)	370.1 (37.0)	−1.27	0.21
QTc (Bazett's), ms	413.6 (32.3)	413.4 (30.7)	0.04	0.97

bpm: beats per minute, ms: millisecond, ECG: electrocardiography; QTc: corrected QT segment, SD: standard deviation.
* $P < 0.05$.

Table 4
Multivariate conditional logistic regression of factors for circulatory mortality in deceased patients.

Variables	Adjusted OR	95% CI for OR	*P*
Age at onset	0.99	0.92–1.05	0.664
Age at first psychiatric admission	0.97	0.93–1.02	0.257
Duration of all antipsychotic treatments	0.95	0.91–0.99	0.014*
Blood urea nitrogen	1.09	0.99–1.20	0.066
Creatinine	1.07	0.10–11.89	0.954
Uric acid	0.91	0.74–1.12	0.368
Thyroxine	1.04	0.90–1.21	0.581
Leukocytes	1.19	1.01–1.40	0.040*
Body mass index at index hospitalization, Day 1	1.11	1.00–1.23	0.056
Diastolic pressure of index hospitalization, Day 1	1.01	0.98–1.04	0.624

CI: confidence interval, SD: standard deviation.
* $P < 0.05$

and a robust predictor of mortality (Koola et al., 2016). Other possible inflammatory indicators must be investigated for addressing concerns regarding the pathophysiology of schizophrenia. Comparisons with the general population were not conducted in this study; therefore, we could not determine more traditional CVD risk factors in the patients with schizophrenia. The traditional CVD risk factors, including smoking, hyperlipidemia, obesity, and blood pressure, failed to predict the circulatory mortality risk in the patients with schizophrenia in this study. However, the deceased group had a significantly higher mean BMI than did the control group. Furthermore, both groups showed high traditional CVD risk factors; approximately one- third of patients in both the groups had concurrent cardiovascular morbidities and smoking habit. Therefore, systemic inflammation is considered an additional risk factor for circulatory mortality in schizophrenia.

Second, the duration of antipsychotic treatment may reduce the risk of early circulatory mortality in schizophrenia. The medications taken by the patients in this study could not be controlled. The control and deceased patients had a similar mean number of psychiatric admissions and mean age at index admission; however, the control patients were significantly older at illness onset and had a higher duration of antipsychotic treatment. These results indicate that the control patients were more compliant and received more effective medical care and that the appropriate treatment may have reduced the mortality rate. The present findings support the results of our previous study on bipolar disorder (Tsai et al., 2005), which reported that psychiatric treatments, particularly pharmacotherapy, may improve not only psychosocial and psychopathological outcomes but also the general health of patients with major psychiatric disorders. Furthermore, studies have reported conflicting results concerning both the benefits and risks of circulatory mortality in patients receiving antipsychotic treatment. However, the present findings support the benefit of antipsychotics in this group (Crump et al., 2013; Suvisaari et al., 2013; Tiihonen et al., 2009).

The anti-inflammatory properties of antipsychotics, in addition to reducing psychotic symptoms, are under investigation. Immune function in patients with schizophrenia treated with antipsychotics may be modulated and normalized by increasing the levels of anti-inflammatory cytokines (interleukin [IL]-4 and IL-10) and reducing the levels of proinflammatory cytokines (interferon-γ) (Al-Amin et al., 2013). Taken together, our two major findings consistently highligh that early circulatory mortality in patients with schizophrenia is associated with systemic inflammation and inadequate antipsychotic treatment.

This study has several limitations. First, the nested case–control study design incorporated the concept of a traditional case–control study within an established cohort and thus had disadvantages associated with case–control studies. Berkson's bias, a selection bias, may have been present because we included formerly hospitalized patients who were severely ill with current physical diseases or comorbid psychiatric disorders as a sample. The nested case–control design minimized selection and recall bias compared with a case–control study (Wolkewitz et al., 2014). Furthermore, even if the differences between the two groups were adjusted by logistic regression model, it was possible to be inadequately powered and therefore yielding Type II errors. Second, the leukocyte count was recorded only once at the index hospitalization; therefore, determining whether systemic inflammation is a state or trait phenomenon was difficult. Moreover, inpatient setting is not the ideal patient population to study inflammation because cytokines may be falsely elevated in response to stress and acute relapse. However, there was no significant difference in infectious morbidity between deceased and living patients, suggesting that inflammation may be mediated by factors other than infection. Third, the misclassification of the cause of death in certificates in the registration system may have masked other types of underlying causes and confounded the study results, despite the fact that the vital event statistics are as accurate and comprehensive as possible in Taiwan. Forth, concurrent physical diseases and CVD risk factors may have been neglected by psychiatrists in outpatient clinics and been not identified in the chart review, resulting in incomplete or missing documentation and absence of information. Finally, with regard to medications, measurement of adherence to antipsychotics may be problematic, and the duration of atypical antipsychotic use was short in both deceased and control groups in our study. Under a typical clinical condition, for patients treated with typical antipsychotics with good responses and without prominent side effects, it is not necessary to replace antipsychotics with atypical antipsychotics. However, in this era where typical antipsychotics are widely used for schizophrenia (Rothbard et al., 2003), the present results may not be generalized to current patient groups. Additionally, we controlled the duration of antipsychotics use, instead of each antipsychotic. It may lead to a systematic confounding because certain antipsychotics might affect leukocyte levels.

In conclusion, systemic inflammation and inadequate antipsychotic treatment, in particular typical antipsychotic treatment, may be risk

factors of early circulatory mortality in patients with schizophrenia. Specific attention must be devoted to patients with schizophrenia to reduce inflammation and improve treatment adherence to prevent early circulatory morbidity and mortality, as well as to facilitate a more efficient integration of mental and physical healthcare services after hospital discharge.

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