MORTALITY RISK OF CHARCOT ARTHROPATHY COMPARED TO DIABETIC FOOT ULCER AND DIABETES ALONE

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**Objective:** To compare mortality risks of patients with Charcot arthropathy to those with diabetic foot ulcer and those with diabetes alone (no ulcer or Charcot arthropathy).

**Research design and methods:** A retrospective cohort of 1,050 patients with incident Charcot arthropathy in 2003 in a large healthcare system was compared to patients with foot ulcer and those with diabetes alone. Mortality was determined during a 5-year follow-up period. Charcot arthropathy patients were matched to individuals in the other two groups using propensity score matching based on patient age, sex, race, marital status, diabetes duration, and diabetes control.

**Results:** During follow-up 28.0% of the sample died; 18.8% with diabetes only and 37.0% with foot ulcer died compared to 28.3% with Charcot arthropathy. Multivariable Cox regression shows that, compared with Charcot arthropathy, foot ulcer was associated with 35% higher mortality risk (HR = 1.35; 95% CI, 1.18 – 1.54) and diabetes alone with 23% lower risk (HR = 0.77; 95% CI, 0.66 – 0.90). Of the Charcot arthropathy patients, 63% experienced foot ulceration before or after the Charcot onset. Stratified analyses suggest that Charcot arthropathy is associated with significantly increased mortality risk independent of foot ulcer and other co-morbidities.

**Conclusions:** Charcot arthropathy was significantly associated with higher mortality risk than diabetes alone and with lower risk than foot ulcer. Foot ulcer patients tended to have higher prevalence of peripheral vascular disease and macrovascular diseases than Charcot arthropathy patients. This may explain the difference in mortality risks between the two groups.
Charcot arthropathy (CA) is a severe joint disease in the foot that can result in fracture, permanent deformity, limb loss, and other morbidities (1,2). It occurs in persons with diabetes complicated by neuropathy and is known to have dramatic negative effects on physical function as well as social, emotional, and mental health (3). However, the mortality implications associated with Charcot arthropathy are not clear.

Two previous studies reported low mortality among patients with this condition (4,5). In contrast, Gazis et al. (6) recently reported a high mortality among 47 patients treated in a specialty clinic. Forty-five percent of CA patients died after a mean follow-up of 3.7 years compared with 34.0% of those with a neuropathic foot ulcer during the same period. Because foot ulcer is a known mortality risk factor (7,8), this finding suggests that CA is also associated with increased mortality risk.

The objective of this study is to examine whether CA is associated with increased mortality risks. Since many CA patients experience foot ulcer sometime before or after its onset, it is not clear how much of the elevated mortality risk can be attributed to CA and how much to foot ulcer or other diabetic complications. In this study, we will compare mortality risks of CA patients with those with diabetes alone (e.g., without CA or foot ulceration) and with those with a foot ulcer to examine if CA increases mortality risk, controlling for foot ulcer, diabetes severity, other diabetic complications, and co-morbidities.

**RESEARCH DESIGN AND METHODS**

Data and Study Sample: The Institutional Review Board at the Edward Hines, Jr. VA Hospital approved the study including a HIPAA waiver of authorization.

The Department of Veterans Affairs (VA) inpatient and outpatient datasets for fiscal year 2003 (October 2002 to September 2003; all years henceforth are fiscal years) were used to identify diabetic patients. A patient in this study was defined as having diabetes if one filled a prescription for a diabetes medication (insulin or oral hypoglycemics) in the current year and/or had 2 or more hospitalizations or outpatient visits with a diabetes code (ICD-9-CM 250.xx) over a 24-month period (9).

**Identification of Cases and Controls:** We used a retrospective cohort design to compare mortality risks of CA patients with diabetic foot ulcer (DFU) patients and diabetes only controls (DMC). The overall VA diabetic population was first divided into three mutually exclusive groups. The first included only patients who were newly diagnosed with CA in 2003. A CA diagnosis was determined by an ICD-9-CM diagnostic code 713.5 in any VA inpatient and/or outpatient records. The second group consisted of patients who were newly diagnosed with a DFU in 2003 but had not experienced CA in 2002 - 2007. DFU was identified by ICD-9-CM diagnostic codes 707.1x or 707.9 in any patient records. These are the two codes used in the VA Computerized Patient Record System for DFU: 707.1x when the specific site of ulceration can be determined and 707.9 when ulceration is found on multiple sites on the lower extremities. This method shows excellent agreement with methods used in previous studies (10,11). For example, compared with the Harrington method (11), this method had 97.2% sensitivity and 99.7% specificity with kappa = 0.93.

The third group consisted of patients who have not had any diagnosis of either CA or DFU in 2002 – 2007. For the first two groups, a condition was determined as newly
Mortality Risk of Charcot Arthropathy diagnosed in 2003 if it was not found in any utilization records in 2002.

Using propensity score matching (12), we selected two controls each from the other two groups for every CA patient in the first group. One-to-two matching was used to ensure that the study sample was adequately powered. Propensity scores were obtained from a logistic regression that provided the conditional probability of a patient developing CA in 2003 given the baseline covariates of age, sex, race/ethnicity, diabetes duration, and diabetes control. When multiple controls with the same propensity score were found, we selected one randomly.

Identification of mortality events: Mortality events were identified by death dates recorded in the VA Vital Status File. This data set contains death dates for all VA beneficiaries and is known to have extremely high completeness (98.3% of all death dates are recorded) and accuracy (97.6% are accurate to the exact date) when compared with death dates from the National Death Index (13). Currently, the VA Vital Status File contains death dates up to April 2007. For deaths that occurred between April and September of 2007, we obtained them from the same data sources used for constructing the VA Vital Status File and followed the same algorithms in choosing the best death date (13).

Covariates: Data for known risk factors for mortality among diabetic persons, including age, sex, race, marital status, diabetes duration, and co-existing conditions (1), were obtained from inpatient and outpatient records in 2003. Age indicates patient’s age at the time of study entry (see below). Diabetes duration was measured by the number of years a patient had had diabetes in 2003. The longest duration that can be ascertained for this study was six years. We obtained A1c measurements from the VA Laboratory Results National Data Extracts for 2003 for all patients in the sample. Due to the seasonal fluctuations in the A1c level (14), we computed a mean of all available A1c values for each patient for use as the baseline measure of diabetes control.

All co-existing conditions in the Elixhauser co-morbidity method (15) were identified from inpatient and outpatient records. Among the 29 conditions identified, we chose only those that showed significant associations with mortality. Macrovascular complications are major mortality risk factors in diabetes (16) and ischemic heart disease and stroke were additionally identified and used in multivariable models. Table A1 (available in the online appendix at http://care.diabetesjournals.org) shows all co-morbidities and their definitions in ICD-9-CM diagnostic codes.

Statistical Analysis: Patients were followed from the date of study entry until September 30, 2007 for up to five years. Entry date was determined as the first date of diagnosis for patients in CA or DFU groups. For the DMC group, we used the first date of VA healthcare utilization in 2003 with a diagnosis of diabetes (250.xx) as the study entry date. The time to event was measured from the study entry date to the date of death or to September 30, 2007. Cox proportional hazards models were used to test whether there were significant differences in mortality risk in the three groups after controlling for co-existing conditions. We tested proportional hazards assumption using analysis of scaled Schoenfeld residuals (17) and goodness-of-fit using Cox-Snell residuals (18). Baseline diabetes control caused the models violate the proportional hazards assumption and was not used in any Cox regression models. The full model reported in this study satisfies the assumption and shows good fit with the data.

To test whether foot ulcers experienced by CA patients can explain part of the mortality risk associated with CA, we estimated two additional models. We stratified the CA group by the presence of
foot ulcer and compared the mortality risks among three groups for two strata separately. We first included patients without foot ulcer in the CA group and their matched controls from the other two groups to construct a restricted sample (1,950 patients). Second, we included patients with foot ulcer in the CA group and their matched controls from the other two groups to construct the second restricted sample (3,330 patients). These two restricted samples were analyzed with Cox proportional hazard models and their results compared with those from the full sample.

The role of peripheral neuropathy in explaining mortality risks of CA and DFU patients has been previously noted (6). Because all CA patients have neuropathy, we could not use it as a covariate in any model we estimated. To check whether neuropathy could have confounded our results, we conducted a sensitivity analysis based on a subsample that included neuropathic DFU patients and their matches in the other two groups.

**RESULTS**

Among the overall diabetic population in 2003, there were 1,050 patients who were newly diagnosed with CA, 16,260 who were newly diagnosed with DFU and have never experienced CA in 2002–2007, and 868,844 patients who neither had CA nor DFU during the same period. After 1-to-2 matching, there were 1,050 patients in the CA group and 2,100 patients in each of the other two groups for a total of 5,250 patients in the study sample. The baseline characteristics of the sample are shown in Table 1. Three-group comparison of factors used in matching suggests that matching was good.

Patient age at the time of study entry was 63 years with a standard deviation of 9.7 years. Overall, 40% had diabetes for 6 years or longer and 31% had an average A1c < 7% in the baseline year.

Patients with a DFU tended to have co-existing conditions more frequently than those in the other two groups, including peripheral vascular disease (PVD), congestive heart failure, ischemic heart disease, stroke, and chronic pulmonary disease.

Of 5,250 patients in the sample, 1,468 (28.0%) died during follow-up with 28.3%, 37.0%, and 18.8% mortality rates in the CA, DFU, and DMC groups, respectively. Table 2 shows unadjusted and adjusted hazard ratios obtained from two Cox regression models estimated from the full sample.

Compared to CA, unadjusted mortality risk was higher for DFU (HR = 1.41; 95% CI, 1.23 – 1.61) but lower for DMC (HR = 0.61; 95% CI, 0.53 – 0.72). Hazard ratios adjusted for co-morbidities show that the difference in mortality risks between the CA and the other two groups were generally smaller than the unadjusted comparisons suggest. Compared with CA patients, those with a DFU had a 35% higher mortality risk (HR = 1.35; 95% CI, 1.18 – 1.54) and those with diabetes alone had a 23% lower mortality risk (HR = 0.77; 95% CI, 0.66 – 0.90).

Among CA patients, 660 (63%) experienced a foot ulcer sometime between 2002 and 2007. Of these, 431 (65.3%) had ulceration concurrently with or before, and 229 (34.7%) after, the Charcot onset. Their unadjusted mortality rates were higher if they had a foot ulcer (30.2%) than if they did not (26.9%). To estimate the contribution to mortality risk of foot ulcer among CA patients, we estimated additional Cox regression models using the two restricted samples (Table 2).

Comparison of unadjusted hazard ratios across three samples shows that the difference in mortality risks between CA and DFU groups is largest in the Restricted Sample 1 (CA without ulcer; HR = 1.63; 95% CI, 1.30 – 2.04) and smallest in the Restricted Sample 2 (CA with ulcer; HR = 1.30; 95% CI, 1.10 – 1.53). On the other hand, the
difference between Charcot arthropathy and diabetes only was larger in unadjusted rates in the Restricted Sample 2 (HR = 0.56; 95% CI, 0.46 – 0.67) and smaller in the Restricted Sample 1 (HR = 0.73; 95% CI, 0.57 – 0.93). When co-morbidities were controlled in the adjusted models, hazard ratios in the three samples became considerably less variable than those from unadjusted comparisons. The adjusted hazard ratios indicate 32% – 41% higher mortality risk for DFU than for CA in the three samples. The adjusted comparisons between CA and DMC groups show 21% - 24% lower mortality risk for the latter.

Table 3 shows the model estimated from the full sample. Mortality risks were significantly increased with older age, male sex, and unmarried status. Among co-morbidities, liver disease, renal failure, and congestive heart failure contributed the most to the mortality risk.

We conducted sensitivity analyses. First, we examined whether the observed results might be different for the non-elderly patients with a 1:4 matched sample for those with ages < 65 and the results are shown in Table A2 in the Online Appendix. Even though none of the hazard ratios indicated statistically significant differences in mortality risk between CA and DFU groups, the overall findings are consistent with the models estimated from the full sample.

Secondly, we selected only patients with peripheral neuropathy in the Charcot and DFU groups and compared their mortality risks. For this comparison, we started with the foot ulcer patients who had ever been diagnosed with neuropathy in 2002 – 2007 (70%) and found their matched pairs in the CA and DMC groups. The results from a Cox regression model (Table A3) suggest that DFU was associated with a significantly higher mortality risk than CA among neuropathic patients (HR = 1.23; 95% CI, 1.06 – 1.43).

**DISCUSSION**

This study shows that patients with Charcot arthropathy or diabetic foot ulcer have significantly increased mortality risk than otherwise comparable patients with diabetes alone. The mortality risk associated with CA was confounded by the presence of foot ulcer; however, CA has significantly increased mortality risk independent of foot ulcer and other diabetic complications. When CA patients without foot ulceration were compared with their matched controls (Restricted Sample 1), the mortality risk was 63% higher in unadjusted rates for foot ulcer patients. This difference was significantly larger than that (30%) from the comparison between CA patients with foot ulceration and DFU patients (Restricted Sample 2). This suggests that the mortality risk in the overall CA group may be in large part attributable to foot ulceration. Moreover, when the hazard ratios were adjusted for co-morbidities, they became similar for both sets of comparisons in all three models, indicating that variations in hazard ratios across three samples were due in part also to differences in the presence of co-morbidities in the three groups. However, there was still significantly increased mortality risk associated with Charcot arthropathy, after controlling for foot ulcer or other diabetic complications such as PVD, congestive heart failure, ischemic heart disease, and renal failure.

Gazis et al. (6) reported a mortality rate of 44.7% for CA patients after a mean follow-up of 3.7 years that is considerably higher than the 5-year mortality rate of 28.3% among our CA patients. It further reported that CA is not statistically different in mortality risk from neuropathic DFU, while our study shows a significant difference between the two groups (Table A3).

Part of these differences can be explained by the high percentage of patients with type I diabetes in the Gazis sample (18%) and partly by the fact that it consisted
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of patients from a large specialty foot clinic who, due to selection by referral (4), were likely to be sicker than patients in the population-based sample used in this study. They experienced Charcot onset 4 years earlier than patients in our sample (59 vs. 63 years), an indication that they had more severe diabetes than patients in our sample. Despite these differences, both studies show greatly increased mortality risks for patients with either CA or DFU compared with those with diabetes alone.

These findings suggest that Charcot arthropathy and foot ulceration are markers of significant systemic pathology in diabetic patients that increases the mortality risk. The pathophysiology of higher mortality risks associated with these two conditions is still largely unknown. One explanation for foot ulcer having the highest mortality risk among the three comparison groups may be that the presence of ulceration increases the risk of infection which in turn increases potential for adverse systemic effects, multi-organ failure, and death. However, CA patients with foot ulceration did not have as high a mortality risk as those with foot ulcer alone. We conjecture that ulceration secondary to CA (about 35% of all foot ulcers experienced by CA patients) may not have as high mortality risk as a DFU does in the absence of CA. These are mostly complications arising from the mismatch between protective footwear and developing foot deformity such as protruding bones (5). The resulting secondary ulceration may be more local than systemic in etiology and hence have lower mortality risk than a typical DFU. Further, on-going Charcot treatment might have led to earlier diagnosis and active treatment of both concurrent and secondary foot ulcers.

Clinically, our findings suggest that early identification and vigilant care of Charcot arthropathy and foot ulcer are important not only for treating these conditions but also for reducing mortality risks associated with them. DFU is often difficult to diagnose early due to peripheral neuropathy and lack of local and systemic signs of infection (19), making quarterly foot screening and patient education for daily foot examinations and self-care imperative for these high-risk patients.

Given that DFU has greater mortality risk than some cancers such as prostate cancer, breast cancer, or Hodgkin’s disease (20), its mortality risk needs to be communicated to the patients as early as possible so that patients can assume more active role in medical management of DFU than they do now (21). Co-existing conditions such as cardiovascular and renal diseases need to be aggressively managed along with foot care.

This study has several limitations. The first is that it relied on inpatient and outpatient records collected for administrative purposes. Although administrative records were supplemented by extensive pharmacy data and laboratory test results, accuracy of these records needs to be considered when the study results are interpreted. A study of VA disease coding in the administrative databases reported that diseases were generally coded accurately but that there were also large variations in accuracy from disease to disease (22). Another study reported an extremely high accuracy of acute myocardial infarction at 96% sensitivity (23). Other conditions may not have been coded as accurately. PVD coding accuracy in the VA data is not well known but, given 60% sensitivity of PVD in the Medicare data (24) and many patients with undiagnosed and/or asymptomatic PVD, the findings about PVD should be interpreted with caution.

Second, co-morbidity measures were obtained from the baseline year and may not account for occurrences in the three groups after the baseline year. In a supplemental analysis, we assessed whether a patient in the sample had congestive heart failure in 2003 – 2007 and used it in a multivariable model
instead of the baseline measure. The results from this model were remarkably consistent with those from the baseline model. The reason may be that congestive heart failure is a chronic condition that persists through the patient’s life span. All other co-morbidities were also chronic in nature.

Third, we did not have access to data for Medicare utilization by elderly veterans. A supplemental analysis showed that, compared with the number of VA users with diabetes estimated from the 2003 Behavioral Risk Factor Surveillance System (BRFSS) national survey, almost 98% of all VA users with diabetes could be identified through VA inpatient and outpatient records alone. Nonetheless, there might have been some VA users who received diabetes care from Medicare providers where Charcot arthropathy, foot ulcer, other diabetic complications or co-morbidities were diagnosed. To the extent that these conditions were not also diagnosed by VA physicians, they might have affected our findings. However, the sensitivity analysis with patients < 65 years old (Table A2) suggests that the unobserved medical conditions listed in Medicare data did not systematically bias the results.

CONCLUSIONS

To the best of our knowledge, this is the first study to compare mortality risks between patients with Charcot arthropathy, foot ulceration, and diabetes without these complications. A previous study by Pinzur and Evans noted that CA was associated with poor quality of life, frequent disability, or premature retirement from the workforce (3). Our study further suggests that it is also associated with increased mortality risk. These findings accentuate the need for early detection of Charcot arthropathy to limit the disease progression and to reduce the risk of foot ulceration and death.

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Table 1: Baseline Characteristics of Patients in Three Comparison Groups (N = 5,250)

| Characteristic                          | Charcot Arthropathy (N = 1,050) | Foot Ulcer (N = 2,100) | Diabetes Only (N = 2,100) |
|-----------------------------------------|---------------------------------|------------------------|---------------------------|
| Age, y (±SD)                            | 63.0 (±9.6)                     | 62.8 (±9.8)            | 62.7 (±9.6)               |
| Race, %                                 |                                 |                        |                           |
| Non-Hispanic White                      | 72.8%                           | 73.8%                  | 72.7%                     |
| Non-Hispanic Black                      | 11.1%                           | 11.8%                  | 11.2%                     |
| Hispanic                                | 3.1%                            | 1.9%                   | 3.2%                      |
| Other or Unknown                        | 13.0%                           | 12.5%                  | 12.9%                     |
| Male, %                                 | 97.1%                           | 97.9%                  | 97.3%                     |
| Married, %                              | 58.0%                           | 58.6%                  | 58.1%                     |
| Diabetes Duration ≥6 years, %           | 40.9%                           | 39.8%                  | 40.9%                     |
| Diabetes Control, %                     |                                 |                        |                           |
| A1c < 7                                 | 31.3%                           | 31.5%                  | 31.4%                     |
| A1c, 7 - 9                              | 38.2%                           | 37.6%                  | 38.2%                     |
| A1c > 9                                 | 15.5%                           | 15.2%                  | 15.5%                     |
| A1c, unmeasured                         | 15.0%                           | 15.8%                  | 14.9%                     |
| Co-Morbidities, %                       |                                 |                        |                           |
| Ischemic Heart Disease*                 | 34.8%                           | 38.4%                  | 30.9%                     |
| Stroke*                                 | 7.8%                            | 14.4%                  | 6.7%                      |
| Peripheral Vascular Disease*           | 26.9%                           | 34.5%                  | 8.7%                      |
| Congestive Heart Failure*               | 12.6%                           | 17.8%                  | 6.8%                      |
| Chronic Pulmonary Disease*             | 9.8%                            | 14.6%                  | 11.1%                     |
| Renal Failure*                          | 15.1%                           | 11.4%                  | 5.2%                      |
| Cancer                                  | 4.0%                            | 4.5%                   | 5.6%                      |
| Deficiency Anemias*                     | 17.3%                           | 13.8%                  | 5.6%                      |
| Paralysis*                              | 1.0%                            | 4.0%                   | 1.2%                      |
| Other Neurological Disorders            | 3.4%                            | 3.9%                   | 2.6%                      |
| Liver Disease*                          | 2.5%                            | 3.8%                   | 1.9%                      |
| Coagulopathy*                           | 1.1%                            | 2.4%                   | 1.4%                      |

* P < 0.05 (two-tailed chi-square tests)
Table 2: Hazard Ratios of Mortality for Foot Ulcer and Diabetes Only Patients Compared to Charcot Arthropathy Patients

| Adjustment | Full Sample (N = 5,250) | Restricted Sample 1 (N = 1,950)‡ | Restricted Sample 2 (N = 3,300)§ |
|------------|-------------------------|---------------------------------|---------------------------------|
|            | Foot Ulcer | Diabetes Only | Foot Ulcer | Diabetes Only | Foot Ulcer | Diabetes Only |
| Unadjusted | 1.411 (1.234 – 1.613) | 0.614 (0.529 – 0.715) | 1.627 (1.300 – 2.036) | 0.726 (0.566 – 0.931) | 1.298 (1.098 – 1.534) | 0.557 (0.461 – 0.674) |
| Adjusted‡  | 1.348 (1.176 – 1.544) | 0.773 (0.661 – 0.903) | 1.409 (1.115 – 1.780) | 0.793 (0.616 – 1.019) | 1.319 (1.112 – 1.563) | 0.760 (0.622 – 0.928) |

‡ Adjusted for matched factors (age, sex, race, marital status, and diabetes duration) and co-morbidities (ischemic heart disease, stroke, peripheral vascular disease, congestive heart failure, chronic pulmonary disease, paralysis, other neurological disorders, liver disease, renal failure, cancer, deficiency anemias, and coagulopathy).

‡ Restricted sample 1 includes Charcot arthropathy patients without foot ulceration in 2002 – 2007 and their matched controls (N = 1,950).

§ Restricted sample 2 includes Charcot arthropathy patients with foot ulceration in 2002 – 2007 and their matched controls (N = 3,300).
Table 3: Adjusted Hazard Ratios (HR) from the Full Cox Proportional Hazards Regression Model (N = 5,250)

| Variables                             | HR     | 95% CI*   | P-Value |
|---------------------------------------|--------|-----------|---------|
| Comparison Group [Charcot arthropathy] |        |           |         |
| Foot Ulcer                           | 1.348  | (1.176 - 1.544) | < 0.001 |
| Diabetes Only                        | 0.773  | (0.661 - 0.903) | 0.001   |
| Age in years                         | 1.039  | (1.033 - 1.045) | < 0.001 |
| Race [Non-Hispanic White]            |        |           |         |
| Non-Hispanic Black                   | 0.978  | (0.828 - 1.155) | 0.793   |
| Hispanic                             | 0.921  | (0.631 - 1.343) | 0.668   |
| Other                                | 0.701  | (0.560 - 0.879) | 0.002   |
| Male [Female]                        | 1.562  | (1.022 - 2.388) | 0.039   |
| Married [Not married]                | 0.781  | (0.703 - 0.868) | < 0.001 |
| Diabetes ≥ 6 years                   | 1.074  | (0.966 - 1.193) | 0.187   |
| Ischemic Heart Disease               | 1.227  | (1.096 - 1.374) | < 0.001 |
| Stroke                               | 1.121  | (0.963 - 1.304) | 0.141   |
| Peripheral Vascular Disease          | 1.243  | (1.107 - 1.397) | < 0.001 |
| Congestive Heart Failure             | 1.953  | (1.709 - 2.232) | < 0.001 |
| Chronic Pulmonary Disease            | 1.268  | (1.105 - 1.453) | 0.001   |
| Renal Failure                        | 1.840  | (1.599 - 2.118) | < 0.001 |
| Cancer                               | 1.569  | (1.295 - 1.901) | < 0.001 |
| Other Neurological Disorders         | 1.592  | (1.264 - 2.006) | < 0.001 |
| Deficiency Anemias                   | 1.323  | (1.152 - 1.519) | < 0.001 |
| Paralysis                            | 1.474  | (1.106 - 1.965) | 0.008   |
| Liver Disease                        | 2.096  | (1.623 - 2.706) | < 0.001 |
| Coagulopathy                         | 1.519  | (1.148 - 2.010) | 0.003   |

* Confidence Interval
† Reference categories are in brackets.