Ankle-brachial index is associated with vascular calcification in pre-dialysis Chronic kidney disease patients

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Abstract

Background

Ankle brachial index (ABI) is a noninvasive measure of subclinical cardiovascular disease (CVD) and atherosclerosis of the lower extremities. Low and high levels of ABI are associated with cardiovascular mortality and vascular calcification in dialysis chronic kidney disease (CKD) patients. However, the association of the spectrum of vascular calcification with low and high ABI is not well studied in pre-dialysis CKD patients. The purpose of this study is to investigate the association of both low and high ABI with the risk of vascular calcification in CKD patients.

Methods

We recruited 243 patients with pre-dialysis CKD from the great New Orleans area between 2010 and 2012. Our study used a cross-sectional design with ABI and CAC measured at the same visit. Continuous ABI measurements were taken and further classified into four categories: \(<=0.9\) (low ABI), \(0.9-<1.0\) (borderline), \(1.0-<1.4\) (normal), \(>=1.4\) (high). Level of vascular calcification were considered as the outcome and calculated by agatston score. Three categories of CAC is defined as: CAC agaston score=0, 0-100, >100. Three cumulative logit models were applied to the data. The first is an unadjusted univariate model, the second adjusts for baseline demographics, and the third adjusts for baseline demographics and covariates that are associated with CAC. Logistic regression methods were used to calculate the odds ratio of having a higher CAC score for CKD patients.

Results
We found a significant association between ABI and vascular calcification. All three models returned consistently significant result (p=0.0005, 0.0005, 0.0037, respectively) for the association between ABI and CAC. In addition, low ABI (ABI≤0.9) is also associated with an increased risk of CAC and severe CAC (OR=6.183, 95%CI(1.085, 35.228)). High ABI (>1.4) is also associated with an increase in CAC and severe CAC (OR=5.064, 95%CI (1.696, 15.122)). Borderline ABI (0.9<ABI<1.0) is not associated with an increase in CAC or severe CAC (OR=2.704, 95% CI (0.702, 10.418).

Conclusion

Compared to normal ABI level, low and high ABIs are both significantly associated with an increased risk of coronary artery calcification and severe coronary artery calcification in CKD patients.

Introduction

Cardiovascular complications are the leading cause of death in patients with chronic kidney disease (CKD) [1-3]. It is therefore important to determine the risk of cardiovascular complications for better prognosis of CKD patients. The prevalence of Coronary artery calcification (CAC) is higher in patients with CKD compared to those without CKD. And the prognosis of CAC in patients with CKD is also worse in patients with CKD than non-CKD patients. [4-9] Moreover, since CAC independently predicts the risk of coronary heart disease and total cardiovascular disease better than traditional risk factors in the CKD population[10], there is an increasing demand for a simple measurement method for CAC. Ankle brachial index is a non-invasive measure of subclinical cardiovascular disease and atherosclerosis of the low extremities. Low level of ABI (ABI≤0.9) is associated with PAD in the leg[11]. PAD affects millions of people and marks an increased risk in cardiovascular diseases[12] and is associated with atherosclerosis [13]. In addition, ABI is by itself a predictor for cardiovascular diseases, impairments [14-15]. We hope to utilize ABI as a simple and
cost-effective measure to predict CAC in CKD patients. Previous studies have found that ABI is significantly and inversely associated with CAC in non-CKD patients as well as in dialysis CKD patients[16]. However the association of the spectrum of vascular calcification and ABI in pre-dialysis CKD patients has not been well studied. The purpose of our study is to define the association between ABI and CAC in pre-dialysis CKD patients.

Methods

Study population

Our study population consists of 243 patients with CKD recruited from the great New Orleans area between 2010 and 2012. All eligible patients with CKD were recruited from nephrology and internal medicine clinics. CKD was defined as estimated glomerular filtration rate (eGFR) <60ml/min/1.73m² or presence of albuminuria (≥30mg/24-hours). Patients were excluded if they are unwilling to give informed consent, had a history of chronic dialysis, kidney transplants, immunotherapy in the past six months, chemotherapy within the past two years, and current clinical trial participation that may have an impact on CKD.

Baseline measurements

Informed consent was obtained from all participants prior to their enrollment in the study. Covariates collected in this study include baseline demographics (age, gender, and race), lifestyle risk factors (cigarette smoking, alcohol drinking, and physical activity), self-reported medical history (cardiovascular diseases, hypertension, diabetes, hyperlipidemia, and aspirin use). Hypertension, diabetes, and hyperlipidemia disease status were defined by asking the patients whether they are taking any medications for corresponding diseases. Three blood pressures were measured using a mercury sphygmomanometer following a standard protocol recommended by American Heart association [17]. Mean arterial pressure is calculated by the equation $MAP = SBP + 2(DBP)/3$. 
Body height (in meters) and weight (in kilograms) were measured by trained staff, and body mass index is calculated by dividing height by weight squared \((BMI = \frac{weight}{height^2})\).

An overnight fasting blood sample was collected to measure LDL-cholesterol level, mean arterial pressure (MAP), glucose level, eGFR, and urine albumin/creatinine ratio. eGFR was estimated using the CKD-EPI equation \((GFR = 141 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018(if \ female) \times 1.159(if \ black),\) where \(\kappa\) is 0.7 for females and 0.9 for males; \(\alpha\) is -0.329 for females and -0.411 for males. A 24-hour collection of urine sample was used to measure albumin and creatinine concentration. Urinary concentration of albumin and creatinine were measured by a DCA 2000 Analyzer (Bayer AG, Leverkusen, Germany). And the urine albumin/creatinine ratio is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams.

Ankle-brachial index

Ankle and brachial blood pressures were measured by trained staff using a sphygmomanometer and a doppler ultrasound blood flow detector. The same protocol were followed by all staff members. ABI is calculated by diving the arterial systolic pressure measured at the ankle by the systolic blood pressure measured in the brachial artery[18]. A left ABI and a right ABI were calculated for each patient. ABI is defined as the higher ABI measurement between left and right ABI. Subjects with ABI<0.9 is categorized as having low ABI; subjects with 0.9≤ABI<1.0 is categorized as having borderline ABI; Subjects with 1.0≤ABI≤1.4 is categorized as normal, whereas subjects with ABI>1.4 is categorized as having high ABI.

Coronary artery calcification

Vascular calcification was assessed using electron-beam tomogram test (EBT). Coronary artery calcification (CAC) agatston score was calculated. A CAC score of 0 indicates no evidence for vascular calcification, a CAC score larger than 0 and less than or equal to 100 indicates risk of mild
vascular calcification, and a CAC score of larger than 100 indicates risk of significant vascular calcification.

Statistical analysis

Statistical analysis were carried out using SAS version 9.4. Descriptive statistics were summarized to understand the distribution of the covariates relating to CAC. For each continuous variable, mean and standard deviation were recorded. For each categorical variable, number and percentages were recorded. T-test/Wilcoxon rank test for continuous covariates or Chi-square test for categorical covariates were applied to compare if there are significant difference among the three CAC groups. We considered a p-value of less than 0.05 to be significant, and otherwise considered it as insignificant.

Crude odds ratio of the association between ABI and CAC were calculated using univariate cumulative logit regression. Reference groups are defined as: 1.0≤ABI≤1.4 (normal ABI) for ABI and CAC=0 (no evidence of coronary artery calcification) for CAC. In addition to the univariate model, two multivariable logistic regression models were used to explore the association between CAC and ABI. The first model adjusts for age, gender, and race. The second model adjusts for all the factors in model 1 and known risk factors for vascular calcification in CKD patients (diabetes, history of CVD, hypertension, hyperlipidemia, and eGFR) [19] as well as factors that we found to be associated with CAC (smoking status). Since we collected a lot of parameters, we assume that missing is at random. Multiple imputation for missing values are performed for the missing values in a sensitivity analysis, and no differences were observed.

Results

Among the 243 subjects that are recruited, only 233 subjects who had results of both ABI and CAC recorded were included in the regression analysis. Among those 233 subjects, the majority (79.0%) of them had normal ABI (1≤ABI≤1.4). While 14 of the 233 subjects had low ABI (ABI<0.9), 13
subjects had borderline ABI (0.9<ABI<1.0), and 22 subjects had high ABI (ABI>1.4). 83 of the 233 subjects had no evidence of vascular calcification (CAC agatston score=0), 54 of the 233 subjects had mild vascular calcification (0<CAC agatston score≤100), and 96 had significant vascular calcification.

Table 1 shows the baseline characteristics of the 233 subjects. Compared to those without CAC, those with CAC is more likely to be older (p<0.0001), to have a lower glomerular filtration rate (p=0.0155). In addition, 57.29% of the subjects that have severe CAC are male, 51.85% of the subjects who have moderate CAC are male, while only 37.35% of the subjects who does not have CAC are male. Those with CAC is more likely to be male (p=0.0087). Among those who show significant evidence of vascular calcification, 57.89% are current smokers. 59.26% of the subjects who have moderate CAC are current smokers, whereas only 32.93% of the subjects who does not have CAC are current smokers. Those with CAC are more likely to be current smokers (p=0.0014). 50.54% of the subjects that have severe CAC had a history of CVD, 37.74% of the subjects who have moderate CAC had a history of CVD, while only 27.16% of the subjects who does not have CAC had a history of CVD. Those with CAC is more likely to have a history of CVD (p=0.0017). 46.88% of the subjects that have severe CAC have diabetes, 22.22% of the subjects who have moderate CAC have diabetes, while 28.92% of the subjects who does not have CAC have diabetes. Those with CAC is more likely to have diabetes (p=0.0068). Moreover, subjects with moderate CAC have the highest level of LDL-cholesterol, while subjects with severe CAC have the lowest level of LDL-cholesterol. Overall, age, gender, smoking status, level of mean LDL-cholesterol, history of cardiovascular disease, mean glomerular filtration rate, and diabetes are significantly associated with coronary artery calcification.

The results of 3 cumulative logit models are presented in Table 2. For the first model, the proportional odds assumption is satisfied (p=0.2029). There exists a significant association between ABI and CAC (p=0.0005). The relative odds of having severe or mild level of CAC vs no sign of
coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 12.388 for low ABI (ABI≤0.9) vs normal ABI (1.0≤ABI<1.4). And the association is significant (95%CI (2.614, 58.703). The relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 2.516 for borderline ABI (0.9<ABI<1.0) vs normal ABI (1.0≤ABI<1.4), however it is not significant (95%CI (0.847, 7.473). And the relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 3.334 for high ABI (ABI≥1.4) vs normal ABI (1.0≤ABI<1.4), it is significant (95%CI (1.369, 8.115). Both low and high ABI are associated with having significant CAC and having severe CAC.

After adjustment for demographic factors age, gender, and race, the proportional odds assumption is satisfied (p=0.1526). There exists a significant association between ABI and CAC (p=0.0005). The relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 14.265 for low ABI (ABI≤0.9) vs normal ABI (1.0≤ABI<1.4). And it is significant (95%CI (2.700, 75.356). The relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 2.132 for borderline ABI (0.9<ABI<1.0) vs normal ABI (1.0≤ABI<1.4), however it is not significant (95%CI (0.661, 6.885). And the relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 4.469 for high ABI (ABI≥1.4) vs normal ABI (1.0≤ABI<1.4), it is significant (95%CI (1.624, 12.302). After adjusting for baseline demographics, both low and high ABI are still associated with having significant CAC and severe CAC.

After further adjustment for important risk factors of coronary artery calcification, the proportional odds assumption is satisfied (p=0.0939). There exists a significant association between
ABI and CAC (p=0.0036). The relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 6.183 for low ABI (ABI≤0.9) vs normal ABI (1.0≤ABI<1.4). And it is significant (95%CI (1.085, 35.228). The relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 2.704 for borderline ABI (0.9<ABI<1.0) vs normal ABI (1.0≤ABI<1.4), however it is not significant (95%CI (0.702, 10.418). And the relative odds of having severe or mild level of coronary artery calcification vs no sign of coronary artery calcification and the relative odds of having severe CAC vs mild or no sign of CAC is 5.064 for high ABI (ABI≥1.4) vs normal ABI (1.0≤ABI<1.4), it is significant (95%CI (1.696, 15.122). After adjusting for all the potential confounders, both low and high ABI are still associated with having significant CAC and severe CAC.

Discussion

In this study of 233 subjects with CKD, we used a cross-sectional design to analyze the relationship between ABI and CAC. Three models were fitted to the data and the cumulative logit regression results showed that overall ABI is strongly and significantly associated with increased risk of CAC. All three models had consistent findings: Both low and high level of ABI can lead to an increased risk in significant CAC and an increased risk in severe CAC. And none of the models found any significant association between borderlineABI and CAC.

Even though we found a significant relationship between mean LDL-cholesterol level and CAC, mean LDL-cholesterol level is excluded from the third model because the relationship is likely biased. Subjects who have severe coronary artery calcification are more likely to take medications to reduce blood LDL level. We thus expect subjects who have severe CAC to have a lower mean LDL-cholesterol level than subjects who have no sign of CAC or subjects who have moderate CAC. This is consistent with our findings. Without taking these medications, subjects who have severe
CAC will likely have highest level of mean LDL-cholesterol among the three groups. Other than mean LDL-cholesterol, factors that we adjusted for are all based on literature [19] or found to be significantly associated with CAC in our study. We did not adjust for factors unrelated to CAC for the purpose of avoiding potential overfitting bias.

The result of our study has important clinical implications. Cardiovascular disease is the major cause of premature deaths in patients with CKD [20-23]. Coronary artery disease is significantly associated with cardiovascular disease in patients with CKD[10]. In our study we found that there is a significant association between ABI and CAC agatston score measurements. Our findings indicate that by measuring a subject’s ABI, doctors can predict the risk of CAC for that individual. Furthermore, there are different stages of prognosis of CKD for pre-dialysis CKD patients. These stages were categorized based on eGFR[24]. eGFR of the subjects that we recruited for our study range from as high as 129.74 to as low as 6.01. Our subject base includes subjects of different stages of pre-dialysis CKD.

Most studies analyzing the association between ABI and coronary artery calcification target the dialysis population[25-26], or the general population[16]. However, the burden of CAC in pre-dialysis CKD patients is also significant, although generally less advanced compared to dialysis patients [27]. Few studies have studied the association in pre-dialysis patients. Yoshitomi et al. reported that in Japanese pre-dialysis patients, low ABI is associated with poor survival and increased cardiovascular events. While we found that low ABI is associated with a vascular calcification in pre-dialysis CKD patients. The outcome of interest for our study is different from theirs: We used CAC agatston score as the result such that we can directly measure the relationship between ABI and CAC, while their study used mortality and treatment endpoint as the outcome of interest. However, both studies indicate that ABI measurements have predictive effect on CAC and CV events. Nevertheless, we argue that ABI is not directly related to cardiovascular events. CAC could act as an intermediate step in the association. The association between ABI and cardiovascular
disease should be analyzed in a two-step manner: the association between ABI and CAC, and the association between CAC and cardiovascular disease should be analyzed separately. Similar to our study, Tullos et al [16] analyzed the direct association between ABI and CAC. However, they found that ABI>1.4 is not associated with CAC in a sample of Jackson Heart study. Their study design is different from ours in (1) Their study used sample from a general population (Jackson Heart Study) while ours focused on CKD patients only. The average ABI and CAC levels are significantly different between general population and pre-dialysis CKD patients, the association between them could be different as well. And (2) Their study design used a model that adjusted for all covariates. However it is worth noting that some of the covariates that they adjusted for could be on the causal pathway from ABI to CAC. Adding those covariates to the model could potentially lead to over adjustment bias. The association would be biased towards the null.

There are several limitations to our study. The major limitation of our study is that the sample size too small. Our study recruited only pre-dialysis CKD patients. There are only 14 patients (6%) that have low ABI(ABI<0.9). The low number of subjects could reduce the statistical power of our study. In addition, our study used a cross-sectional design. Although we found a strong association between ABI and CAC, the direction of the causal relationship cannot be determined from our study.

ABI is an non-invasive, easy to perform technique that is useful for early detection of vascular calcification. The association between CAC and cardiovascular event and mortality is well documented [28-33]. It is therefore important to study the association between ABI and CAC for a better understanding of the causal relationship between ABI and CVD related events and mortality in pre-dialysis CKD patients. High CAC level has important clinical implications. Low or high level of ABI can be used not only as a diagnostic tool for peripheral arterial disease but also as a predictive method in pre-dialysis CKD patients. We can predict an increased CAC score and consequently an increased risk of CVD events and mortality early with regular ABI measurements. Our findings are essential for better prognosis of pre-dialysis CKD patients. Future studies could use a longitudinal
design, and recruit a larger sample for ample power. A subgroup analysis of the association for patients with different stages of pre-dialysis CKD marked by rate of eGFR is also needed.

Conclusion

Ankle-brachial index is significantly associated with coronary artery calcification in pre-dialysis chronic kidney disease patients. Both low and high ABI are associated with increased risk of having CAC and the risk of having severe CAC in pre-dialysis CKD patients. ABI as an non-invasive, low cost early predictive tool or as an alternative to assessing vascular calcification using electron beam computed tomography can reduce the harm of radiation for vulnerable pre-dialysis CKD patients. The potential of ABI as a new assessment method requires further longitudinal studies involving a larger population of pre-dialysis CKD patients.

References:


Table 1 – Baseline characteristics of 233 patients by CAC categories

<table>
<thead>
<tr>
<th>Variables</th>
<th>CAC agatston score=0</th>
<th>0&lt;CAC agatston score≤100</th>
<th>CAC agatston score&gt;100</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, yrs</td>
<td>53.85±10.18</td>
<td>61.57±7.71</td>
<td>64.86±7.87</td>
<td>&lt;0.0001</td>
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<tr>
<td>Male, %</td>
<td>37.35</td>
<td>51.85</td>
<td>57.29</td>
<td>0.0087</td>
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<td>Black, %</td>
<td>69.88</td>
<td>74.07</td>
<td>57.29</td>
<td>0.0593</td>
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<td>High school, %</td>
<td>56.10</td>
<td>44.44</td>
<td>51.04</td>
<td>0.5487</td>
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<tr>
<td>Current smoker, %</td>
<td>32.93</td>
<td>59.26</td>
<td>57.89</td>
<td>0.0014</td>
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<td></td>
<td>Weekly drinking, %</td>
<td>alcohol</td>
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<tr>
<td>Mean BMI, kg/m²</td>
<td>32.91±7.43</td>
<td>30.80±6.02</td>
<td>32.04±6.82</td>
<td>0.4306</td>
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<tr>
<td>Mean LDL-cholesterol, mg/dL</td>
<td>105.52±52.87</td>
<td>112.19±36.86</td>
<td>92.47±33.94</td>
<td>0.0351</td>
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<tr>
<td>Physical activities, %</td>
<td>49.38</td>
<td>44.44</td>
<td>55.32</td>
<td>0.3997</td>
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<td>Mean arterial pressure, mmHg</td>
<td>94.33±13.21</td>
<td>94.72±16.64</td>
<td>92.11±13.84</td>
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<td>Glucose</td>
<td>114.27±46.17</td>
<td>111.67±34.85</td>
<td>128.58±67.55</td>
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<td>History of CVD</td>
<td>27.16</td>
<td>37.74</td>
<td>50.54</td>
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<td>Mean glomerular filtration rate, ml/min/1.73m²</td>
<td>50.51±24.26</td>
<td>49.50±23.00</td>
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<td>Urine</td>
<td>133.20±268.51</td>
<td>222.44±484.17</td>
<td>238.36±415.80</td>
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<td>albumin/creatinine ratio, ug/g</td>
<td>69 (83.13)</td>
<td>46 (85.19)</td>
<td>87 (90.62)</td>
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<td>Treatment for hypertension, %</td>
<td>24 (28.92)</td>
<td>12 (22.22)</td>
<td>45 (46.88)</td>
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<td>Diabetes, %</td>
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<td>15 (27.78)</td>
<td>37 (38.54)</td>
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<td>Hyperlipidemia, %</td>
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<td>18 (33.33)</td>
<td>41 (42.71)</td>
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<td></td>
<td>ABI</td>
<td>OR (95% CI)</td>
<td>p</td>
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<td><strong>Univariate model</strong></td>
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<td>12.388 (2.614, 58.703)</td>
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<td>2.515 (0.847, 7.473)</td>
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<td>1.0-1.4 (normal)</td>
<td>1.00 (ref)</td>
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<td>&gt;1.4 (high)</td>
<td>3.334 (1.369, 8.115)</td>
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<td><strong>Multivariate model 1</strong></td>
<td>≤0.9 (low)</td>
<td>14.265 (2.700, 75.356)</td>
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<tr>
<td></td>
<td>&gt;0.9-&lt;1.0 (borderline)</td>
<td>2.132 (0.661, 6.885)</td>
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<td>1.0-1.4 (normal)</td>
<td>1.000 (ref)</td>
<td>0.0005</td>
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<td>&gt;1.4 (high)</td>
<td>4.469 (1.624, 12.302)</td>
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<td><strong>Multivariate model 2</strong></td>
<td>≤0.9 (low)</td>
<td>6.183 (1.085, 35.228)</td>
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<td>&gt;0.9-&lt;1.0 (borderline)</td>
<td>2.704 (0.702, 10.418)</td>
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