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Timed up and go and bone density tests for fracture prediction

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\textbf{Running title: TUG, BMD and fracture risk}

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\textbf{Conflict of interest}

All authors have no conflicts of interest
Abstract

Background: The two major factors associated skeletal fracture in older people are intrinsic bone strength and the risk of falling. This study aimed to examine Timed Up and Go (TUG) test performance, a validated predictor of falling and hip areal bone density (aBMD), a validated predictor of bone strength at fracture prediction in a 10-year longitudinal study.

Methods: The study subjects were 1,126 women aged 75.0±2.6 years at baseline living in Perth, Australia. Measurements performed include TUG test at baseline and total hip DXA aBMD at year one. Incident clinical osteoporotic fractures over 10 years were confirmed from radiographic report. Complete incident hip fracture data were obtained from a Hospital Morbidity Database.

Results: One-third of subjects had low performance in the TUG test (>10.2 seconds) and 55% subjects had low hip BMD (T-score<-1). Compared to those with normal TUG and BMD, risks for non-vertebral and hip fracture were significantly higher in subjects who had low TUG but normal BMD (HR: non-vertebral 1.84; hip 2.51) or both low TUG and low BMD (HR: non-vertebral 2.48; hip 4.68). For non-vertebral and hip fracture, the population attributable risk of low TUG but normal BMD was 19.3% and 32.3%, of low BMD but normal TUG was 31.3% and 50.3%, and of the combination of the two was 23.6% and 55.9%, respectively.

Conclusions: TUG test is an independent risk factor for incident non-vertebral fracture and a feasible, inexpensive test of physical performance for screening patients with increased risk of fracture in clinical practice.
Introduction

Fracture presents a major public health problem, and is a leading cause of morbidity, mortality and hospitalization in the elderly. Since the development of Dual Energy X-ray Absorptiometry (DXA) measurement of areal Bone Mineral Density (aBMD) in the 1980’s, great progress has been made in our understanding of the important role of bone structure in resistance to fracture. However, less attention has been paid to the role of risk factors of falling which in addition to bone mass are important determinants of the occurrence of most appendicular skeletal fractures.

The Timed Up and Go (TUG) test in which the subjects are timed whilst rising from a chair, walking 3 meters, turning to sit on the chair, is a commonly used method of assessing functional mobility in older adults in geriatrics clinics for assessing physical performance. In community-dwelling older adults aged above 65 years, TUG test has been shown to be a sensitive and specific measure for identifying older people who are prone to fall. A meta-analysis which summarized the findings of 21 studies had reported the reference TUG value for people aged 70-79 years as 9.2 (95% CI 8.2-10.2) seconds and suggested that patients with test results above the upper limit of the reference confidence interval could be regarded as having performance worse than the average. To our knowledge, the association of low performance in the Timed and Up and Go test and incident fracture risk in older women has not been evaluated.

We hypothesis that low performance in the TUG test is a predictor of fracture in older women independent of BMD and other risk factors. The aim of this study was to examine the effects of low performance in the TUG test in relation to BMD in fracture prediction in a longitudinal study of 1,126 women aged 75.0 ± 2.6 years.
Subjects and methods

Subjects

This paper reports data on 1,126 older postmenopausal Caucasian women who had a baseline Timed Up and Go test and one year hip bone mineral density (BMD) data from a cohort of 1,500 women aged 70-85 years when recruited in 1998 from the population. This cohort first finished a five-year randomised controlled trial of calcium supplementation (Calcium Intake Fracture Outcomes Study, CAIFOS), and then were recruited into a five year epidemiology study, the CARE study. The CAIFOS subjects were recruited from the population using the Australian electoral roll, which has contact details of over 98% of subjects of this age, by means of a letter inviting participation in the study. The CAIFOS inclusion and exclusion criteria were: aged over 70 years old, likely to survive a five-year study, and not receiving bone active agent. There were no other specific exclusions so that the results could be generalised to the whole ambulant population. During the calcium intervention phase, subjects were randomised to calcium 1.2 g or placebo for 5 years. Figure 1 shows the study timeline and details of recruitment, retention and loss to follow-up. Informed consent was obtained from each subject and the study was approved by the Human Research Ethics Committee of the University of Western Australia.

Bone measurements

Due to the restricted availability of human resources, total hip aBMD of subjects were measured by Dual Energy X-ray Absorptiometry (DXA) using the same Hologic Acclaim 4500A fan beam densitometer (Hologic Corp, Waltham, MA, USA) at year one. The CV at the total hip was 1.2% in our laboratory. The total hip BMD T-score was determined using the American third National Health and Nutrition Examination Survey (NHANES III) reference database. WHO defined low bone density as BMD T-score between -1 to -2.5 and
osteoporosis as T-score -2.5 or below\textsuperscript{7}. Therefore, we categorised subjects with hip BMD T-score below -1 as having low bone density.

Timed Up and Go Test

The Timed Up and Go test in which the patient is timed while rising from a chair, walking 3 meters, turning, returning to sit on the chair was performed at baseline\textsuperscript{1}. Subjects were allowed to practise once then timed. The inter-observer CV error was 7% in our laboratory as assessed on a random sample of 20 subjects.

Fracture ascertainment

Prevalent fractures were determined at baseline by obtaining a fracture history from each subject that included age at the time of fracture, the site, and how the fracture was sustained. A prevalent fracture was included if the fracture occurred after the age of 50 years; occurred with minimal trauma as defined by falling from a height of one metre or less; and not of the face, skull, fingers, or toes. Incident atraumatic clinical fractures and atraumatic symptomatic vertebral fractures were recoded in an adverse events diary which was collected every 4 months during the first 5 years and 6 months during the second 5 years. The diagnosis of clinical vertebral and non-vertebral fractures was confirmed by reference to radiographic records. In addition, incident hip fracture data were retrieved from the Western Australia Hospital Morbidity Data System (HMDS) for each of the study participants from 1998 when they entered the study until 10 years after their baseline visit. As the HMDS captures coded diagnosis data pertaining to all public and private inpatient contacts in Western Australia\textsuperscript{8}, it allows complete ascertainment of verified hip fracture independently of patient report with the associated problems such as loss to follow-up. As BMD measurement was performed at year one, fractures from year one to ten were regarded as incident fracture in the data analysis, whereas fractures during the first year were treated as prevalent fracture.

Other assessments
Height and weight were measured with the subjects in light clothing and without shoes at baseline. Body mass index (BMI) was calculated as weight (kg)/height (m)². Nutrient intakes were determined from a self-administered semi-quantitative food frequency questionnaire⁹, ¹⁰. Physical activity level was assessed by a questionnaire¹¹, ¹², and activity levels were calculated in kcal/day using a validated method utilizing body weight, questions on the number of hours and type of physical activity and energy costs of such activities¹³, ¹⁴.

**Data analysis**

Descriptive statistics are reported as mean ± SD for all variables unless otherwise stated. The effects of baseline TUG and one year hip BMD on incident fractures were examined using logistic regression and Cox proportional hazards regression adjusting for baseline age, prevalent fracture, calcium treatment, current smoking, rheumatoid arthritis and alcohol use. Other potential covariates considered in the analyses include baseline body weight, height, calcium intake and physical activity. The proportional hazards assumption was tested for each covariate and no violations were detected. Nine-year fracture risk was calculated using odds ratio obtained from logistic regression models ¹⁵. Population attributable risk and associated 95% confidence intervals are calculated for both TUG and BMD. The predicted fracture probabilities from logistic regression were grouped into 9-year risk of ≤10%, 10%-15% and ≥15% on models with hip BMD T-score and both hip BMD T-score and TUG test performance and the net reclassification improvement (NRI) was calculated. A P value of less than 0.05 in two tailed testing was considered significant. The statistical analyses were performed using PASW software (version 18, SPSS Inc., Chicago, IL) and STATA (version 11, StataCorp LP, College Station, TX).
Results

Characteristics of study participants (Table 1)

The mean age at baseline was 75.0 ± 2.6 years, 94% participants were aged between 70-79 years, and 30.3% had prevalent osteoporotic fracture at year one. The median baseline Timed Up and Go test was 9.2 secs, 368 (32.7%) subjects took more than 10.2 seconds to complete the test and thus were regarded as having low TUG test performance. At one year the mean total hip BMD T score was -1.1 ± 1.0 and 534 (47.4%) subjects had low bone density (T score -1 to -2.5) and 76 (6.7%) subjects had osteoporosis (T score < -2.5).

When subjects were grouped according to baseline TUG performance and hip BMD T score, as expected, there were significant differences in anthropometry, calcium intake and physical activity (Table 1). Body weight and BMI were higher in those with normal hip BMD and those with slower TUG times. Subjects with hip BMD T-score ≥ -1 and TUG ≤ 10.2 seconds had significantly higher calcium intake and physical activity level compared to those with BMD T-score ≤ -1 and TUG ≥ 10.2 seconds. There were no significant differences between the four groups in the percentage of subjects with prevalent osteoporotic fracture or rheumatoid arthritis, received calcium treatment during the intervention phase of the study, consuming three or more units of alcohol per day, currently smoking, or fell in the past three months (Table 1).

Fracture rates and population attributable risk

From year one to ten, the self reported incident fracture rate was 17.5% for non-vertebral fractures and 6.0% for clinical vertebral fractures with 1.6% subjects having at least one incident fracture of each type. With data obtained for the Hospital Morbidity Database, 74 (6.6%) subjects had incident hip fractures.

Individuals with a slow TUG test time had a significantly higher rate of incident non-vertebral fracture (21.2% vs 15.7%, P = 0.02) and hip fracture (9.2% vs 5.3%, P = 0.02) but not clinical
vertebral fracture (5.7% vs 6.1%, P = 0.89), compared with those who had normal TUG performance. Subjects with low bone density had a significantly higher incidence of non-vertebral (21.0% vs 13.4%), hip (8.9% vs 3.9%) and clinical vertebral (7.7% vs 3.9%) fractures compared to those with normal bone density (all P < 0.01). Low TUG performance increased the population attributable risk for non-vertebral (10.3%) and hip fracture (19.7%) but not clinical spine fracture. Low hip BMD substantially increased the risk of all fracture types (23.6 - 41.0%). The effect of baseline TUG performance dichotomised into normal (< 10.2 seconds) and slow (≥ 10.2 seconds) on the relationship between the 9-year non-vertebral risk and hip BMD T score is illustrated in Figure 2. At all hip BMD T scores participants with a slow TUG test had higher fracture risk.

The combined effects of a slow TUG performance and a low hip BMD T-score on incidence of non-vertebral and hip fracture and population attributable risk are shown in Table 2. Subjects with normal TUG performance and bone density had a significantly lower rate of non-vertebral and hip fracture than any other category.

**Time to event analysis**

To validate the predictive ability of the TUG test in relation to hip BMD further, a time to event analysis with censoring for patient death or loss to follow up was undertaken using the Cox proportional hazard procedure. A slow baseline TUG test was associated with a 54% higher risk of 10-year incident non-vertebral fractures (Figure 3) compared to those with a normal TUG performance after adjustment for baseline age, prevalent fracture, calcium treatment, current smoking, rheumatoid arthritis and use alcohol and 1 year total hip BMD T score. Similar effects were observed for hip fracture (HR: 1.86, 95% CI 1.16-2.97) but not clinical vertebral fracture (HR: 0.92, 95% CI 0.54-1.56).

In a further time to event analysis, the magnitude of the combined effects of slow TUG test and low hip BMD on fracture rates adjusted for age, prevalent fracture, calcium treatment,
current smoking, rheumatoid arthritis and use alcohol were examined (Figure 4). Patients who had low TUG performance but normal BMD had a higher hazard ratio for non-vertebral fractures compared to patients with normal TUG performance and bone density. Although the hazard ratio was smaller than the hazard ratio for patients who had both low TUG performance and low BMD, it was similar to the hazard ratio for those with low hip BMD and normal TUG time (Figure 4).

Hip fracture were analysed using the same approach. The other three groups had significant higher risk (normal BMD low TUG, HR 2.48 95% CI 1.02-6.02; low BMD normal TUG, HR 2.91 95% CI 1.38 – 6.13; low BMD and low TUG, HR 4.68 95% CI 2.14 – 10.22) compared to those with normal BMD and TUG performance. For all the Cox regression models, further analysis by including baseline body weight, height, calcium intake and physical activity level as covariates had little influence on the results.

Sensitivity analysis

During the 10-year follow up, 195 subjects (32%) with low BMD and 50 (9.7%) with normal BMD began taking osteoporosis medication (P < 0.001). In the sensitivity analysis excluding these women, the association with non-vertebral fracture was weaker for hip BMD but not TUG test (normal BMD low TUG, HR 2.07 95% CI 1.20-3.57; low BMD normal TUG, HR 1.59 95% CI 0.97-2.60; low BMD and low TUG, HR 2.45 95% CI 1.40-4.28 compared to those with normal BMD and TUG performance). The HRs for hip fracture were similar to those obtained in the whole cohort (data not shown).

Net reclassification improvement

Table 3 shows the change in non-vertebral fracture risk category for models with hip BMD T-score and both hip BMD T-score and TUG test performance. The net reclassification improvement was 8.1% (P = 0.01).
Discussion

Low bone strength as detected by low DXA bone density is a well recognised predictor of fracture and as such it is the target for interventions to reduce osteoporotic fracture risk. Besides low bone mass, other clinical risk factors are related to fracture risk, including past falls. Previous shorter term studies using other physical performance tests have shown an association between physical performance and fracture risk in older people. This study demonstrates that low performance in the TUG test is also a predictor of incident non-vertebral and hip fracture risk in elderly women. The effect is independent of age, bone mineral density, prevalent osteoporotic fracture and lifestyle factors.

The TUG test is an effective method of assessing functional mobility in older adults and has high reliability. One important finding of the present study is that even in women with normal hip BMD (T-score > -1) low performance in TUG is associated with 84% higher risk for non-vertebral fracture and 148% higher risk of hip fracture after adjustment for other known risk factors. The significance of this is shown by the high attributable risk for non-vertebral (19.3%) and hip fracture (32.3%) for slow TUG performance in patients with normal BMD. This finding is consistent with the limited data from previous cross-sectional and shorter term studies on the association between physical performance and fracture in older people. In a cross-sectional study of 484 women aged average 55.1 years, it was found that in those subjects who were post-menopausal, low TUG performance was related to previous peripheral fractures. In a study of 3,851 men and women aged over 60 years it has been shown that quadriceps strength and postural sway were independent predictors of fractures over 3 years. Hand grip strength has also been shown to be one of the predictors of fracture in a 5-year follow-up study with a cohort of healthy postmenopausal women mean age 59.1 ± 9.8 years. The Study of Osteoporotic Fractures followed up 9,516 women 65 years or older for 4.1 years, and found that those who were unable to rise from a chair five
consecutive times had 70% higher risk for hip fracture after adjustment for calcaneal BMD and prevalent fracture\textsuperscript{21}. In the Osteoporotic Fractures in Men Study with 5,902 men aged 65 years and above, subjects with worst performance on at least three of five physical performance tests had 214% higher risk of incident hip fracture in the 5.3 years follow-up period compared with men with high performance on all exams\textsuperscript{22}.

Although some previous studies have proposed other cut-offs for poor performance on the TUG test\textsuperscript{2,25}, the cut-off (10.2 seconds) used in the present study was derived from a recent meta-analysis\textsuperscript{3} which summarized the findings of 21 studies including the studies of Bischoff et al. and Shumway-Cook et al.\textsuperscript{2,25}. Furthermore, in the present study, compared to the model with hip BMD T-score alone, the net reclassification improvement was 8.1% for the model with both hip BMD T-score and TUG test performance. Therefore, should the findings of the present study be replicated in other cohort studies of fracture, it could be concluded that fracture prediction should include assessment of both physical performance and skeletal structural risk as assessed by the Timed Up and Go test and DXA bone density.

The population based sample and prospective design is a strength of this study. All incident fractures during the study were confirmed by x-ray reports and complete ascertainment of verified hip fracture was obtained from the Western Australian Hospital Morbidity Data System. A limitation of the study is that the study subjects were community-dwelling older women and 94% of them were aged 70-79 years. Therefore the application of these finding are currently limited to this population. The predictive value of TUG in male and other age groups deserves further study. TUG test was only performed once after one practice in our study, thus making it more easily applicable in practice than performing the test three times.

In conclusion, this study shows that low performance in the Timed Up and Go test is an independent predictor of non-vertebral and hip fracture. Therefore, TUG test, as a feasible, inexpensive test of physical performance is a useful test in clinical practice for screening
patients with increased risk of fracture.
Acknowledgement

We thank all study participants for their cooperation and the Data Linkage Branch of Department of Health Western Australia for providing the Hospital Morbidity Data.

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Conflict of interest statement

We declare that we have no conflict of interest.
References


**Figure legends**

**Figure 1** Participants flow of the study

**Figure 2** The relationship between hip BMD T-score and 9-year non-vertebral fracture risk by baseline Timed Up and Go test performance (calculated using a previously described odds ratio logistic regression calculation with the addition of TUG test category as an independent category, see methods section for details).

**Figure 3** Effects of increased Timed Up and Go Test performance on risks of non-vertebral fractures. Timed Up and Go Test performance cut-off: 10.2 seconds. Percentage of subjects without non-vertebral fracture calculated from Cox proportional hazards analysis adjusted for age, hip BMD T-score, prevalent fracture, calcium treatment, current smoking, rheumatoid arthritis and alcohol use. HR: hazard ratio

**Figure 4** Effects of increased Timed Up and Go Test performance and low hip BMD T score on risks of non-vertebral fractures. Timed Up and Go Test performance cut-off: 10.2 seconds and 1 year total hip BMD T-score cut-off: -1. Percentage of subjects without non-vertebral fracture calculated from Cox proportional hazards analysis adjusted for age, prevalent fracture, calcium treatment, current smoking, rheumatoid arthritis and alcohol use. HR: hazard ratio compared to normal TUG performance and normal hip BMD.
<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of subjects (n = 1126)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total group</th>
<th>Hip BMD T-score ≥ -1</th>
<th>Hip BMD T-score &lt; -1</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>TUG ≤ 10.2 secs</td>
<td>TUG &gt; 10.2 secs</td>
</tr>
<tr>
<td>Age (year)</td>
<td>75.0 ± 2.6</td>
<td>74.5 ± 2.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75.2 ± 2.7&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.3 ± 11.9</td>
<td>72.4 ± 11.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75.7 ± 12.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.0 ± 5.8</td>
<td>159.9 ± 5.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>159.4 ± 6.1&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>27.0 ± 4.5</td>
<td>28.4 ± 4.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.7 ± 4.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>955 ± 347</td>
<td>994 ± 340&lt;sup&gt;a&lt;/sup&gt;</td>
<td>949 ± 362&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calcium treatment (%)</td>
<td>50.4</td>
<td>48.4</td>
<td>53.2</td>
</tr>
<tr>
<td>Physical activity (Kcal/day)*</td>
<td>118 (45, 209)</td>
<td>138 (60, 222)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>118 (0, 201)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prevalent osteoporotic fracture (%)†</td>
<td>30.3</td>
<td>26.2</td>
<td>30.1</td>
</tr>
<tr>
<td>Rheumatoid arthritis (%)</td>
<td>0.6</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>0.3</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Taking 3 or more units alcohol per day (%)</td>
<td>3.5</td>
<td>4.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Falls in the past 3 months (%)</td>
<td>10.8</td>
<td>10.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Timed Up and Go (Seconds)*</td>
<td>9.2 (8.0, 10.8)</td>
<td>8.4 (7.6, 9.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.5 (10.8, 12.8)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>One-year hip aBMD (mg/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>811 ± 125</td>
<td>920 ± 81&lt;sup&gt;a&lt;/sup&gt;</td>
<td>916 ± 88&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>One-year hip aBMD T-score</td>
<td>-1.1 ± 1.0</td>
<td>-0.2 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.2 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise stated. *Median and inter-quartile range. † Including incident fracture during first year. Values in a row with different superscript letters are significantly different, P < 0.05 (ANOVA with Tukey’s test) or P < 0.008 in non-parametric test.
Table 2 The combined 9-year fracture risk and population attributable risk of low baseline Timed Up and Go (TUG) performance and total hip bone mineral density (BMD) T-score at one year

<table>
<thead>
<tr>
<th>Non-vertebral fracture</th>
<th>Hip BMD T-score ≥ -1</th>
<th>Hip BMD T-score &lt; -1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TUG ≤ 10.2 secs (n = 343)</td>
<td>TUG &gt; 10.2 secs (n = 173)</td>
</tr>
<tr>
<td>Incidence %</td>
<td>10.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Population attributable risk % (95% CI)</td>
<td>Reference</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>(3.5 – 35.7)</td>
<td>(13.2 – 47.1)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence %</td>
<td>2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Population attributable risk % (95% CI)</td>
<td>Reference</td>
<td>32.3</td>
</tr>
<tr>
<td></td>
<td>(0.8 – 61.4)</td>
<td>(17.0 – 72.8)</td>
</tr>
</tbody>
</table>

Values in a row with different superscript letters are significantly different in logistic regression analysis.
Table 3 9-year risk of non-vertebral fracture predicted by models with hip BMD T-score and both hip BMD T-score and Timed Up and Go test performance

<table>
<thead>
<tr>
<th>Model with BMD and TUG test performance</th>
<th>Reclassified as higher risk</th>
<th>Reclassified as lower risk</th>
<th>Net correctly reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD ≤10%</td>
<td>8</td>
<td>18 (9.1%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>10-15%</td>
<td>4</td>
<td>12</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>≥15</td>
<td>0</td>
<td>8</td>
<td>133</td>
</tr>
</tbody>
</table>

Net reclassification improvement (NRI) = 8.1%, P = 0.01.