

# $\beta_2$ -Microglobulin for Risk Stratification of Total Mortality in the Elderly Population

## Comparison With Cystatin C and C-Reactive Protein

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**Background:** The clinicoepidemiologic relevance of moderately elevated concentrations of circulating  $\beta_2$ -microglobulin ( $\beta_2$ -M) has not been established.

**Methods:** We examined whether serum  $\beta_2$ -M concentration independently predicts total mortality in community-dwelling older populations and compared its predictive value with that of cystatin C and C-reactive protein (CRP) using a prospective cohort study of 1034 initially nondisabled persons 65 years and older as part of the Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging. Cox proportional hazards models were used to examine independent associations between baseline  $\beta_2$ -M levels and total mortality.

**Results:** During a median follow-up of 7.9 years, 223 persons died. A strong dose-response relationship was found between baseline serum  $\beta_2$ -M concentration and mortality risk, even after multiple adjustments. Compared with individuals in the lowest tertile of serum  $\beta_2$ -M concentra-

tion, those in the middle (hazard ratio, 2.02; 95% confidence interval [CI], 1.35-3.04) and highest (hazard ratio, 2.84; 95% CI, 1.92-4.20) tertiles had a substantially increased mortality risk. Respective values were 1.28 (95% CI, 0.86-1.90) and 1.95 (95% CI, 1.31-2.89) for cystatin C and 1.39 (95% CI, 0.98-1.98) and 1.44 (95% CI, 1.00-2.06) for CRP; only the highest tertiles showed significantly higher mortality risks. The area under the receiver operating characteristic curve for 8-year mortality was greatest for  $\beta_2$ -M (0.70; 95% CI, 0.66-0.74), followed by cystatin C (0.66; 95% CI, 0.62-0.70) and CRP (0.57; 95% CI, 0.53-0.61). Additional adjustment for renal function measures, inflammation markers, or both only partially reduced the association between  $\beta_2$ -M and mortality.

**Conclusion:** Serum  $\beta_2$ -M is an independent predictor of total mortality in a general population of older adults and may be a better predictor than cystatin C or CRP.

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**K**NOWLEDGE ABOUT BIOLOGICAL risk markers for mortality in the elderly population remains limited.<sup>1-4</sup> Such knowledge is relevant because it may provide important clues about the characterization of causal mechanisms for mortality or the development of predictive screening algorithms for identifying high-risk individuals. In this context, a search for novel mortality risk markers is warranted.

$\beta_2$ -microglobulin ( $\beta_2$ -M) constitutes a light chain of the class I major histocompatibility antigens. Widely distributed in nucleated cells in the body, it is especially rich in immunocompetent cells, such as lymphocytes and monocytes. Various stimuli cause substantial amounts of the molecule to be shed into the circulation.<sup>5</sup> Owing to a small molecular mass (11.8 kDa), circulating  $\beta_2$ -M passes freely through the glomeruli and is reabsorbed and metabolized in the proximal tubules of the kidneys.<sup>5</sup> As such,  $\beta_2$ -M concentra-

tion in the blood is largely affected by the glomerular filtration rate (GFR) of the kidneys.<sup>6</sup> In healthy individuals,  $\beta_2$ -M concentration is fairly constant. On the other hand, blood levels of  $\beta_2$ -M have been documented to increase in disease states such as renal dysfunction (owing to reduced catabolism) and in certain malignancies, autoimmune diseases, and infections (owing to increased production).<sup>7-10</sup> In the clinical setting, serum  $\beta_2$ -M has been particularly useful as a marker of chronic kidney disease-related dysfunction.

Advanced aging also seems to affect the circulating  $\beta_2$ -M concentration. Moderately elevated circulating  $\beta_2$ -M levels are often found in older people. Whether this elevation merely reflects decreased renal function or a presence of low-grade inflammation in older adults<sup>11-13</sup> or also has its own clinical prognostic relevance in this population remains unclear.

The objectives of this study are 2-fold: (1) to test the hypothesis that increased serum  $\beta_2$ -M concentration is a risk factor for

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total mortality in community-dwelling older adults independent of the impact of renal dysfunction, inflammation, and other major potential confounders and (2) to compare the predictive value of  $\beta_2$ -M for total mortality with that of the renal function measures estimated GFR and cystatin C<sup>14</sup> and the inflammation marker CRP, all of which are major mortality predictors.<sup>15-17</sup>

## METHODS

### STUDY POPULATION

The Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging (TMIG-LISA) is a long-term prospective study on aging and health in Japanese older people who reside in Koganei City, a suburb of Tokyo, and Nangai Village, a rural area in northern Japan.<sup>18</sup> Details of the cohort selection process were previously published.<sup>19</sup> Briefly, in Koganei City, a random sample consisting of one-tenth of the population aged 65 to 84 years ( $n=996$ ) was recruited. Of those, 814 persons (81.7%) responded to the initial home visit interview survey in 1991, and 405 of those (49.8%) further participated in the baseline medical examination conducted at a community hall in 1991. In Nangai Village, of all community-dwelling residents 65 years and older ( $n=940$ ), 852 ambulatory persons (90.6%) were invited to participate in the baseline survey conducted at a community hall in 1992. Of those, 748 (87.8%) were interviewed, and 735 (86.3%) also underwent medical examination.

Overall, 1140 men and women aged 65 to 89 years participated in the baseline interview and medical examination in the TMIG-LISA. Of those, 1091 persons reported no dependency in any of 5 basic activities of daily living (moving, dressing, eating, toileting, and bathing); this subset constituted the cohort of our study. Study participants were followed up through January 31, 1999 (Koganei), and August 31, 2000 (Nangai) (the end of the first term of the TMIG-LISA). Of the original 1091 in the cohort, 11 had missing  $\beta_2$ -M values, 18 had missing creatinine values, 26 had missing cystatin C values, 22 had missing CRP values, and 40 had missing data on one of the other covariates. The final sample size for this analysis was 1034. The Tokyo Metropolitan Institute of Gerontology review committee approved the study protocol, and informed consent was obtained from all the participants.

### DATA COLLECTION

The baseline interviews and medical examinations included demographic questions, self-rated health status, functional status in instrumental and basic activities of daily living, medical history, smoking habits, alcohol intake, anthropometry, standard blood pressure measurement, a resting 12-lead electrocardiogram, collection of blood specimens, and performance-based physical function.

Blood samples were centrifuged at the examination sites, and the resulting serum samples were kept at 4°C until analysis or storage at -80°C within 24 hours. Serum  $\beta_2$ -M concentrations at baseline were determined at a laboratory (SRL, Inc, Tokyo) in 1991 or 1992 using the latex immunoprecipitation method and an autoanalyzer (JCA-BM12; Nippon Denshi, Tokyo). The calibration and quality control data were as follows: the intra-subject coefficient of variation range was 0.5% to 1.5%, and the interday coefficient of variation range was 1.1% to 5.5% across a wide range of  $\beta_2$ -M concentrations.

Other laboratory measurements (total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, hemoglobin A<sub>1c</sub>, and hematologic values) at baseline were conducted using standardized procedures. The presence or absence of proteinuria was assessed using a casual dipstick, and its grade was cat-

egorized as "none," "trace," or "greater than trace." Serum creatinine, cystatin C, and high-sensitivity CRP levels were determined at SRL, Inc, in 2006 using serum samples collected in 1991-1992 and stored at -80°C. Creatinine was measured using the enzyme colorimetric method and an autoanalyzer (Hitachi7170; Hitachi Ltd, Tokyo). Cystatin C and CRP were measured using particle-enhanced immunonephelometric assays (N Latex Cystatin C and N Latex CRP II, respectively; Dade Behring Inc, Deerfield, Illinois) and a nephelometer (BN II; Dade Behring). Intrasubject and interday coefficient of variation ranges were, respectively, 1.7% to 1.9% and 1.6% to 2.3% for cystatin C and 0.9% to 1.7% and 2.3% to 3.0% for CRP across a wide range of cystatin C and CRP levels.

Body mass index was calculated as weight in kilograms divided by height in meters squared. Medical history included the self-report of physician-diagnosed stroke, heart disease, type 2 diabetes mellitus, and hypertension. Performance-based measures of physical function included a 5-m measured walk at a usual pace (timed to the 0.1 second) and 2 measures of maximal grip strength in the dominant hand (to the nearest kilogram) using a Smedley-type dynamometer (Yagami Co, Tokyo). Mortality data were obtained through a comprehensive surveillance system that has been used successfully since the beginning of the TMIG-LISA. All deaths were ascertained by checking the local registries.

### STATISTICAL ANALYSIS

Cumulative survival through the end of follow-up by tertiles of baseline  $\beta_2$ -M, cystatin C, and CRP concentrations were calculated using the Kaplan-Meier method. Differences in survival curves were evaluated using the log-rank test. The independent role of  $\beta_2$ -M as a predictor of total mortality was evaluated using Cox proportional hazards regression models, with adjustments for age, sex, preexisting diseases, and other major potential confounding factors selected on the basis of previous literature findings. These factors included body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol levels, albumin level, hemoglobin A<sub>1c</sub> level, smoking and alcohol drinking status (current, former, or never), self-rated health (excellent or good vs fair or poor), and usual walking speed (meters per second), which were entered into the models as continuous variables, except for smoking and alcohol status and self-rated health. Preexisting diseases included physician-diagnosed stroke, heart diseases (ischemic heart disease or others), hypertension, and type 2 diabetes mellitus, and each was entered into the models as dichotomous data (present vs absent). In these analyses, predictive values of  $\beta_2$ -M for total mortality were evaluated using adjusted relative risks in each of the middle and highest tertiles of baseline  $\beta_2$ -M concentration compared with the lowest tertile.

To further examine whether the association of  $\beta_2$ -M and mortality was independent of renal function and inflammation, additional adjustment was made for renal function measures (degree of proteinuria, estimated GFR, and cystatin C level), inflammation markers (white blood cell [WBC] count and CRP level), or both using Cox regression models. We estimated the GFR using the 6-variable version of the Modification of Diet in Renal Disease equation<sup>20</sup>; we further multiplied the calculated figure by 0.741 to correct for the Japanese build.<sup>21</sup> Estimated GFR, cystatin C level, WBC count, and log-transformed CRP level were entered into the models as continuous variables, and degree of proteinuria was entered as a categorical variable.

Receiver operating characteristic (ROC) curves were plotted for 3 risk markers ( $\beta_2$ -M, cystatin C, and CRP). We used occurrence compared with nonoccurrence of events in 8 years as the outcome measure for this analysis. For statistical significance, 2-tailed  $P < .05$  was used throughout the analysis. All data analyses were performed using a statistical software program (SPSS version 14.0 for Windows; SPSS Inc, Chicago, Illinois).

**Table 1. Baseline Characteristics of Elderly Participants in the TMIG-LISA According to Tertiles of Serum  $\beta_2$ -Microglobulin Concentration**

Characteristic	Lowest Tertile ( $\leq 1.5$ mg/L) (n=413)	Middle Tertile (1.6-1.8 mg/L) (n=295)	Highest Tertile ( $\geq 1.9$ mg/L) (n=326)	P Value for Trend <sup>a</sup>
Study area, No. (%)				
Koganei (urban)	150 (36.3)	99 (33.6)	114 (35.0)	1.0 [Reference]
Nangai (rural)	263 (63.7)	196 (66.4)	212 (65.0)	.66
Age, mean (SD), y	69.8 (4.2)	71.4 (4.9)	74.0 (5.6)	<.001
Sex, No. (%)				
M	149 (36.1)	133 (45.1)	149 (45.7)	1.0 [Reference]
F	264 (63.9)	162 (54.9)	177 (54.3)	.005
Body mass index, mean (SD) <sup>b</sup>	22.5 (3.3)	22.7 (3.2)	22.6 (3.4)	.46
Medical history, No. (%)				
Stroke	9 (2.2)	11 (3.7)	22 (6.7)	.003
Ischemic heart disease	22 (5.3)	23 (7.8)	39 (12.0)	<.001
Other heart diseases	46 (11.1)	38 (12.9)	49 (15.0)	.05
Hypertension	143 (34.6)	108 (36.6)	159 (48.8)	<.001
Diabetes mellitus	26 (6.3)	18 (6.1)	32 (9.8)	.10
Proteinuria, No. (%)				
Trace	22 (5.3)	13 (4.4)	29 (8.9)	.05
Greater than trace	5 (1.2)	3 (1.0)	26 (8.0)	<.001
Systolic blood pressure, mean (SD), mm Hg	143 (21)	144 (23)	148 (23)	.001
Blood variables, mean (SD)				
Hemoglobin, g/dL	13.1 (1.2)	13.0 (1.5)	12.8 (1.5)	.01
Albumin, g/dL	4.2 (0.2)	4.1 (0.3)	4.1 (0.3)	<.001
HbA <sub>1c</sub> , % of total hemoglobin	5.7 (0.8)	5.6 (0.6)	5.7 (0.9)	.98
Total cholesterol, mg/dL	204 (38)	195 (35)	193 (37)	<.001
HDL cholesterol, mg/dL	53 (13)	49 (13)	47 (13)	<.001
Creatinine, mg/dL	0.62 (0.12)	0.71 (0.14)	0.87 (0.25)	<.001
Estimated GFR, mL/min/1.73 m <sup>2</sup>	82 (15)	73 (13)	60 (15)	<.001
Cystatin C, mg/L	0.76 (0.08)	0.87 (0.09)	1.12 (0.26)	<.001
WBC, / $\mu$ L	5370 (1290)	5480 (1470)	5600 (1640)	.22
CRP, log-transformed, mg/L	-0.34 (0.48)	-0.25 (0.49)	-0.09 (0.58)	<.001
Alcohol drinking status, No. (%)				
Current	171 (41.4)	113 (38.3)	121 (37.1)	1.0 [Reference]
Former	21 (5.1)	13 (4.4)	35 (10.7)	.006
Never	221 (53.5)	169 (57.3)	170 (52.1)	.53
Smoking status, No. (%)				
Current	66 (16.0)	52 (17.6)	48 (14.7)	1.0 [Reference]
Former	55 (13.3)	44 (14.9)	73 (22.4)	.02
Never	292 (70.7)	199 (67.5)	205 (62.9)	.79
Self-rated health, fair or poor, %	89 (21.5)	74 (25.1)	100 (30.7)	.005
Usual walking speed, mean (SD), m/s	1.18 (0.24)	1.14 (0.27)	1.05 (0.29)	<.001

Abbreviations: CRP, C-reactive protein; GFR, glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; TMIG-LISA, Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging; WBC, white blood cell.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; total and HDL cholesterol to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4; CRP to nanomoles per liter, multiply by 9.524; hemoglobin to grams per liter, multiply by 10; HbA<sub>1c</sub> to proportion of total hemoglobin, multiply by 0.01; WBC to  $\times 10^9$  per liter, multiply by 0.001.

<sup>a</sup>P for trend was determined using the Kendall rank-sum test.

<sup>b</sup>Body mass index was calculated as weight in kilograms divided by height in meters squared.

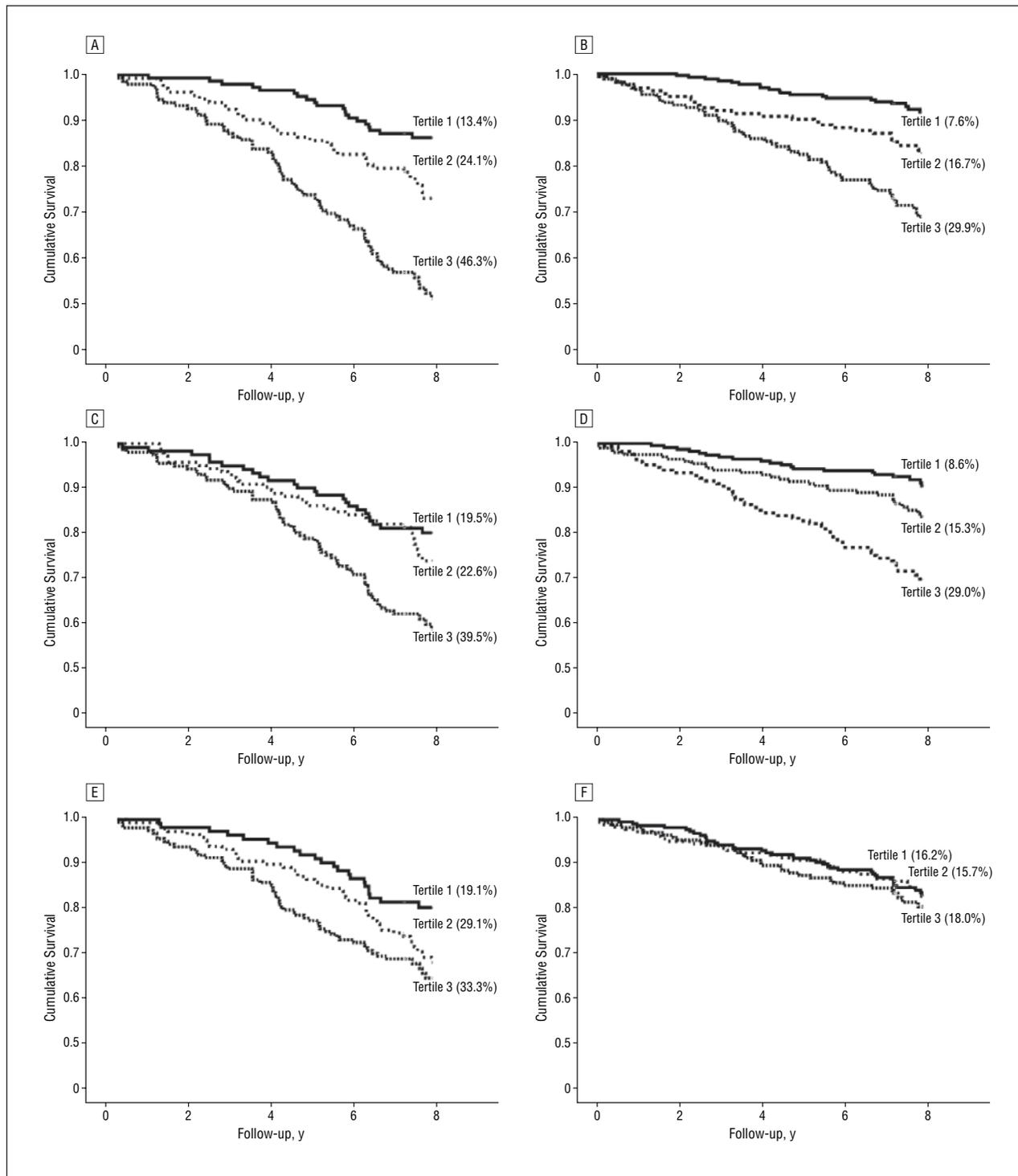
## RESULTS

### DISTRIBUTION OF SERUM $\beta_2$ -M CONCENTRATIONS IN OLDER PARTICIPANTS

Serum  $\beta_2$ -M concentrations at baseline in 1034 nondisabled older participants ranged from 0.8 to 6.6 mg/L, with a mean (SD) of 1.77 (0.55) mg/L and a leftward-skewed distribution. The distributions for men and women were similar, and the mean values were not significantly different ( $P = .12$ ,  $t$  test). Thus, we categorized the participants into 3 tertile groups based on the distribution of  $\beta_2$ -M concentrations in the whole population: lowest tertile, 1.5 mg/L or less; middle tertile, 1.6 to 1.8 mg/L; and highest tertile, 1.9 mg/L or greater.

### PREDICTORS OF BASELINE SERUM $\beta_2$ -M CONCENTRATIONS

Characteristics of the study population at baseline by  $\beta_2$ -M categories are presented in **Table 1**. We observed strong and significant associations of increased serum  $\beta_2$ -M levels with increased age and renal dysfunction, as assessed by proteinuria, serum creatinine level, estimated GFR, and cystatin C level. In addition,  $\beta_2$ -M concentration was positively associated with preexisting medical conditions such as stroke, ischemic heart disease, and hypertension; CRP level; and former alcohol drinking and smoking habits and was negatively associated with albumin level, total and high-density lipoprotein cholesterol level, self-rated health, and usual walking speed.

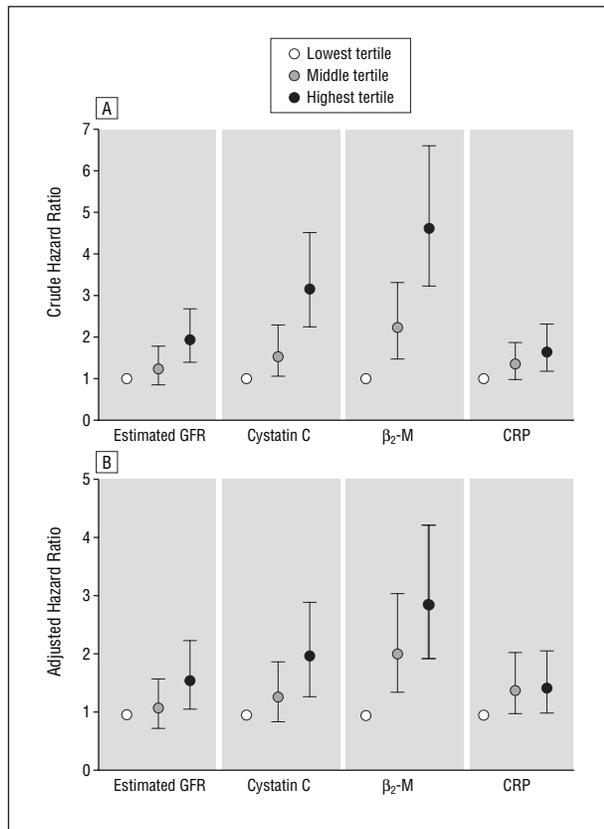


**Figure 1.** Kaplan-Meier estimates of survival according to tertiles of  $\beta_2$ -microglobulin (A and B), cystatin C (C and D), and C-reactive protein (E and F) concentrations in men (A, C, and E) and women (B, D, and F). Tertiles 1 (lowest), 2 (middle), and 3 (highest) represent 1.5 mg/L or less, 1.6 to 1.8 mg/L, and 1.9 mg/L or greater for  $\beta_2$ -microglobulin; 0.80 mg/L or less, 0.81 to 0.93 mg/L, and 0.94 mg/L or greater for cystatin C; and 0.33 mg/L or less, 0.34 to 0.85 mg/L, and 0.86 mg/L or greater for C-reactive protein (to convert to nanomoles per liter, multiply by 9.524), respectively. Cumulative mortality rates during 8-year follow-up are given in parentheses.

### SERUM $\beta_2$ -M CONCENTRATION AND MORTALITY

During a median follow-up of 7.9 years, 121 men (28.1%) and 102 women (16.9%) died. We observed a graded relationship between serum  $\beta_2$ -M level and total mortality (**Figure 1** A and B). The cumulative mortality rates dur-

ing 8-year follow-up were 13.4% (20/149), 24.1% (32/133), and 46.3% (69/149) for men and 7.6% (20/264), 16.7% (27/162), and 29.9% (53/177) for women in the lowest, middle, and highest tertiles of  $\beta_2$ -M concentration. The respective 1000 person-year mortality rates were 18.0, 34.8, and 74.2 for men and 10.1, 23.1, and 44.4 for women. There were clear differences in survival curves among the tertiles

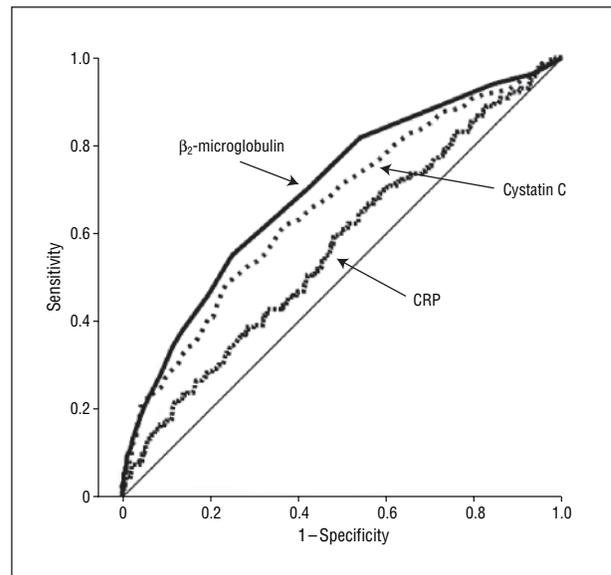


**Figure 2.** Crude (A) and adjusted (B) hazard ratios of  $\beta_2$ -microglobulin ( $\beta_2$ -M), the renal function measures estimated glomerular filtration rate (GFR) and cystatin C, and the inflammation marker C-reactive protein (CRP) for 8-year mortality using the Cox proportional hazards model. Error bars represent 95% confidence intervals.

in men and women. The 3 cystatin C categories exhibited a similar pattern to those of  $\beta_2$ -M in women, but the Kaplan-Meier estimates of mortality did not differ between the lowest (tertile 1) and middle (tertile 2) tertiles in men ( $P = .43$ , log-rank test). The 3 CRP categories did not grade mortality risk in women ( $P = .52$ , log-rank test).

These results were upheld in the Cox regression analysis (**Figure 2**). Multiple adjustments somewhat weakened the  $\beta_2$ -M relationships, but they remained significant in subgroups with higher  $\beta_2$ -M levels. When participants in the middle and highest tertiles of  $\beta_2$ -M concentration were compared with those in the lowest tertile, the adjusted hazard ratios were 2.02 (95% confidence interval [CI], 1.35-3.04) and 2.84 (95% CI, 1.92-4.20).

Estimated GFR, cystatin C, and CRP also predicted mortality after multiple adjustments, but the prognostic ability of these indexes was inferior to that of  $\beta_2$ -M. For example, although the intermediate and highest tertiles of  $\beta_2$ -M concentration were associated with increased mortality risk compared with the lowest tertile, only the highest tertiles of estimated GFR, cystatin C, and CRP levels were significantly associated with higher mortality risks; the adjusted hazard ratios of the intermediate and highest tertiles were 1.09 (95% CI, 0.76-1.58) and 1.55 (95% CI, 1.07-2.23) for estimated GFR, 1.28 (95% CI, 0.86-1.90) and 1.95 (95% CI, 1.31-2.89) for cystatin C, and 1.39 (95% CI, 0.98-1.98) and 1.44 (95% CI, 1.00-2.06) for CRP, respectively (Figure 2).



**Figure 3.** Receiver operating characteristic curves of 3 risk markers for 8-year mortality. The areas under the receiver operating characteristic curves are 0.70 (95% confidence interval [CI], 0.66-0.74), 0.66 (95% CI, 0.62-0.70), and 0.57 (95% CI, 0.53-0.61) for  $\beta_2$ -microglobulin, cystatin C, and C-reactive protein (CRP), respectively.

The ROC curves of 3 risk markers ( $\beta_2$ -M, cystatin C, and CRP) were generated for 8-year mortality (**Figure 3**). The area under the ROC curve was greatest for  $\beta_2$ -M (0.70; 95% CI, 0.66-0.74), followed by cystatin C (0.66; 95% CI, 0.62-0.70) and CRP (0.57; 95% CI, 0.53-0.61). Additional adjustment for renal function measures, inflammation markers, or both partially reduced the association of  $\beta_2$ -M and mortality (models 3A, 3B, and 4 in **Table 2**).

Exclusion of the deaths that occurred during the first 2 years of follow-up ( $n = 36$ ) did not materially alter the results (adjusted hazard ratios for the middle and highest tertiles of  $\beta_2$ -M, 1.66 [95% CI, 1.07-2.55] and 2.56 [95% CI, 1.70-3.85], respectively). Likewise, exclusion of individuals who had abnormal (within the worst 3%) values at baseline ( $n = 294$ ) in body mass index, walking speed, handgrip strength, systolic blood pressure, hemoglobin, albumin, hemoglobin A<sub>1c</sub>, CRP, WBC count, creatinine, or glutamic pyruvic transaminase, plus those who rated their health as poor ( $n = 34$ ), did not affect the association of  $\beta_2$ -M and mortality (adjusted hazard ratios for the middle and highest tertiles, 2.14 [95% CI, 1.29-3.54] and 3.12 [95% CI, 1.89-5.13], respectively).

## COMMENT

We observed a strong and independent association between  $\beta_2$ -M concentration and total mortality during 8-year follow-up in 65- to 89-year-old men and women enrolled in the population-based TMIG-LISA in 1991-1992. To our knowledge, this is the first study to document the clinical prognostic value of circulating  $\beta_2$ -M concentration as an independent predictor of total mortality in a general population of older adults. We found evidence that the predictive value of circulating  $\beta_2$ -M concentration may surpass that provided by established prognostic factors for mortality, such as estimated GFR and cystatin C (chronic kid-

**Table 2. Hazard Ratios of  $\beta_2$ -Microglobulin for 8-Year Mortality After Additional Adjustment for Renal Function Measures, Inflammation Markers, and Both**

$\beta_2$ -Microglobulin Tertile	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3A <sup>c</sup>	Model 3B <sup>d</sup>	Model 4 <sup>e</sup>
Lowest	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Middle	2.21 (1.48-3.30)	2.02 (1.35-3.04)	2.06 (1.35-3.13)	1.99 (1.33-3.00)	2.05 (1.35-3.11)
Highest	4.60 (3.22-6.58)	2.84 (1.92-4.20)	2.55 (1.62-4.01)	2.68 (1.81-3.98)	2.55 (1.62-4.03)

<sup>a</sup>Model 1 shows the crude, unadjusted results.

<sup>b</sup>Model 2 is adjusted for demographics (age, sex, and study area) and clinically relevant variables (history of stroke, heart disease, hypertension, and type 2 diabetes mellitus; alcohol drinking and smoking status; body mass index; hemoglobin, albumin, hemoglobin A<sub>1c</sub>, and total and high-density lipoprotein cholesterol levels; self-rated health; and usual walking speed).

<sup>c</sup>Model 3A is adjusted for all the variables in model 2 plus renal function measures (proteinuria, estimated glomerular filtration rate, and cystatin C).

<sup>d</sup>Model 3B is adjusted for all the variables in model 2 plus inflammation markers (white blood cell count and log-transformed C-reactive protein).

<sup>e</sup>Model 4 is adjusted for all the variables in model 2 plus renal function measures and inflammation markers.

ney disease markers) and CRP (inflammation marker). In terms of risk stratification, serum  $\beta_2$ -M levels significantly discriminated mortality risk in a dose-response manner across 3 tertile groups, whereas only the highest tertiles of estimated GFR, cystatin C level, and CRP concentration showed a significantly increased risk. Also, the area under the ROC curve for  $\beta_2$ -M was greater than that for cystatin C or CRP. Compared with previously reported risk markers in terms of strength of association, high  $\beta_2$ -M levels seem to be a better predictor of mortality than CRP,<sup>16</sup> interleukin 6,<sup>17,22</sup> fibrinogen,<sup>23</sup> and total homocysteine levels.<sup>24,25</sup>

Cystatin C, a cysteine protease inhibitor, has been proposed to represent a superior marker for the detection of renal impairment compared with creatinine or a creatinine-based estimate of GFR and was recently documented to have significant prognostic value for total mortality and cardiovascular morbidity and mortality.<sup>15</sup> C-reactive protein is a strong mortality predictor in older persons as well as an inflammation marker.<sup>16,17</sup> The present study builds on the literature not only by replicating previous findings on the association of cystatin C and CRP in community-dwelling older Japanese persons but principally by documenting the independent value of  $\beta_2$ -M as a predictor of mortality and by comparing its predictive value with that of cystatin C and CRP. These results are consistent with the previous finding that serum  $\beta_2$ -M predicted the onset of functional decline in the Nangai cohort of the TMIG-LISA during 6 years of follow-up.<sup>26</sup> Taken together, these findings suggest that serum  $\beta_2$ -M could be a useful prognostic tool in the evaluation of elderly persons.

What potential explanations are there for the close link between  $\beta_2$ -M and mortality? There is the possibility that  $\beta_2$ -M is a better marker of reduced renal function than conventional measures, such as creatinine or estimated GFR, and even than cystatin C. Recent studies<sup>15,27</sup> have documented that individuals with moderately reduced renal function are at increased risk for total mortality and cardiovascular morbidity and mortality. Older persons with higher  $\beta_2$ -M concentrations may well be at increased risk for mortality via a renal dysfunction mechanism. However, as evidenced by the fact that additional adjustment for renal function measures, including estimated GFR and cystatin C, only moderately reduces the association of  $\beta_2$ -M and mortality, such a renal mechanism alone could not fully explain the close link between  $\beta_2$ -M and total mortality in this healthy older cohort.

Another possibility is that  $\beta_2$ -M is an inflammation marker. Considering the relevant role of  $\beta_2$ -M in immune responses, higher circulating  $\beta_2$ -M concentrations may derive from increased systemic or local inflammation, possibly associated with subclinical cardiovascular diseases or malignancies. In addition to the low expected rate of  $\beta_2$ -M-related malignancies (eg, multiple myeloma) in the 2 study sites of the TMIG-LISA, the close relationships between  $\beta_2$ -M and preexisting cardiovascular diseases at baseline suggest the involvement of cardiovascular diseases. Also, there was a significant relationship between serum  $\beta_2$ -M and log CRP. Low-grade inflammation characterized by increased levels of cytokines and acute-phase proteins as well as elevated WBC counts have been documented to predict all-cause mortality and cardiovascular mortality in the elderly population.<sup>16,17,22,23,28</sup> In summary, the hypothesis that circulating  $\beta_2$ -M concentrations reflect low-grade inflammation is attractive. However, as evidenced by the fact that additional adjustments for WBC counts and CRP levels only slightly reduced the association of  $\beta_2$ -M and mortality, inflammation does not likely explain the association between  $\beta_2$ -M and total mortality. Nonetheless, CRP and WBC count do not reflect the total inflammation burden, and the possibility of residual confounding by prevalent chronic disease burden, explaining (at least in part) the association observed herein, cannot be excluded.

In the clinical setting,  $\beta_2$ -M is known to relate to several diseases with high mortality rates. To examine whether serious underlying illnesses would have confounded the association of  $\beta_2$ -M with mortality, we analyzed data after exclusion of the deaths in the first 2 years of follow-up or after exclusion of those performing worst in a variety of variables at baseline. Neither analysis altered the association of  $\beta_2$ -M and mortality, which speaks against the notion that the observed association may be totally explained by residual confounding from serious illnesses.

Several other unresolved issues remain. It remains to be established whether high levels of circulating  $\beta_2$ -M have a direct pathogenic effect, analogously to what has been speculated for high CRP levels. In addition, knowledge about clinical factors that may affect  $\beta_2$ -M concentrations beyond age, sex, chronic conditions, renal function, and inflammation remains limited. It also remains to be determined whether circulating  $\beta_2$ -M levels are potentially modifiable and, if so, what the impact of such changes would be on  $\beta_2$ -M levels.

This study has several strengths that should be acknowledged, particularly the use of a population-based sample of the TMIG-LISA cohort and 8-year follow-up. Also, the availability of comprehensive information in the TMIG-LISA database allowed us to adjust for important factors that might have confounded the relationship between elevated  $\beta_2$ -M levels and total mortality. The study participants were all initially nondisabled older persons, enabling us to extend the results to general community-dwelling elderly persons.

In conclusion, serum  $\beta_2$ -M concentration is an independent predictor of total mortality in a general population of older adults, and it may be a better predictor than cystatin C or CRP levels. Knowledge about the mechanisms of this association remains limited, but because of the strong association with mortality, investigation of potential mechanisms is warranted. Information about cause of death could provide clues about potential mechanisms (eg, atherosclerotic events and increased risk of infection).

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