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High levels of an endothelial dysfunction marker (sVCAM-1) are associated with injurious and recurrent falls and mortality over a 5-year interval in an older population

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Abstract

We investigated the association between elevated plasma concentrations of circulating soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) and injurious falls and mortality over a 5-year period. We studied the prospective relationship between levels of circulating adhesion molecules and falls in 680 community-dwelling participants in the MOBILIZE Boston Study. The mean sVCAM-1 ($\pm$ SD) concentration was 1192 ± 428 ng/mL. Over 5-years of follow-up, 10.2% of participants died. The baseline sVCAM-1 ($\pm$ SD) concentration was 1434 ± 511 ng/mL in those who died vs. 1162 ± 402 ng/mL in those who survived ($P < 0.0001$). sVCAM-1 level was associated with recurrent falls ($P < 0.01$); compared to the lowest quintile, the highest quintile of sVCAM-1 was associated with increased risk of injurious falls [multivariable adjusted Incidence Rate Ratio = 1.9, 95% CI (1.2–2.9), $P = 0.009$]. On survival analysis, the highest sVCAM-1 quintile was associated with the greatest mortality over 5 years (log-rank test, $P < 0.0001$). The adjusted hazard ratio was 2.4 [95% CI (2.1–2.7), $P = 0.002$]. High sVCAM-1 blood concentration was strongly associated with recurrent falls, injurious falls, and mortality in older adults.

Keywords

Endothelial dysfunction; Adhesion molecule; Injurious falls; Mortality; Elderly

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1. Introduction

Fall-related injuries are the third leading cause of years lived with disability, according to the World Health Organization's report, Global Burden of Disease (Tinetti and Speechley, 1989). Falls rank among the 10 leading causes of death in the United States, associated with over \$19 billion in annual healthcare costs (Gorina et al., 2005). Despite a growing body of scientific evidence supporting the associations between certain risk factors and falls, efforts to translate these findings into effective fall prevention strategies have been limited (Gates et al., 2008; Rubenstein, 2006).

Falls are linked to many cardiovascular diseases, but little is known about the relationships between the levels of circulating cell adhesion molecules (CAMs) and falls occurring in elderly." CAMs are well-known biomarkers of the endothelial activation and dysfunction associated with hypertension and atherosclerosis (Mulvihill et al., 2002). In human studies, increased concentrations of circulating soluble CAM have been reported in patients with systemic inflammatory response syndrome and cardiovascular diseases (Kriegelstein and Granger, 2001). Soluble vascular cell adhesion molecule-1 (sVCAM-1) promotes adhesion of inflammatory cells to the vascular endothelial wall, particularly the wall of the cerebral microvasculature, and facilitates cell migration through the endothelium (Kallmann et al., 2000). Previously, we showed that higher CVAM levels were associated with mobility impairment and increased fall frequency over 12 months (Tchalla et al., 2012, 2015). However, the long-term relationship between adhesion molecule concentrations and fall frequency has not yet been studied; this is important because sVCAM-1 should perhaps be added to the list of plasma inflammatory biomarkers, such as interleukin 6, known to be associated with both cardiovascular risk and mobility limitations in elderly people (Cesari et al., 2004). The associations between one or several plasma biomarkers and the vascular component of mobility limitation are of considerable interest because these may allow identification of subjects who might benefit from targeted interventions (Dumurgier and Elbaz, 2015).

In the present study, we hypothesized that increased levels of soluble CAM in older adults might predict injurious falls over a 5-year period. Additionally, we examined whether the 5-year results were consistent with those for the first year. We therefore used plasma biomarkers and data from the MOBILIZE (Maintenance Of Balance, Independent Living, Intellect, and Zest in the Elderly) Boston Study to explore the relationship between plasma CAM levels and the rate of injurious falls over 5 years in a community-based population of older adults.

2. Materials and methods

2.1. Participants

The study sample consisted of 680 individuals from the MOBILIZE Boston Study (MBS), a prospective cohort study evaluating a unique set of risk factors for falls in community-dwelling seniors living in the Boston area. The design and methodology of the study have been previously described in detail (Leveille et al., 2008; Samelson et al., 2008). In brief, 765 subjects were enrolled using door-to-door population-based recruitment. To be included,

an individual had to be > 70 years of age (or > 65 years of age if living with another participant) during baseline assessment performed in 2004–2005; participants were prospectively followed up with respect to falls for 5 years. The exclusion criteria included terminal disease, severe vision or hearing deficits, and a Mini-Mental State Examination score < 18 (Leveille et al., 2008; Samelson et al., 2008). All subjects underwent complete home and laboratory assessment of demographic characteristics, medical conditions, medications, functional status, gait speed, smoking status, alcohol use, and blood pressure; they were then prospectively followed up using a monthly calendar (described below).

2.1.1. Assessment of falls and injurious falls—During the follow-up period, a fall was defined as unintentionally coming to rest on the ground or another lower level in an event that did not result from of a major intrinsic cause (e.g., myocardial infarction, stroke, or seizure) or an overwhelming external hazard (e.g., being hit by a vehicle) (Gibson et al., 1987; Leveille et al., 2008). Participants were instructed to complete and return monthly fall calendar postcards posted on their refrigerators. On the postcards, participants were to record an “F” for each fall, on the day it occurred, and an “N” on days when no fall occurred. This approach has been well validated for use in epidemiological cohort studies and has been described previously (Tinetti et al., 1993). All subjects who reported falls were telephoned to determine the circumstances of the fall and the clinical outcomes, including whether any injury (e.g., a fracture) had occurred and whether it had been necessary to visit an Emergency Department or a hospital. An injurious fall was identified by a “Yes” to the question, “Did you hurt yourself in any way when you fell?”

2.1.2. Mortality assessment—Mortality was assessed via a combination of family statements and National Death Index searches (Fillenbaum et al., 2009).

2.2. Biomarker measures

Soluble intercellular adhesion molecule-1 (sICAM-1), sVCAM-1, and interleukin-6 (IL-6) levels were measured by ELISA (R&D Systems, Minneapolis, MN). The sICAM-1 assay has a sensitivity of 0.35 ng/mL, and the day-to-day variabilities at concentrations of 64.2, 117, 290, and 453 ng/mL are 10.1, 7.4, 6.0, and 6.1%, respectively. The sVCAM-1 assay has a sensitivity of 2.0 ng/mL, and the day-to-day variabilities at concentrations of 9.8, 24.9, and 49.6 ng/mL are 10.2, 8.5, and 8.9%, respectively. The IL-6 assay has a sensitivity of 0.094 pg/mL, and the day-to-day variabilities at concentrations of 0.49, 2.78, and 5.65 pg/mL are 9.6, 7.2, and 6.5%, respectively. High-sensitivity C-reactive protein (hsCRP) levels were determined immunoturbidimetrically using a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, USA), employing reagents and standards from DiaSorin (Stillwater, MN, USA). This assay has a limit of detection of 0.03 mg/L. The day-to-day variabilities at concentrations of 0.91, 3.07, and 13.38 mg/L are 2.81, 1.61, and 1.1%, respectively. All assays were performed by Dr. Nader Rifai’s group at Boston Children’s Hospital.

2.3. Other covariates

The covariates studied included sociodemographic characteristics, physiological risk factors, health status, and the extent of physical activity. Sociodemographic characteristics assessed during home interviews included age, sex, race (self-identified), and years of education. We

used the validated Physical Activity Scale for the Elderly (PASE) to measure physical activity during the previous week (Washburn et al., 1993). Participants were asked about physician-diagnosed major medical conditions. Details of the study methods have been published previously (Leveille et al., 2008; Samelson et al., 2008). Diabetes was defined using an algorithm that included self-reported diabetes, the use of antidiabetic medications, and laboratory measures made at the baseline clinic visit including the random glucose level (cutoff: 200 mg/dL) and hemoglobin A1C (cutoff: 7%). Body mass index (calculated as weight in kilograms divided by height in meters squared) was calculated from the measured height and weight. The comorbidity index value was the number of comorbidities or medical conditions (Charlson et al., 1987). We have included all chronic diseases. The levels of other biomarkers (IL6 and CRP) were assessed as described above. The use of medications (antihypertensives, antidepressants, and benzodiazepines) was also assessed. *Hypertension:* Three blood pressure (BP) categories were created: Normotension, no history or current evidence of hypertension; controlled hypertension, a history of hypertension and antihypertensive treatment but with a normal BP [systolic BP (SBP) < 140 mm Hg and diastolic BP (DBP) < 90 mm Hg during baseline clinical assessment]; and uncontrolled hypertension [a history of hypertension with an abnormal BP (SBP ≥ 140 or DBP ≥ 90 mm Hg) at baseline examination] (James et al., 2014; Wellenius et al., n.d.). *Smoking and alcohol use status:* Smoking status was determined by asking whether the participant currently smoked cigarettes. Alcohol use was assessed by asking whether the individual consumed two or more drinks of beer, wine, or liquor each week.

2.4. Ethics statement

The MOBILIZE Boston Study was reviewed and approved by the Hebrew SeniorLife Institutional Review Board (IRB). Written informed consent was obtained from each participant. The study was conducted according to the principles of the Helsinki Declaration.

2.5. Data analysis

The sVCAM-1 and sICAM-1 concentrations were log-transformed to approximate a normal distribution prior to modeling as continuous variables. We also divided the sVCAM-1 distributions into quintiles, reflecting their distributions in the entire study population, prior to categorical analyses. Participant characteristics and risk factors were summarized by calculating means (with standard deviations) or percentages. We estimated the rates of total injurious falls (indoors and outdoors) per 1000 person-years. We used negative binomial regression modeling to test our hypothesis that differences in injurious fall rates would be largely explained by differences in CAM concentrations.

Predictive fall-rate models reflecting baseline CAM measures were performed using negative binomial modeling (the Proc GENMOD routine). The models yielded multivariable-adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

We constructed a series of models; the first model was unadjusted, and this was then adjusted for the following groups of confounders: 1) other biomarkers (IL6 and C-reactive protein levels); 2) socio-demographic features (age, gender, white race, educational level, body mass index, current smoker, and alcohol use); 3) health conditions (diabetes,

hypertension, congestive heart failure, hyperlipidemia, cognitive status, use of any cardiovascular medication, coronary disease, previous stroke, previous fall, visual impairment, and/or urinary disorder); and, 4) physical activity level and other fall risk factors.

We calculated the IRRs with 95% confidence interval (CIs) when the higher sVCAM-1 and sICAM-1 quintiles were compared to the lowest quintile, with serial adjustment of confounders. We used one exposure time in our negative binomial regression models. To evaluate injurious fall numbers, we employed the total person-time under observation.

For the mortality outcome, Kaplan Meier estimates of survival functions were made and compared using log-rank tests. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were estimated using univariate Cox regression analysis. Variables associated with an univariate effect on 5-year mortality (P -value < 0.20) were included in the multivariable Cox regression model using the enter method.

2.5.1. Dealing with missing data—Very few baseline interview or examination data were missing; no single covariate lacked $> 2.4\%$ of data. In fact, in the fully adjusted models that included all covariates, only 1.8% of records ($n = 12$) were excluded because information was missing.

All analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA). A two-sided P -value < 0.05 was considered to reflect statistical significance.

3. Results

3.1. Participants

Table 1 summarizes the demographic and clinical characteristics of all participants. The mean age was 78.1 ± 5.4 years, and 62.0% of subjects were female. At baseline, 111 (16.4%) participants had experienced a prior injurious fall, and 189 (27.8%) slow gait speed. The mean sVCAM-1 ($\pm$ SD) concentration was 1192 ± 428 ng/mL. Over 5 years, 67 (10.2%) subjects died; their mean sVCAM-1 ($\pm$ SD) concentration was 1433 ± 511 ng/mL, compared with 1161 ± 401 ng/mL for survivors ($P < 0.0001$).

A total of 1185 injurious falls were reported by the 680 participants for whom baseline biomarker levels were available during 52 months of follow-up (mean follow-up time, 48 ± 4 months). The injurious fall rate per year was higher in the fifth quintiles of sVCAM-1 and sICAM-1 and lower in the first quintiles (Fig. 1).

3.2. Soluble sVCAM-1 levels and injurious falls

3.2.1. Soluble VCAM-1—The unadjusted model (Model 1) showed that the highest quintile of sVCAM-1 values was associated with the highest IRR of injurious falls [2.0 (1.3–3.1); $P = 0.0016$]. After adjustment, the final multivariate negative binomial model (Model 4) showed that the highest quintile of sVCAM-1 values (compared to the lowest quintile) was significantly associated with the highest incidence of injurious falls [multivariable adjusted IRR = 1.8 (1.2–2.9); $P = 0.0095$ (Table 2)].

When analyzed as a continuous variable, the soluble sVCAM-1 level was linearly associated with increased risk of injurious falls.

3.2.2. Soluble ICAM-1—The highest quintile of sICAM-1 was also associated with the highest incidence of injurious falls [IRR = 1.8 (1.2–2.7); $P = 0.007$]. After adjustment, this association remained significant in the final model [IRR = 1.6 (1.1–2.5); $P = 0.03$ (Table 3)].

3.3. Soluble sVCAM-1, falls, and recurrent falls

Over the 5 years, 30.1% of subjects had no falls, 46.1% one fall, and 22.8% had at least two falls. The mean concentration of sVCAM-1 ($\pm$ SD) was 1150 ± 410 ng/mL in the no-fall, 1201 ± 43 ng/mL in the one-fall, and 1280.1 ± 492 ng/mL in the recurrent fall group ($P < 0.01$) (Table 4).

3.4. Soluble CAM levels and mortality

3.4.1. Soluble VCAM-1—On survival analysis, the highest quintile of sVCAM-1 was associated with the highest mortality after 1 year (log-rank test, $P < 0.0001$; adjusted hazard ratio 2.4, 95% CI (2.1–2.7); $P = 0.002$) (Fig. 2 and Table 5).

3.4.2. Soluble ICAM-1—We found no significant relationship between the circulating levels of sICAM-1 and mortality.

4. Discussion

In this 5-year prospective cohort study, we explored the relationship between soluble CAM levels and injurious falls in community-dwelling older adults. We found that the highest quintiles of sVCAM-1 and, to some extent, sICAM were associated with the greatest risk of falls over the 5-year period. To the best of our knowledge, these findings are novel, and are consistent with the hypothesis that the sVCAM level is strongly associated with the frequency of injurious falls. In addition, we found that subjects with the highest levels of sVCAM-1 exhibited the highest mortality over the 5 years (Fig. 3).

As populations increasingly age worldwide, it is becoming important to understand how mobility becomes limited and how poor physical performance develops in the elderly. One of the most obvious complications of poor physical performance is an increased risk of falls, which may have tragic consequences. After a hip fracture, for example, the 1-year risk of mortality is nearly 30% (Parker and Johansen, 2006), higher than that after acute myocardial infarction. Overall, poor physical performance is associated with an increased risk of disability, institutionalization, and death (Studenski et al., 2011). The causes of mobility limitations are complex and multifactorial, involving the osteoarticular and cardiovascular systems, sensory abilities, and the central nervous system (Rosso et al., 2013). An increasing number of studies have focused on the roles played by cardiovascular risk factors. Dyslipidemia, diabetes mellitus, and hypertension have all been shown to be associated with poor physical performance (Dumurgier et al., 2010). One possible explanation for the association between cardiovascular risk and poor physical performance involves the role played by cerebral small vessel disease and related brain white matter abnormalities (Soumare et al., 2009; Tchalla et al., 2012, 2015). Cardiovascular risk factors are associated

with cerebral small vessel disease, which impairs brain connectivity and the pathways controlling cognition, balance, and motor function. These associations may be mutually reinforcing, creating a vicious circle: mobility limitations may generate sedentary behavior, which increases cardiovascular risk, and so on.

We previously reported a relationship between cerebral microvascular disease and falls (Tchalla et al., 2012, 2015). Soluble VCAM-1 is a presumptive biomarker of endothelial activation, which is elevated in microvascular disorders. Therefore, we hypothesized that an elevation in sVCAM-1 would be associated with the development of falls and, ultimately, mortality, in older adults. Assay of sVCAM-1 plasma concentrations may help clinicians to plan appropriate measures to prevent progression of cerebral microvascular disease and associated injurious falls. sVCAM-1 promotes the adhesion of inflammatory cells to the vascular endothelial wall, particularly the wall of the cerebral microvasculature, and facilitates the migration of such cells through the endothelium (Kallmann et al., 2000). The mechanistic hypothesis is that sVCAM is associated with cerebral microvascular disease (Tchalla et al., 2012, 2015). sVCAM-1 is an endothelial ligand for integrins expressed on leukocytes and platelets, and it facilitates the endothelial adhesion of circulating leukocytes. Inflammatory cytokines increase endothelial cell expression of VCAM-1 (Constans and Conri, 2006). The soluble ectodomain of VCAM-1 (sVCAM-1) is proteolytically released from the endothelial cell surface into the circulation upon endothelial activation and injury. Elevated plasma sVCAM-1 levels have been reported in many disease conditions, including coronary and peripheral atherosclerosis, hypertension, and diabetes mellitus (Li et al., 1997). sVCAM-1 is now a well-accepted marker of endothelial injury during inflammatory processes.

sVCAM-1 has been implicated in a variety of disorders; its enhanced expression has been suggested to explain the exaggerated microvascular dysfunction associated with hypertension (Mulvihill et al., 2002; Novak et al., 2011).

We previously found that elevated sVCAM-1 levels were associated with an increase in white matter intensity and depressive symptoms (Tchalla et al., 2012, 2015). Cerebral microvascular disease, which often manifests as white matter hyperintensity on brain imaging, has been reported to be associated with slow gait, executive dysfunction, and depressive symptoms (Hajjar et al., 2011). As sVCAM-1 is known to be associated with ischemic injury in, and endothelial dysfunction of, the brain and other areas of the circulation, a relationship between the sVCAM-1 level and the incidence of injurious falls is biologically plausible.

Our study had certain limitations. Some participants had experienced falls before the study commenced, and these falls were thus censored. It is possible that some non-fallers experienced falls before the study began. In addition, all study participants lived within a 5-mile radius of the Institute for Aging Research in Boston, MA, USA; our data may thus not be generalizable. However, a comparison of the demographics of our participants to those of the most recent US Census showed that the distributions by sex and racial group were similar to those aged 70 years and older. sVCAM-1 levels may change over a 5-year period; the baseline values may thus not reflect the state of the vasculature at later times. Rather, a

baseline level may simply predict who is likely to have heart disease and atherosclerosis, and who may therefore fall because s/he is sick and weak, not because the cerebral vasculature has experienced any particular problem. However, the sVCAM-1 concentration may predict a high risk of fall in both the short and long term, independent of the etiology of the elevated concentration. The decision to categorize the distribution of sVCAM-1 using quintiles may be also a limitation, because the cutoffs were not chosen independent of the dataset.

Our study had several strengths. First, the levels of the adhesion molecule sVCAM-1 were comparable to those found in previous studies (Novak et al., 2011). We used longitudinal data and a 5-year follow-up to explore the relationship between sVCAM-1 levels and falls. Also, we previously showed a correlation between sVCAM-1 concentrations and some parameters of blood flow and mobility impairments (Tchalla et al., 2012, 2015). That may explain the association between mortality and increasing risk of falls over 5 years. Finally, our findings may have practical implications for clinicians who may be able in the future to use sVCAM-1 measurements to target older subjects with endothelial dysfunction and a high risk of injurious falls over the following 5-year period.

In summary, we observed a prospective association between sVCAM-1 levels and the number of injurious falls over the subsequent 5 years. This is consistent with the 1-year data that we previously published. Soluble VCAM-1 levels were also strongly associated with mortality. Our findings have several practical implications for clinicians who seek to identify those at high risk of injurious falls and their consequences. Our study suggests that circulating baseline VCAM-1 concentrations are strongly associated with the incidence of injurious falls during the following 5 years. Older adults with elevated VCAM-1 levels should be targeted by clinicians and should receive interventions seeking to prevent subsequent injury and mortality.

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Fig. 1.

Association between the baseline quintiles of plasma concentrations of Vascular Cell Adhesion Molecule-1 (sVCAM-1) and the incidence of injurious falls (N = 679).

Fig. 2.

Association between the baseline quintiles of the plasma concentrations of Vascular Cell Adhesion Molecule-1 (sVCAM-1) and the proportions of deaths over 5 years ($N = 679$).

Fig. 3. Kaplan–Meier survival curve showing the association between the highest baseline quintile of plasma Vascular Cell Adhesion Molecule-1 (sVCAM-1) concentration and deaths (N = 679).

Table 1

Baseline demographics and clinical characteristics of all participants: The MOBILIZE Boston Study. N = 679^a.

Baseline characteristic	Total sample N = 679
Demographics	
Age, mean (SD), years	78.1 ± 5.4
Females	421 (62.0)
Educational achievement, N (%)	
< High school	73 (10.8)
High school graduate/vocational training	277 (40.8)
At least 4 years of college/graduate education	329 (48.5)
White race	545 (83.7)
Body mass index, mean (SD), kg/m ² , ^b	
< 25	213 (31.4)
25–29.9	291 (42.9)
30	175 (25.8)
Medical conditions	
Comorbidity Index, median (IQR)	3 (2–4)
Hypertension	
Controlled hypertensive	365 (54.3)
Uncontrolled hypertensive	164 (24.4)
Systolic hypotension	54 (7.9)
Hyperlipidemia	393 (60.7)
Diabetes	128 (18.9)
Previous stroke	69 (10.2)
Congestive heart failure	34 (5.1)
Slow gait speed, < 0.80 m/s ^f	189 (27.8)
Slow chair stand, > 16.37 s ^g	81 (11.9)
Balance impairment ^e	286 (42.1)
MMSE < 24 ^c	73 (10.8)
Previous injurious fall	111 (16.4%)
Vision impairment	263 (38.7)
Physical activity score ^d	
0–66	210 (31.3)
66.01–124	226 (33.7)
124.01–559	235 (35.0)
Medication	
Any cardiovascular medication	461 (68.5)
Psychotropic medication	46 (6.8)
Biomarker concentrations	

Baseline characteristic	Total sample N = 679
C-reactive protein, mean (SD), mg/L	4 ± 13
Interleukin-6, mean (SD), pg/mL	4 ± 7
Soluble ICAM-1, mean (SD), ng/mL	261 ± 81
Soluble VCAM-1, mean (SD), ng/mL	1192 ± 428

^aMissing values = 1 of 680.

^bBody mass index was calculated as weight in kilograms divided by height in meters squared.

^cMini-Mental State Examination (MMSE) cutoff point for cognitive impairment.

^dPhysical activity tertiles measured using the Physical Activity Scale for the Elderly.

^eBalance score was based on four progressively difficult stands: feet side-by-side, semitandem, tandem, and one leg.

^fSlower gait speed (m/s) is the lowest 25% of all time spans required to complete two usually paced 4-m walks.

^gHighest quartile (slowest performance) of time spans required to complete five repeated chair stands.

Table 2

Rate ratios (95% confidence intervals) for the associations between quintiles of baseline sVCAM-1[‡] and the rate of injurious falls over a 5-year interval. N = 668[‡].

No.	Quintiles of sVCAM-1; median (IQR), ng/mL					P for trend
	736 (660–810)	937 (899–970)	1115(1071–1169)	1332 (1277–1389)	1711 (1567–2011)	
Model 1	132	134	136	134	136	
Incidence Rate Ratio (IRR)	1.0	1.1	1.0	1.4	2.0	
(95% CI)	Reference	(0.7, 1.8)	(0.6, 1.7)	(0.9, 2.3)	(1.3, 3.1)	
P value	-	0.64	0.97	0.14	0.002	0.0001
Model 2						
Incidence Rate Ratio (IRR)	1.0	1.1	1.0	1.4	1.9	
(95% CI)	Reference	(0.7, 1.9)	(0.6, 1.6)	(0.9, 2.3)	(1.2, 3.0)	
P value	-	0.62	0.99	0.15	0.003	0.0001
Model 3						
Incidence Rate Ratio (IRR)	1.0	1.1	1.0	1.3	1.8	
(95% CI)	Reference	(0.7, 1.8)	(0.6, 1.6)	(0.8, 2.2)	(1.1, 2.8)	
P value	-	0.67	0.89	0.24	0.013	0.0102
Model 4						
Incidence Rate Ratio (IRR)	1.0	1.2	1.0	1.4	1.9	
(95% CI)	Reference	(0.72, 1.93)	(0.6, 1.7)	(0.9, 2.3)	(1.2, 2.9)	
P value	-	0.51	0.88	0.19	0.009	0.0341

Abbreviations:

[‡]sVCAM-1: soluble vascular cell adhesion molecule-1; CI, confidence interval; IQR, interquartile range.

[‡]Missing values: 8 of 680;

* Model 1 = Model without adjustments;

** Model 2 = Model 1 adjusted for IL6 and C-reactive protein levels;

*** Model 3 = Model 2 additionally adjusted for age, gender, white race, educational level, body mass index, current smoking, and alcohol use;

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Model 4 = Model 3 additionally adjusted for previous falls, diabetes, hypertension, orthostatic hypotension, stroke, congestive heart failure, coronary artery disease, hyperlipidemia, cognitive status, depression, any cardiovascular medication, psychotropic medication, comorbidity index, and physical activity level.

Rate ratios (95% confidence intervals) for the association between quintiles of baseline sICAM-1[‡] and the rate of injurious falls over a 5-year period. N = 668[‡].

Table 3

		Quintiles of sICAM-1; median (IQR), ng/mL					P for trend
		179 (148–196)	224 (215–230)	253 (245–260)	284 (276–295)	353 (325–402)	
No.		132	135	135	132	134	
Model 1							
Incidence Rate Ratio (IRR)	1.0	0.8	1.0	1.0	1.2	1.8	
(95% CI)	Reference	(0.5, 1.3)	(0.6, 1.5)		(0.7, 1.8)	(1.2, 2.7)	
P value	-	0.4	0.9	0.5	0.006	0.0001	
Model 2							
Incidence Rate Ratio (IRR)	1.0	0.8	1.0	1.0	1.1	1.7	
(95% CI)	Reference	(0.5, 1.3)	(0.6, 1.5)		(0.7, 1.8)	(1.1, 2.5)	
P value	-	0.4	0.8	0.6	0.02	0.0001	
Model 3							
Incidence Rate Ratio (IRR)	1.0	0.8	0.9	0.9	1.2	1.6	
(95% CI)	Reference	(0.5, 1.4)	(0.6, 1.5)		(0.7, 1.8)	(1.1, 2.5)	
P value	-	0.5	0.8	0.5	0.02	0.0026	
Model 4							
Incidence Rate Ratio (IRR)	1.0	0.9	0.9	0.9	1.3	1.6	
(95% CI)	Reference	(0.5, 1.4)	(0.6, 1.5)		(0.7, 1.8)	(1.1, 2.5)	
P value	-	0.7	0.8	0.6	0.03	0.0168	

Abbreviations:

[‡]sVCAM-1: soluble vascular cell adhesion molecule-1; CI, confidence interval; IQR, interquartile range.

[‡]Missing values: 8 of 680;

* Model 1 = Model without adjustments;

** Model 2 = Model 1 adjusted for IL6 and C-reactive protein levels;

*** Model 3 = Model 2 additionally adjusted for age, gender, white race, educational level, body mass index, current smoking, and alcohol use;

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Model 4 = Model 3 additionally adjusted for previous falls, diabetes, hypertension, orthostatic hypotension, stroke, congestive heart failure, coronary artery disease, hyperlipidemia, cognitive status, depression, any cardiovascular medication, psychotropic medication, comorbidity index, and physical activity level.

Table 4

Biomarker concentrations by the rate of falls (no fall, one fall, and recurrent [2] falls) over a 5-year period. N = 668[‡].

Biomarker	No fall	One fall	Recurrent falls	P-value[‡]
	201 (30.1%)	308 (46.1%)	159 (23.8%)	
C-reactive protein, mean (SD), mg/L	3.30 ± 13	3.42 ± 15	4.8 ± 5	< 0.01
Interleukin-6, mean (SD), pg/mL	3.33 ± 7	4.1 ± 8	4.2 ± 5	<0.01
Soluble ICAM-1, mean (SD), ng/mL	262 ± 78	259 ± 74	261 ± 87	0.80
Soluble VCAM-1, mean (SD), ng/mL	1094 ± 438	1195 ± 445	1270 ± 330	<0.01

Abbreviations: *VCAM-1*: vascular cell adhesion molecule-1; *ICAM-1*: Intercellular Adhesion Molecule-1;

[‡]Missing values = 12 of 680.

[‡]Analysis of variance for continuous variables.

Table 5

Adjusted hazard ratios for 5-year mortality, N = 654[†], Events = 67, Censored 587 (86.76%).

	Hazard ratio	95% confidence interval	P-value
sVCAM-1 as a continuous variable			
sVCAM-1 ng/mL (log)*	2.3	(1.9, 2.7)	0.03
sICAM-1 ng/mL (log)	0.6	(0.2, 1.1)	0.34
IL6 pg/mL (log)	1.4	(1.2, 1.6)	0.04
hsCRP mg/L (log)	1.0	(0.9, 1.1)	0.89
sVCAM-1 as a binary variable			
Highest quintile (q5) of sVCAM-1**	2.4	(2.1, 2.6)	0.002
Lowest quintiles (q1 to q4) of sVCAM-1	1.0	Reference	-

Abbreviations: *sVCAM-1*: soluble vascular cell adhesion molecule-1;

^{*}*sICAM-1*: soluble intercellular adhesion molecule-1; IL6: Interleukin-6; hsCRP: High sensitivity C-reactive protein;

[†]Missing values = 26 from 680; Adjusted for IL6 and C-reactive protein levels; age, gender, white race, educational level, body mass index, current smoking, alcohol use; previous falls, diabetes, hypertension, orthostatic hypotension, stroke, congestive heart failure, coronary artery disease, hyperlipidemia, cognitive status, depression, any cardiovascular medication, psychotropic medication, comorbidity index, and physical activity level.