Risk of Parkinson disease Following Gout: A Population-Based Retrospective Cohort Study in Taiwan

CURRENT STATUS: UNDER REVIEW

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DOI: 10.21203/rs.3.rs-19373/v1

SUBJECT AREAS
Neurology Rheumatology

KEYWORDS
gout, National Health Insurance Research Database, Parkinson disease
Abstract

Background and Purpose The progressive neurodegenerative disorder Parkinson disease (PD) is well-established as the second most common neurodegenerative disease. Associations between the sequential risk of PD and gout have been addressed in other studies, but findings have been inconclusive. Accordingly, we executed the present study with the purpose of assessing PD risk in patients with gout.

Methods From Taiwan’s National Health Insurance Research Database, we identified the data of patients newly diagnosed as having gout between January 1, 2000 and December 1, 2000. A cohort of patients without gout, matched for sex and age, was constructed for comparison. Hazard ratios (HRs) and the incidence rate of subsequent PD were calculated for both cohorts and separately for male and female groups. The gout and comparison cohorts consisted of 7900 patients each.

Results The HR for PD was not significantly higher in the gout cohort compared with the control cohort (HR 1.01, 95% confidence interval [CI], 0.93–1.31, P = .268), even after adjustment for age, urbanization, monthly income, sex, and comorbidities. We did not observe gender differences in the gout–PD association (male: HR 1.01, 95% CI, 0.88–1.36, P = .400; female: HR 1.11, 95% CI, 0.84–1.46, P = .466).

Conclusions Our study identified no association between gout and PD in Taiwan.

Background

The well-known progressive neurodegenerative disorder Parkinson disease (PD) involves dopaminergic nigrostriatal neuron degeneration, which typically results in motor deficits. It has an estimated worldwide prevalence of 1–2% for individuals over the age of 65 years, rendering it the second most common neurodegenerative disease, with the most common being Alzheimer disease [1]. This disorder’s global burden has increased by over two times over the past generation because of the increase in the number of elderly individuals [2]. The underlying pathogenic mechanisms of PD remain unclear, although there has been considerable progress in determining the environmental as well as genetic factors that influence the development of PD. Additionally, accumulating evidence indicates oxidative stress to play a major role in the PD etiology [3; 4].
Uric acid (UA) has been demonstrated by previous research to have an antioxidative effect [5; 6; 7]. However, a high level of UA is associated with gout. Thus, due to the antioxidative effect of UA, the study described herein hypothesized a negative gout-PD risk association. Findings reported by previously executed research have been inconsistent with respect to the gout-PD risk association, despite some of such research being large retrospective studies [8; 9; 10; 11; 12; 13]. For example, an English study found that in the gout group, the increase in the risk of subsequent PD was modest (rate ratio 1.11, 95% confidence interval [CI], 1.05–1.17) [9]. However, another study in the United Kingdom used a large population-based database and concluded that the risk PD development is relatively low in individuals having a gout history (odds ratio [OR] 0.69, 95% CI, 0.48–0.99). In addition, other studies have demonstrated variations in PD incidence regarding ethnicity and race [14; 15]. Asian studies on gout and PD risk are, however, few [12].

To address the previously described inconsistencies in findings regarding the gout-PD risk association and the paucity of Asian studies concerning said association, we executed the present nationwide population-based retrospective cohort study to seek to identify whether an association exists between the two aforementioned illnesses. The following hypothesis constituted the basis for our study: patients with gout would have a relatively low risk of PD.

Methods
Data Sources
Taiwan’s 1995-established National Health Insurance (NHI), covering approximately 99% of residents of Taiwan, is a compulsory program covering comprehensive medical care, such as emergency, outpatient, inpatient, and traditional Chinese medicine services [16]. The National Health Insurance Research Database (NHIRD), which is overseen by the National Health Research Institutes, comprises exhaustive information concerning clinic visits, including prescription details as well as diagnostic codes based on the A code and International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). For this database, data confidentiality is subject to the directives of the NHI Bureau. For executing the present study, we retrieved Longitudinal Health Insurance Database 2000 (LHID2000) data; the LHID2000 comprises the information of 1 million people who were randomly and
systematically sampled from the NHIRD. Comparing patients whose information is contained in the NHIRD and those whose information is contained in the LHID2000 demonstrated no significant differences with regard to average distribution of sex or age or the amount of insured payroll [17].

Ethics Statement
The Institutional Review Board (IRB) of Taipei Veterans General Hospital ratified our executed study (IRB number: 2018-07-016AC). Because the NHIRD comprises secondary data that had been deidentified and maintained for research purposes, written consent from the patients evaluated in this study was unnecessary. Accordingly, the aforementioned IRB provided a formal written waiver of the requirement to obtain patients’ written consent.

Study Population
From the LHID2000, we included the data of patients (≥ 20 years) who received a new diagnosis of gout between January 1, 2000 and December 31, 2000. Gout was defined according to ICD-9-CM code 274. To ensure patient homogeneity and diagnostic validity, we enrolled patients only if they had at least two consensus diagnoses of gout. Patients diagnosed as having PD before enrollment (A code: A221; ICD-9-CM code: 332) were excluded. Moreover, for each gout patient included in our final cohort, we randomly selected from the LHID2000 the data of a control patient (i.e., a patient not diagnosed as having gout or PD) matched for age, enrollment date, and sex. Observations of all control patients and patients with gout were made until (1) PD diagnosis by a neurologist, (2) death, or (3) the end date, December 31, 2013. Neurologist-diagnosed PD constituted our primary clinical outcome.

Statistical Analysis
By applying independent t and chi-squared tests, we probed differences between demographic characteristics of patients with gout and control patients. The incidence of newly diagnosed PD in the patient groups was also calculated after stratification of the data by age (≥ 65 or < 65 years), sex, and time since gout diagnosis.

By executing Cox proportional hazards regression, we identified variables predicting PD in the two groups. Many control variables were included in the univariate model as covariates; these were sex, age, urbanization, typical comorbidities (diabetes mellitus, chronic liver disease, dyslipidemia,
cerebrovascular disease, hypertension, autoimmune disease, nephropathy, and chronic lung disease), and monthly income. We estimated patients’ monthly income by using their insurance premiums, typically derived on the basis of the beneficiary’s total income. We categorized the estimated monthly income the following groups: no income, low (< NT$20,000), medium (> NT$20,000 to < NT$40,000), and high (≥ NT$40,000). In addition, we divided urbanization into the following categories: urban, suburban, and rural. In our univariate analysis, we executed the forward selection technique to apply multivariate Cox proportional hazards regression to factors exhibiting a moderate to statistically significant relationship (i.e., P < .1) with the aforementioned outcome.[18] Variables predicting PD in male and female groups separately were also identified using the same regression.

For executing data extraction and computation, we employed Perl (Version 5.12.2). Furthermore, we executed data linkage and processing as well as control sampling through Microsoft SQL Server 2005 (Microsoft Corp., Redmond, WA, USA). All statistical analysis processes were completed using SPSS (Version 19.0 for Windows; IBM Corp., New York, NY, USA) and SAS (Version 9.2; SAS Institute Inc., Cary, NC, USA). We deemed P < .05 as signifying statistical significance.

Results

Participant Selection

Of the 7900 control individuals and 7900 patients with gout, 83.9% were determined to be men. We noted the median (interquartile range [IQR]) age at the time of enrollment to be 50 (40–64) years; in addition, we observed the median (IQR) follow-up periods for patients with gout and controls to be 13.36 (13.04–13.65) and 13.36 (13.04–13.65) years, respectively. Patients with gout more frequently had comorbidities such as hypertension, cerebrovascular disease, diabetes mellitus, dyslipidemia, nephropathy, autoimmune disease, chronic lung disease, and chronic liver disease than did controls. Clinical and demographic variables of patients with gout and controls are shown in Table 1.

Incidence of PD in Gout and Control Cohorts

We determined that during the study period, 247 controls (2.63 per 1000 person-years) and 339 patients with gout (3.56 per 1000 person-years) receive a PD diagnosis. Between the patients with gout and controls, the PD incidence risk ratio (IRR) was 1.36 (95% CI, 1.15–1.60, P < .001), with the
IRR remaining higher in patients with gout than in controls after stratification for age (≥65 or <65 years) and sex (male or female) (Table 2). For stratification by follow-up duration (0–1, 1–5, ≥5 years), the IRR of newly diagnosed PD was determined to remain significantly higher in the patients with gout.

**Gout and PD Risk**

Compared with controls, the gout cohort did not have a significantly higher hazard ratio (HR) for PD development during the follow-up period (HR 1.01, 95% CI, 0.93–1.31, \( P = 0.268 \)), even after adjustment for sex, age, urbanization, monthly income, and comorbidities (Table 3). After stratification by sex (male or female), the HR for PD was not significantly higher among patients with gout than among controls (HR 1.01, 95% CI, 0.88–1.36, \( P = 0.400 \); HR 1.11, 95% CI, 0.84–1.46, \( P = 0.466 \)) (Tables 4 and 5).

**Discussion**

Results indicate that the IRR of newly diagnosed PD was significantly increased in the gout cohort relative to the control cohort in our study. In this study’s gout cohort, the HR for PD was not significantly higher than that in the control cohort. Patients with gout more frequently had hypertension, cerebrovascular disease, diabetes mellitus, nephropathy, dyslipidemia, autoimmune disease, chronic liver disease, and chronic lung disease than did controls. Other previously executed studies have also demonstrated an association between gout and various metabolic and cardiovascular diseases [19; 20; 21]. In addition, no gender difference was evident in the gout–subsequent PD risk association.

Results of our study fail to demonstrate an association between gout and PD, even though many studies have determined that UA has an antioxidative effect [5; 6; 7]. The possible explanation for this finding is twofold. First, gout is determined to be associated with metabolic and cardiovascular diseases [19; 20]; as demonstrated by previously executed research, these diseases constitute independent risk factors for PD [22; 23]. For example, a prospective study of the Finnish population revealed that the HR of PD among individuals with type 2 diabetes relative to those without the disease was 1.85 (95% CI, 1.23–2.80) [24]. The increased prevalence of metabolic diseases may
offset the protective effect afforded by UA against the sequential PD risk in patients with gout. The finding of a higher frequency of hypertension, cerebrovascular disease, dyslipidemia, and diabetes mellitus in this study’s gout cohort compared with the control cohort supports this explanation.

Second, studies have shown an association between gout, a chronic inflammatory disease, and high levels of various inflammatory cytokines, chiefly interleukin (IL)-1, IL-6, and IL-8 [21; 25]. Additionally, previously executed research has reported PD risk to be increased by chronic inflammation [26; 27]. Thus, the protective effect of UA in patients with gout may be due to chronic inflammation.

The relationship between gout and PD risk has been evaluated in some retrospective studies, which have yielded inconsistent results [8; 9; 10; 11; 12; 13]. A modestly increased risk of subsequent PD in the gout group was observed in one of the studies [9]. However, a decreased risk of PD was found for patients with gout in two other studies [10; 11]. Similar to our study result, two studies failed to identify an association between gout and PD [12; 13]. Different study designs may partially account for the conflicting results. Furthermore, the question as to whether genetic differences along racial or ethnic lines influence PD risk in patients with gout warrants consideration because previously executed research has revealed that race and ethnicity have an influence on the incidence of PD [14; 15].

Risk factors for PD have been found to be gender specific [28; 29; 30]. For example, one meta-analytic study determined an association between aspirin use by men but not by women with an increased PD risk (men: on 1.22, 95% CI, 1.03–1.44; women: RR 0.98, 95% CI, 0.71–1.37) [29]. With respect to gout and the subsequent risk of PD, one previous study also demonstrated a gender-specific difference, finding a decreased PD risk among men with gout (OR 0.60, 95% CI, 0.40–0.91) but not among women with gout (OR 1.26, 95% CI, 0.57–2.81).[11] However, in our study, no gender difference was identified regarding the gout-subsequent PD association. Additional studies are required to identify whether the gout-subsequent PD risk association is affected by gender.

Our study has two main strengths: large sample size and specialist-executed PD diagnoses. Moreover, the patient selection process was unbiased. Due to compulsory enrollment in NHI and easy access to low-cost health care, the patient population exhibits low referral biases and high follow-up
compliance. However, we must discuss our study’s limitations. First, the NHIRD does not have information regarding a family history of PD, environmental factors (such as exposure to herbicides or pesticides), or lifestyle factors (such as coffee or tobacco consumption), but all of these may be associated with PD risk [31; 32; 33; 34]. Second, NHIRD-using studies could not obtain records of serum UA levels; accordingly, further research should be performed on whether serum UA levels affect PD risk. Third, this study’s follow-up period may have been inadequate for the detection of late-onset PD. Hence, future research must include a longer follow-up period to clarify the long-term risk of PD in patients with gout. Finally, in NHI claims, the indicated diagnoses are primarily for administrative billing purposes; they are not subject to verification for scientific purposes. Accordingly, the manner in which diagnoses were classified remains unclear in studies using the NHIRD. Thus, we cannot determine the accuracy of the diagnoses.

Conclusion
In conclusion, no gout–PD association was found in this nationwide population-based retrospective cohort study of patients in Taiwan. We did, however, identify further evidence of associations between gout and metabolic and cardiovascular diseases. Population-based prospective studies in the future should include longer follow-up periods to further probe the gout–PD risk association in different racial or ethnic groups.

Abbreviations
PD
parkinson disease
UA
uric acid
CI
confidence interval
NHI
National Health Insurance
NHIRD
National Health Insurance Research Database
ICD-9-CM
International Classification of Disease, Ninth Revision, Clinical Modification
LHID2000
Longitudinal Health Insurance Database 2000
IRB
Institutional Review Board
IQR
interquartile range
IRR
incidence risk ratio
HR
hazard ratio
IL
interleukin
RR
relative risk

Declarations
Ethics approval and consent to participate
The present study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (2018-07-016AC). No written consent from the study participants was required, because the NHI data set comprised de-identified secondary data for use in research. The Institutional Review Board of Taipei Veterans General Hospital issued a formal written waiver for the requirement of consent.

Consent for publication
The authors of the report would be most grateful if this manuscript could be considered for publication in the BMC neurology. We understand that the text and any pictures or tables published in this article will be freely available on the internet and is seen by the general public. These may also appear on other websites or in print, may be translated into other languages or used for commercial purposes.

Availability of data and material
The data that support the findings of this study are available from the Taiwan National Health Insurance Research Database (NHIRD). Interested individuals should contact the NHIRD to gain access.

Competing interests
The authors declare no conflict of interest.

Funding
This work was supported by grant V108C-038 from the Taipei Veterans General Hospital and grant MOST 108-2314-B-367-001 from the Ministry of Science and Technology. The funders had no role in the study design or procedures; in the collection, management, analysis, or interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

Authors' contributions
Study conception and design: S.J.H., C.C.S. and C.K.H.
Acquisition of data: A.C.Y., C.C.S. and S.J.T.
Analysis and interpretation of data: Z.H.Y., S.J.H. and C.C.S.
Draft manuscript: L.Y.H. and S.C.L.
All authors had read and approved the final manuscript.

Acknowledgements
This manuscript was edited by Wallace Academic Editing.

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Tables
Table 1 Baseline Characteristics of Patients with and without Gout
Demographic data | Patients with Gout ($n = 7,900$) | Patients without Gout ($n = 7,900$)  
|-----------------|--------------------------|--------------------------|
| Age (years)$^a$ | 50 (40-64) | 50 (40-64)  
| ≥65 | 1,791 | 1,791  
| <65 | 6,109 | 5,409  
| Sex | |  
| Male | 5,409 | 5,409  
| Female | 2,491 | 2,491  
| Comorbidities | |  
| Diabetes mellitus | 1,664 | 950  
| Hypertension | 3,240 | 1,887  
| Dyslipidemia | 2,230 | 1,000  
| Cerebrovascular disease | 1,147 | 829  
| Chronic lung disease | 989 | 684  
| Nephropathy | 1,219 | 661  
| Chronic liver disease | 2,713 | 1,638  
| Autoimmune disease | 316 | 163  
| Degree of urbanization | |  
| Urban | 4,186 | 4,552  
| Suburban | 2,853 | 2,694  
| Rural | 861 | 654  
| Income group | |  
| High income | |  
| Medium income | 1,314 | 1,261  
| Low income | 4,184 | 4,073  
| No income | 1,418 | 1,559  
| Follow-up years$^a$ | 13.36 (13.04–13.65) | 13.36 (13.04–13.63)  

$^a$ indicates Median (interquartile range); * indicates statistical significance.

Table 2 Incidence of Parkinson Disease in Patients with and without Gout
|                  | Patients with Gout | Patients without Gout | Risk ratio (95% CI) |
|------------------|--------------------|-----------------------|---------------------|
|                  | No. of Parkinson   | Per 1,000 person-years| No. of Parkinson   | Per 1,000 person-years|                  |
|                  | Disease            |                       | Disease            |                       |                  |
| Total            | 339                | 3.56                  | 247                | 2.63                  |                  |
| Age              |                    |                       |                    |                      |                  |
| ≥65              | 214                | 12.37                 | 159                | 9.31                  |                  |
| <65              | 125                | 1.60                  | 88                 | 1.14                  |                  |
| Sex              |                    |                       |                    |                      |                  |
| Male             | 204                | 3.13                  | 154                | 2.41                  |                  |
| Female           | 135                | 4.49                  | 93                 | 3.10                  |                  |
| Follow-up        |                    |                       |                    |                      |                  |
| 0–1              | 33                 | 702.13                | 17                 | 257.58                |                  |
| 1–5              | 90                 | 62.54                 | 65                 | 37.06                 |                  |
| ≥5               | 216                | 2.30                  | 165                | 1.79                  |                  |

CI indicates confidence interval; * indicates statistical significance.

Table 3 Analyses of Risk Factors for Parkinson Disease in Patients with and without Gout
| Predictive variables           | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | HR (95% CI)         | P value               | HR (95% CI) |
| Gout                          | 1.36 (1.15–1.60)    | <.001                 | 1.01 (0.93–1.31) |
| Age (<65 = 0, ≥65 = 1)        | 8.20 (6.93–9.71)    | <.001                 | 4.41 (3.61–5.39) |
| Sex (Male = 0, Female = 1)    | 1.37 (1.16–1.62)    | <.001                 | 0.90 (0.76–1.08) |
| Comorbidities                 |                     |                       |              |
| Diabetes mellitus             | 2.83 (2.38–3.36)    | <.001                 | 1.32 (1.08–1.60) |
| Hypertension                  | 4.62 (3.90–5.48)    | <.001                 | 1.85 (1.52–2.27) |
| Dyslipidemia                  | 2.01 (1.69–2.38)    | <.001                 | 0.90 (0.74–1.09) |
| Cerebrovascular disease       | 4.63 (3.91–5.48)    | <.001                 | 2.04 (1.69–2.45) |
| Chronic lung disease          | 2.89 (2.38–3.52)    | <.001                 | 1.25 (1.02–1.53) |
| Nephropathy                   | 2.16 (1.77–2.63)    | <.001                 | 1.07 (0.86–1.32) |
| Chronic liver disease         | 1.80 (1.53–2.13)    | <.001                 | 1.23 (1.02–1.47) |
| Autoimmune disease            | 1.66 (1.13–2.42)    | .009                  | 1.19 (0.81–1.75) |
| Degree of urbanization        |                     |                       |              |
| Urban                         | Reference           | Reference             |
| Suburban                      | 1.34 (1.12–1.59)    | .001                  | 1.11 (0.92–1.33) |
| Rural                         | 2.00 (1.57–2.54)    | <.001                 | 1.32 (1.02–1.71) |
| Income group                  |                     |                       |              |
| High income                   | Reference           | Reference             |
| Medium income                 | 5.51 (3.59–8.44)    | <.001                 | 1.90 (1.21–2.99) |
| Low income                    | 3.94 (2.60–5.95)    | <.001                 | 0.98 (1.04–2.47) |
| No income                     | 1.30 (0.26–2.54)    | .304                  | 1.26 (0.76–2.10) |

HR indicates hazard ratio; CI indicates confidence interval; * indicates statistical significance.

Table 4 Analyses of Risk Factors for Parkinson Disease in Male Patients with and without Gout
| Predictive variables | Univariate analysis | Multivariate |
|----------------------|---------------------|--------------|
|                      | HR (95% CI)         | P value      | HR (95% CI) |
| Gout                 | 1.30 (1.06–1.60)    | .014         | 1.01 (0.88–1.36) |
| Age (<65 = 0, ≥65 = 1) | 10.20 (8.20–12.68)  | <.001        | 5.28 (4.04–6.90) |
| Comorbidities        |                     |              |              |
| Diabetes mellitus    | 2.90 (2.30–3.66)    | <.001        | 1.27 (0.97–1.65) |
| Hypertension         | 4.89 (3.95–6.04)    | <.001        | 1.81 (1.40–2.33) |
| Dyslipidemia         | 1.86 (1.47–2.36)    | <.001        | 0.83 (0.64–1.09) |
| Cerebrovascular disease | 5.36 (4.30–6.68)  | <.001        | 2.12 (1.67–2.70) |
| Chronic lung disease | 3.51 (2.76–4.47)    | <.001        | 1.27 (0.99–1.65) |
| Nephropathy          | 2.20 (1.68–2.90)    | <.001        | 0.91 (0.68–1.22) |
| Chronic liver disease| 1.75 (1.41–2.17)    | <.001        | 1.23 (0.98–1.56) |
| Autoimmune disease   | 1.93 (1.15–3.23)    | .013         | 1.24 (0.74–2.09) |
| Degree of urbanization|                     |              |              |
| Urban                | Reference           | Reference    | Reference |
| Suburban             | 1.34 (1.07–1.68)    | .010         | 1.15 (0.91–1.45) |
| Rural                | 2.08 (1.53–2.84)    | <.001        | 1.46 (1.05–2.02) |
| Income group         |                     |              |              |
| High income          | Reference           | Reference    | Reference |
| Medium income        | 5.40 (3.37–8.66)    | <.001        | 1.73 (1.05–2.86) |
| Low income           | 3.72 (2.40–5.75)    | <.001        | 1.42 (0.89–2.27) |
| No income            | 1.08 (0.61–1.92)    | .792         | 1.05 (0.59–1.87) |

HR indicates hazard ratio; CI indicates confidence interval; * indicates statistical significance.

Table 5 Analyses of Risk Factors for Parkinson Disease in Female Patients with and without Gout
| Predictive variables | Univariate analysis | Multivariate |
|----------------------|---------------------|--------------|
|                      | HR (95% CI)         | P value      | HR (95% CI) |
| Gout                 | 1.45 (1.11–1.89)    | <.001        | 1.11 (0.84–1.46) |
| Age (<65 = 0, ≥65 = 1) | 5.56 (4.25–7.28) | <.001        | 3.50 (2.59–4.74) |
|                      | 3.56 (2.56–4.98)    | <.001        | 1.20 (0.99–1.44) |

Comorbidities

| Comorbidities            | Univariate analysis | Multivariate |
|--------------------------|---------------------|--------------|
|                          | HR (95% CI)         | P value      | HR (95% CI) |
| Diabetes mellitus        | 2.54 (1.95–3.31)    | <.001        | 1.38 (1.03–1.86) |
| Hypertension             | 4.04 (3.02–5.40)    | <.001        | 1.90 (1.37–2.64) |
| Dyslipidemia             | 2.03 (1.56–2.63)    | <.001        | 0.99 (0.73–1.33) |
| Cerebrovascular disease  | 3.55 (2.72–4.64)    | <.001        | 1.91 (1.44–2.54) |
| Chronic lung disease     | 2.03 (1.45–2.84)    | <.001        | 1.17 (0.83–1.64) |
| Nephropathy              | 1.94 (1.44–2.60)    | <.001        | 1.26 (0.93–1.72) |
| Chronic liver disease    | 1.82 (1.40–2.37)    | <.001        | 1.23 (0.92–1.63) |
| Autoimmune disease       | 1.29 (0.74–2.25)    | .376         | .62 (0.36–1.06)  |

Degree of urbanization

| Degree of urbanization | Univariate analysis | Multivariate |
|------------------------|---------------------|--------------|
| Urban                  | Reference           | Reference    |
| Suburban               | 1.31 (0.99–1.74)    | .059         | 1.08 (0.81–1.46) |
| Rural                  | 1.81 (1.23–2.65)    | .002         | 1.20 (0.79–1.82) |

Income group

| Income group           | Univariate analysis | Multivariate |
|------------------------|---------------------|--------------|
| High income            | Reference           | Reference    |
| Medium income          | 6.85 (1.69–27.81)   | .007         | 2.52 (0.61–10.38) |
| Low income             | 5.26 (1.30–21.30)   | .020         | 2.15 (0.52–8.81)  |
| No income              | 2.32 (0.53–10.16)   | .263         | 2.04 (0.47–8.94)  |

HR indicates hazard ratio; CI indicates confidence interval; * indicates statistical significance.