ABSTRACT

Objective: To evaluate post-stroke outcomes in patients with Parkinson's disease (PD)

Methods: A matched cohort study was performed. Stroke patients with PD and non-PD controls were extracted from the Thailand Universal Insurance Database. Logistic regressions were used to evaluate the association between PD and in-hospital outcomes (mortality and complications). The PD-associated long-term mortality was evaluated using Royston-Parmar models.

Results: 1,967 patients with PD were identified between 2003 and 2015 and matched to controls (1:4) by age, sex, admission year, and stroke type. PD patients had decreased odds of in-hospital death: OR (95% CI) 0.66 (0.52 – 0.84) and 0.61 (0.43 – 0.85) after ischaemic and haemorrhagic strokes, respectively. PD was associated with a length-of-stay greater than median (4 days) after both stroke types: 1.37 (1.21 – 1.56) and 1.45 (1.05 – 2.00), respectively. Ischaemic stroke patients with PD also had increased odds of developing pneumonia, sepsis and AKI: 1.52 (1.2 – 1.83), 1.54 (1.16 – 2.05), and 1.33 (1.02 – 1.73). In haemorrhagic stroke patients, PD was associated with pneumonia: 1.89 (1.31 – 2.72). Survival analyses showed that PD was protective against death in the short term (HR=0.66; 95% CI 0.53–0.83 ischaemic, and HR=0.50; 95% CI 0.37 – 0.68 haemorrhagic stroke), but leads to an increased mortality risk approximately 1 and 3 months after ischaemic and haemorrhagic stroke, respectively.

Conclusion: PD is associated with a reduced mortality risk during the first 2-4 weeks post-admission but an increased risk thereafter, in addition to increased odds of in-hospital complications and prolonged hospitalisation.

INTRODUCTION

Despite previous studies having evaluated the incidence of stroke in people with co-morbid Parkinson's Disease (PD)[1-4], the relationship between these two disabling neurological conditions remains controversial. Although the most recent studies suggest a positive association between PD and stroke risk, the impact of pre-existing PD on stroke outcomes has not yet been investigated. Furthermore, there are two streams of translational evidence regarding the relationship of PD and stroke on a molecular level. On one hand, it has been shown that in PD, neurons may be more vulnerable to ischaemic damage due to their disease-mediated impaired ability to withstand oxidative stress[5,6]. Oxidative stress is recognised to be implicated in the pathophysiology of both stroke and PD[7,8], and therefore, it may thus be the case that patients with PD have worse stroke outcomes than those without PD. On the other hand however, previous experimental models have shown that cerebral ischaemia provokes an acute exaggerated release of dopamine, which leads to excess neuronal degeneration[9]. This effect has not been observed in *in vivo* models in which dopamine release is impaired[10]. Thus, in the context of this phenomenon, it is possible that PD-associated hypodopaminergia could protect neurons from excess damage during ischaemic events, and thus result in less severe stroke outcomes.

Given the lack of literature regarding the prognosis of stroke in patients with PD, we aimed to evaluate the impact of co-morbid PD on the outcomes of stroke using a retrospective, matched cohort study design.

METHODS

Data source

Data for this matched control study was extracted from the Universal Coverage (UC) Health Security Insurance Scheme Database of Thailand. This database contains clinical and demographic data of 615,758 patients admitted with a stroke diagnosis between 2003 and 2015 in all eligible healthcare centres in Thailand, covering ~ 80% of the Thai population. Admissions, co-morbidities, and complications were registered using ICD10 (*International Classification of Disease, tenth revision*) codes (Supplementary Table 1). Further details about this database can be found in our previously published studies[11,12].

Compliance with Ethical Standards

Ethical approval was obtained from the Ethics Committee in Human Research, Khon Kaen University, Khon Kaen, Thailand. Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. The data that support the findings of this study are available from the corresponding author upon reasonable request. There are no conflict of interest or funding sources to declare.

Patient Population and Match Selection

We performed a matched cohort study of patients with co-morbid PD admitted with a stroke diagnosis against patients without PD admitted with the same diagnosis (unexposed controls). PD patients and their controls were extracted from a pool of 608,890 stroke patients (ICD10 codes I61 (Haemorrhagic Stroke), I63 (Ischaemic Stroke), I64 (Stroke of Undetermined Pathology)), obtained after the exclusion of patients younger than 18 years of age (n = 1427), those older than 100 years (n = 43) and those with missing post-discharge follow-up data (n = 5398, 0.88% of total eligible sample). Pre-existing co-morbidities,

demographic and clinical data were extracted from the database as detailed in Supplementary Table 1. The exposed population was identified as all patients recorded to have PD (ICD10 code G20; n = 1970) as a co-morbidity on stroke admission. For each exposed patient, we randomly selected 4 unexposed controls matched by age, sex, year of admission, and stroke type, yielding a total of 1,967 exposed and 7,868 unexposed controls after excluding those with insufficient number of matches (n = 3) (Supplementary Figure 1).

Statistical Analysis

Descriptive Statistics

Stroke type-specific demographic and clinical characteristics were compared between those with co-morbid PD and the matched controls using the independent-sample t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables and the Chi-squared test for categorical variables.

Analysis of in-hospital adverse events

Multivariable logistic regression models were constructed to evaluate the effect of co-morbid PD on in-hospital mortality and adverse events. We evaluated post-stroke adverse events deemed to be relevant (length of stay in hospital (LOS) greater than median, pneumonia, sepsis, respiratory failure, and acute kidney injury) based on a reference list of most common and serious post-stroke adverse events by Hesse et al[13]. All models were adjusted for potential confounders of adverse events post-stroke in line with previous reports (hypertension, hyperlipidaemia, ischaemic heart disease, atrial fibrillation, heart failure, diabetes mellitus, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, liver disease and alcohol related illness)[11,14,15]. Additionally, we adjusted for occurrence of the adverse events listed above as potential confounders. Covariates were

incorporated into the regressions using a bidirectional step-wise selection model with inclusion and exclusion thresholds of 5% and 20%, respectively. All models were adjusted for the covariates which reached the inclusion criteria during the stepwise selection.

Analysis of post-discharge mortality

Post-discharge mortality was evaluated for ischaemic and haemorrhagic strokes separately. Strokes of undetermined pathology were excluded from this part of the analysis due to the impossibility of extrapolating these results in the long-term. This outcome was compared between the exposed and unexposed using a flexible parametric restricted cubic spline (Royston-Parmar) survival regression[16]. Both models were adjusted for all covariates used in the analyses evaluating the in-hospital outcomes. Median follow-up time was estimated using the reverse Kaplan-Meier method[17].

Post-hoc analysis

To complement the results obtained from our pre-determined analyses, we decided to model mortality using date of admission instead of discharge date as the start of follow-up in order to better demonstrate the effects we observed during the hospitalisation period. We constructed Royston-Parmar models for both ischaemic and haemorrhagic strokes as those above while modifying the observation period to start from date of admission.

RESULTS

Descriptive Statistics

In total, 1970 patients with known PD were identified within this cohort (Supplementary Figure 1). Of these cases, 3 could not be matched with 4 controls as per a

priori defined matching variables, and were therefore excluded. A summary of patient characteristics and comorbidities are depicted in Table 1. We found statistically significant differences in prevalence of some comorbidities between the two groups, as well as significant differences in length of hospital stay.

Descriptive data regarding in-hospital complications and in-hospital mortality are detailed in Table 2. For all stroke types, a smaller proportion of patients with PD died in hospital compared to their controls (9.35% vs. 12.02%, $p<0.001$). Additionally, more PD patients had a length of stay greater than median (4 days) compared to controls (48.65% vs. 38.97%, $p<0.001$), and a greater proportion of PD patients developed pneumonia (15.66% vs. 10.50%, $p<0.001$), sepsis (5.29% vs. 3.13%, $p<0.001$), and acute kidney injury (AKI) (5.74% vs. 3.77%, $p<0.001$).

Post-Stroke Adverse Events

The results of the multivariable logistic regression are reported in Figure 1. Patients with PD presenting with an ischaemic stroke had significantly reduced odds of death in hospital (OR=0.66; 95% CI, 0.52-0.84) despite having higher odds of pneumonia (OR=1.52; 95% CI, 1.27 - 1.83), sepsis (OR=1.54; 95% CI, 1.16 – 2.05), and AKI (OR=1.33; 95% CI, 1.02 – 1.73), and increased odds of having a length of hospital stay greater than median (OR=1.37; 95% CI, 1.21 - 1.56). Patients with PD presenting with a haemorrhagic stroke had lower odds of in-hospital mortality (OR=0.61; 95% CI, 0.43 - 0.85), and were more likely to develop pneumonia (OR=1.89; 95% CI, 1.31 - 2.72) and to have greater than median LOS (OR=1.45; 95% CI, 1.05 - 2.00). Lastly, patients with PD presenting with strokes of undetermined pathology were at increased odds of pneumonia (OR=1.86; 95% CI, 1.14 - 3.02).

Post-Discharge Mortality

The results of the survival regression models of post-discharge mortality for each stroke type are depicted in Figure 2A and 2B. The median follow-up time was 3.7 (95% CI: 3.6 – 3.8) and 4.0 (95% CI: 3.4 – 4.5) years for patients with ischaemic and haemorrhagic strokes, respectively. Patients with PD in both stroke categories had an increased mortality risk compared to their unexposed controls in the long term. For ischaemic strokes, this increased risk appeared after the 34th day post-discharge (HR=1.20; 95% CI, 1.02 – 1.42). The HR function then remains approximately constant throughout the follow-up period (HR=1.50; 95% CI, 1.26 – 1.80). For haemorrhagic strokes, mortality risk reached statistical significance after ~ 6 months (188 days) (HR=1.38; 95% CI, 1.00 – 1.91), and was double that of controls at the end of the 12-year follow-up period (HR=1.98; 95% CI, 1.12 – 3.48).

Post-hoc analysis

The results of the survival regression models of post-admission mortality for each stroke type are depicted in Figure 2C and 2D. After ischaemic stroke, PD was associated with a decreased risk of mortality up to the 12th day post admission (range from HR=0.66; 95% CI 0.53 – 0.83 at day 3 to HR=0.90; 95% CI 0.77 – 1.05 at day 13). After this period, there is no significant difference in mortality between patients with PD and controls until day 36, at which point PD patients show an increased mortality risk (HR=1.18; 95% CI 1.02 – 1.37). Similarly, after haemorrhagic strokes, PD patients have a decreased risk of mortality up to the 22nd day post-admission (ranging from HR=0.50; 95% CI 0.37 – 0.68 on day 3 to HR=0.76; 95% CI 0.56 – 1.03 on day 23). Following this period, mortality between them and controls is

no different until day 106, after which PD is associated with an increased mortality risk (HR=1.26; 95% CI 1.00 – 1.58).

DISCUSSION

To the best of our knowledge, we are the first study to report on the outcomes of stroke in patients with PD. We have found that these patients were less likely to die during the acute phase despite having higher odds of some common post-stroke complications. Additionally, they were more likely to stay in hospital longer than controls. PD patients had higher odds of pneumonia regardless of stroke type, and sepsis and AKI after an ischaemic stroke. Our survival analyses showed that PD is associated with an increased risk of long-term mortality after stroke.

In the present study, we have shown that patients with PD were 35% and 42% less likely to die in hospital after ischaemic and haemorrhagic strokes, respectively. This protective effect was short-lived, disappearing 13 days after admission in the ischaemic stroke sub-group and 22 days after admission in the haemorrhagic stroke sub-group. After this 'protective window', the post-stroke PD-associated mortality excess risk was not significant until 36 and 106 days after admission for ischaemic and haemorrhagic strokes, respectively. From then onwards, the PD-associated excess mortality risk becomes significant and increases from 20% to 57% during the 12-year follow-up period after ischaemic stroke, and from 38% to 98% increased risk after haemorrhagic stroke.

Our results may be interpreted in the context of the effects of stroke on the dopaminergic system[9] and the inherent sensitivity of neurons to ischaemia observed in PD models[5,6,8]. A possible mechanism for the PD-associated protective effect on acute mortality after stroke may be the lack of dopamine-induced neuronal damage during the course of ischaemia in the brain. A recent review by Gower & Tiberi on the effects of stroke

on the dopaminergic system found that many experimental studies have reported an exaggerated release of dopamine into the striatum immediately after stroke[9]. It is argued that this has a detrimental effect on neurons, as models in which dopamine release is inhibited showed protection from excess ischaemic damage[10]. Thus, it is possible that due to the inherent dopaminergic dysfunction of PD, the exaggerated dopamine release does not take place and consequently, no excess ischaemic damage occurs. Nevertheless, after the acute period, our study shows that the PD is associated with excess mortality, which increases with time. This may indicate that the potential to avoid dopamine-induced damage early may not translate to a reduction in mortality in the longer term. Still, these mechanisms and their interaction with the clinical course of patients with PD after stroke is a subject that warrants further investigation. For example, to explore the potentially summative effect of dopamine-induced damage and stroke one could consider the laterality of PD in the context of stroke location. There is extensive evidence to suggest that in PD, the substantia nigra and putamen contralateral to the dominantly-affected side show greater degeneration and reduced dopamine activity compared to the opposite side[18]. Therefore, it would be interesting to compare mortality between PD patients who have a stroke on the dominantly-affected side (with less dopamine activity), and those who have a stroke on the opposite side. Differences in outcomes between these two sub-groups could further strengthen the hypothesis that hypodopaminergia is protective against ischaemic injury, however in this study, we did not have data on PD dominance or stroke location to explore this avenue.

We also found that patients with PD spent longer in hospital after stroke compared to their controls, even after adjusting for in-hospital complications. Previous studies have shown that amongst emergency department admissions of any cause, patients with pre-existing PD spent longer times in hospital than patients without[19-21]. The results of our study are in line with the findings of these previous reports in the context of stroke admissions. It would

be interesting to examine the reasons for prolonged hospitalisation, such as poorer mobility or more extensive intervention requirements in the PD group (physiotherapy, PD management optimisation, etc.). Our data did not contain information on mobility status or interventions post-stroke to investigate this further.

Another finding of this report is that patients with PD are at a higher risk of pneumonia post stroke, and additionally, sepsis and AKI after ischaemic stroke. Respiratory complications have been widely reported in patients with PD throughout the literature[22]. Moreover, about a third of patients with PD exhibit an obstructive ventilation pattern, with evidence that autonomic dysfunction and abnormal muscle control result in poor clearance of secretions and the consequences thereof[23]. Consequently, all of these factors make patients with PD more susceptible to airway infections, especially aspiration pneumonia. Along with this increased risk, there is the added risk of respiratory infections due to stroke complications, most importantly dysphagia. Dysphagia is one of the highest incident complications of stroke and one of the most important predictors of pneumonia and aspiration pneumonia post-stroke[24,25]. One could hypothesise that, given the potentially poor airway function of PD patients, stroke-induced dysphagia may not only occur more easily, but also be longer lasting in these patients. Furthermore, although most patients who develop stroke-induced dysphagia recover satisfactorily from the episode[26], the same may not be true for those with PD. Nevertheless, the association between PD and the susceptibility to develop post-stroke dysphagia and its impact on clinical outcomes is a subject requiring further investigation.

Parallel to the positive association between post-stroke pneumonia and PD, we found that patients with PD had significantly higher odds of developing sepsis and AKI after ischaemic stroke. Notably, these observations remain significant even after adjusting for pneumonia. This suggests that stroke patients with PD are more likely to develop sepsis

independently of whether they developed pneumonia in ischaemic stroke. Sepsis is a systemic inflammatory reaction to infection and must therefore be preceded by it. Most patients with PD exhibit some degree of autonomic dysfunction, including disordered cardiovascular, gastrointestinal, respiratory, urogenital and thermoregulatory function[27]. There is an argument that these organ system dysfunctions may make patients with PD more vulnerable to acquire infections and less able to fight them once infection has occurred[28,29]. Similarly, it is possible patients with PD are more susceptible to AKI due to autonomic dysfunction of the bladder and increased incidence of infections. We hypothesise that these factors may make patients with PD more vulnerable to develop these complications after stroke.

Our study has several strengths. We used a prospectively-identified multi-centre national database cohort to identify patients with co-morbid PD, minimising the potential for selection and recall bias. We have utilised novel flexible time-to-event models to render the varying nature of the PD-associated mortality risk over time. Additionally, we have described the length of stay and other adverse events of clinical relevance in these patients, which may serve as reference points for further research.

We do acknowledge some limitations. Our case ascertainment and analyses were based on insurance reimbursement data classified using ICD10 codes. This reimbursement database lacked clinical characteristics of diagnoses, and therefore we did not have information regarding disease severity such as stroke disability. In addition, the database used did not include information regarding pre-admission and post-discharge management, and thus, we were unable to investigate the effect of different treatment regimens on outcomes. Also, the management of PD and stroke may have changed over the twelve-year recruitment period. Although this remains one of the inherent limitations of long follow-up studies, we minimised its effect by using strict matching criteria, including year of admission as one of

the matching variables for controls. Finally, our data did not include information regarding stroke location or PD lateralisation.

CONCLUSION

Whilst the relationship between PD and stroke incidence has been previously explored, the effect of PD on stroke outcomes has not been examined previously. We have shown that PD is associated with a differential risk of post-stroke mortality depending on the time course. Whilst in the short-term PD has a protective effect on mortality after stroke, this effect is reversed 2-4 weeks thereafter. Additionally, our findings show that PD is associated with more adverse events and a greater length of stay during hospitalisation. These results help elucidate the relationship between PD and stroke and serve as evidence for further research.

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FIGURE TITLES / LEGENDS

Figure 1 - Association between co-morbid PD and post-stroke adverse events, stratified by outcome and stroke type.

PD = Parkinson's Disease, OR = Odds Ratio, CI = Confidence Interval, LOS = Length Of Stay, AKI = Acute Kidney Injury, UTI = Urinary Tract Infection, NS = Not Significant. All ORs were adjusted for hypertension, hyperlipidaemia, ischaemic heart disease, atrial fibrillation, heart failure, diabetes mellitus, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, liver disease and alcohol related illness according to a stepwise selection model. Additionally, each individual model was adjusted for all other complications.

Figure 2 - Post-discharge (A and B) and Post-admission (C and D) excess mortality (hazard ratio) associated with co-morbid Parkinson's in stroke patients.

Hazard ratio (solid line) and 95% confidence intervals (shaded area) are shown as a function of time. (A and C) Post ischaemic stroke. The hazard ratio was calculated as a function of restricted cubic splines with 2 internal knots. (B and D) Post haemorrhagic stroke. The hazard ratio was calculated as a function of restricted cubic splines with 2 internal knots.