Published in final edited form as:
J Crit Care. 2013 October ; 28(5): . doi:10.1016/j.jcrc.2012.11.002.

Inflammatory and Endothelial Activation Biomarkers and Risk of Sepsis: A Nested Case-Control Study

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Abstract

PURPOSE—Elevated biomarkers of inflammation and endothelial cell activation have been associated with severity of sepsis. We sought to determine the association between these baseline markers and subsequent episodes of sepsis.

MATERIALS AND METHODS—We performed a nested case-control analysis using subjects from the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. We compared 162 sepsis cases (hospitalized for a serious infection with two or more systemic inflammatory response syndrome criteria) with 162 non-sepsis controls (hospitalized for a serious infection but not sepsis) matched by age, sex and observation time epoch. Using conditional logistic regression, we evaluated the associations between sepsis and baseline levels of interleukin-6 (IL-6), tumor necrosis factor (TNF-α), E-selectin, inter-cellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), adjusting for smoking status, hypertension and chronic kidney disease.

RESULTS—Compared with controls, individuals with higher baseline IL-6, E-Selectin and ICAM-1 were more likely to develop sepsis (p-trend 0.02, 0.02, 0.04). Baseline TNF-α and ICAM-1 were not associated with future sepsis (p-trend 0.29, 0.33).

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COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS
HEW, NIS, MMS and GH designed the study. HEW, SJ, MMS and GH coordinated data collection. HEW and RG performed the analysis, and all authors reviewed the results. HEW drafted the manuscript, and all authors contributed to its critical review. HEW assumed responsibility for the paper as a whole.

CONCLUSIONS—Individuals with higher baseline IL-6, E-Selectin and ICAM-1 were more likely to develop future sepsis episodes. These biomarkers may play a role in the early characterization, mitigation or prevention of sepsis.

Keywords

sepsis; infections; biomarkers; inflammation; endothelium

INTRODUCTION

Sepsis, the clinical syndrome arising from systemic inflammatory response to microbial infection, is a major public health problem resulting in over 750,000 hospitalizations, 570,000 Emergency Department visits and 215,000 deaths each year in the United States.[1–3] To identify therapeutic targets, predict the clinical course of patients, and develop an improved understanding of disease mechanisms, numerous studies have evaluated biomarkers associated with the sepsis pathophysiologic process. For example, in a cohort of 1,886 subjects hospitalized for community-acquired pneumonia, Kellum, et al. observed that inflammatory cytokines (interleukin-6, interleukin-10, tumor necrosis factor-α) were higher in individuals that developed severe sepsis or septic shock.[4] Recent attention has focused on the role of endothelial activation and dysfunction in sepsis pathophysiology.[5,6] In a prospective observational study of 221 adult patients presenting to the Emergency Department with a serious infection, Shapiro, et al. found associations between biomarkers of endothelial cell activation and sepsis severity.[7]

Inflammation and endothelial activation are prominent components of sepsis pathophysiology.[4,5] While prior investigations have demonstrated associations between acute inflammation and acute endothelial dysfunction/activation with sepsis outcomes, the links between chronic baseline inflammation and endothelial cell activation/dysfunction with increased susceptibility to sepsis have not been studied. Identification of biomarker abnormalities at baseline – prior to the onset of disease – could have utility in sepsis management, differentiating those at heightened risk of developing sepsis after a serious infection. This knowledge could lead to strategies to prevent the onset of or mitigate the consequences of sepsis. A population-based cohort study with biomarker measurements at baseline is necessary to evaluate the predictive properties of biomarkers in this manner.

In this nested case-control study conducted within a large prospective cohort study, we sought to determine the association between baseline markers of inflammation and endothelial cell activation and the subsequent development of sepsis.

METHODS

Study Design

This study was approved by the Institutional Review Board of the University of Alabama at Birmingham. The larger study utilized a population-based longitudinal cohort design using the national REasons for Geographic and Racial Disparities in Stroke (REGARDS) cohort. For this biomarker study we performed a matched case-control analysis using a selection of subjects of the REGARDS cohort.

The REGARDS Cohort

Containing 30,239 individuals ≥45 years old from across the United States, REGARDS is one of the largest ongoing national cohorts of community-dwelling individuals in the United States.[8] Designed to evaluate geographic and black-white stroke mortality variations,

REGARDS encompasses representation from all regions of the continental US, with emphasis on participants from the Southeastern US. The cohort consists of 41% African Americans, 45% men, and 69% individuals over 60 years old. By design the cohort does not include Hispanics.

The REGARDS study obtained baseline information on each participant from structured interviews and in-home visits. Baseline data includes physical characteristics (height, weight), physiology (blood pressure, pulse, electrocardiogram), diet, family history, psychosocial factors and prior residences, as well as biological specimens (blood, urine, etc.). The study contacts each participant on a semi-annual basis to determine the date, location and attributed reason for all hospitalizations during the prior 6 months. Upon participant death, the study interviews proxies to ascertain the circumstances of the death events. Follow-up on participants in this manner has occurred since 2003.

Identification of Sepsis Events

We identified and reviewed all reported hospitalizations attributed to a serious infection during the observation period February 5, 2003 – October 14, 2011. Definitions for serious infection were based upon previously published taxonomies.[1] Two trained abstractors independently reviewed all relevant medical records to confirm 1) the presence of a serious infection on initial hospital presentation, and 2) the relevance of the serious infection as a major reason for hospitalization. The abstractors identified clinical and laboratory information for the first 28-hours of hospitalization to allow for care received in the Emergency Department as well as the first 24-hours of inpatient care.

We defined sepsis using the international consensus definition, consisting of presentation to the hospital with an infection plus two or more systemic inflammatory response syndrome (SIRS) criteria.[9] SIRS criteria included 1) heart rate >90 beats/minute, 2) fever (temperature >38.3°C or <36°C), 3) tachypnea (>20 breaths/min) or PCO_2<32 mmHg, and 4) leukocytosis (white blood cells >12,000 or <4,000 cells/mm^3 or >10% bands). We defined presentation to the hospital as the time of Emergency Department triage or admission to inpatient unit (for participants admitted directly to the hospital). To account for acute changes in the participant's condition during early hospitalization, we used vital signs and laboratory test results for the first 28-hours of hospitalization. We did not include vital signs or laboratory findings at later time points of hospitalization, nor sepsis developing at later time periods as a result of other major illness. For this analysis, we did not include organ dysfunction in the definition of sepsis.

Abstractors resolved all data discordances by consensus review with additional physician-level adjudication as needed. Initial review of 1,349 hospital records indicated excellent inter-rater agreement for the presence of a serious infection (kappa=0.92) and the presence of sepsis (kappa=0.90).

Selection of Sepsis Cases and Non-Sepsis Controls

This study utilized a nested case-control design. For cases, we randomly selected individuals that experienced a hospitalization for sepsis during the observation period. To avoid bias due to secular trends, we divided the observation period into 2-year time epochs, selecting an even number of cases in each period. We selected controls from individuals that did not experience a hospitalization for sepsis, matching for age (±5 years), sex and time epoch. We sampled cases and controls with replacement; therefore, an individual developing sepsis at a later time epoch could be selected as a control for an earlier time epoch.

While the original matching strategy called for 300 sepsis cases and 300 non-sepsis matched controls, the controls were heterogeneous, including individuals hospitalized for a serious

infection (but not meeting sepsis criteria) as well as individuals hospitalized for conditions unrelated to infections. Because we were most interested in differentiating those at risk of developing sepsis from those at risk for developing infection, we limited the analysis to the 162 non-sepsis controls that were hospitalized for a serious infection (but did not meet sepsis criteria) and their corresponding 162 matched sepsis cases.

Selection and Determination of Biomarkers

The selection of biomarkers for this analysis was based upon a variety of considerations including biological plausibility, prior supportive evidence, the availability of assays, sample volume requirement and the accuracy of assays given the long-term storage of the study serum samples. Because of the pilot nature of this study, we chose to focus on markers of inflammation and endothelial cell activation, which are prominent in sepsis pathophysiology. Selected biomarkers include baseline interleukin-6 (IL-6), tumor necrosis factor (TNF-α), soluble endothelium selectin (E-Selectin – also known as endothelial-leukocyte adhesion molecule 1 (ELAM)), inter-cellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). These biomarkers have been associated with inflammatory response and endothelial cell activation.[7,10] Because of the pilot nature of this effort, we did not evaluate other markers of inflammation or endothelial cell activation such as interleukin-10, soluble fms-like tyrosine kinase-1 (sFlt-1) or plasminogen activator inhibitor-1 (PAI-1).

All biomarker samples were obtained at the participant's enrollment examination at the beginning of the REGARDS study. Trained personnel collected blood samples from all REGARDS participants at subjects' homes following a 10–12 hour fast. Samples were centrifuged and serum or plasma separated within 2 hours of collection (mean 97 minutes, SD 127 minutes) and shipped overnight on ice packs to the central laboratory at the University of Vermont. Overnight shipping of samples was achieved for 95% of the cohort. On arrival, samples were centrifuged at 30,000*g* and 4°C, and either analyzed (general chemistries) or stored at −80°C. REGARDS enrollment examinations occurred during 2003–2007.

Biomarker measurements were accomplished using commercial kits. For IL-6 we used the HS ELISA kit (R&D Systems, Minneapolis, Minnesota). For TNF-α, we used a Millipore Singleplex system (Millipore, Billerica, Massachusetts, USA). For E-Selectin, ICAM-1 and VCAM-1 we used Millipore multiplex assays (Cardiovascular Panel 1, Millipore, Billerica, Massachusetts, USA). All assays were performed in duplicate, with the average value used in the analysis. Assays were performed by the Laboratory for Clinical Biochemistry Research at the University of Vermont.

Covariates

Covariates evaluated in the analysis included demographics (age, sex, race, education, income), health behaviors (tobacco and alcohol use) and chronic medical conditions (hypertension, diabetes, dyslipidemia, coronary artery disease, atrial fibrillation, myocardial infarction, stroke, deep vein thrombosis, peripheral artery disease and chronic kidney disease). We defined tobacco use as current, past and never. We defined alcohol use according to the National Institute on Alcohol Abuse and Alcoholism classification; i.e., moderate (1 drink per day for women or 2 drinks per day for men) and heavy alcohol use (>1 drink per day for women and >2 drinks per day for men).[11]

Hypertension consisted of individuals with systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive agents. Diabetes included individuals with a fasting glucose ≥126 mg/dL, a non-fasting glucose ≥200 mg/dL, or the

use of insulin or oral hypoglycemic agents. Dyslipidemia included individuals with self-reported high cholesterol or the use of lipid lowering medications. Heart disease consisted of individuals with a self-reported history of myocardial infarction, coronary artery bypass grafting, or cardiac angioplasty or stenting, or baseline electrocardiographic evidence of myocardial infarction. Atrial fibrillation was based upon participant self-report or baseline electrocardiographic evidence. Participants self-reported the prior history of stroke (including transient ischemic attacks) or deep vein thrombosis. Peripheral artery disease consisted of self-reported history of lower extremity arterial bypass or leg amputation. Chronic kidney disease included individuals with an estimated glomerular filtration rate <60 ml/min/1.73 m2, calculated using the CKD-EPI equation and based upon baseline serum creatinine.[12]

We defined infection types as lung (pneumonia, bronchitis, etc), kidney (urinary tract infection, pyelonephritis, genitourinary infections), abdominal (perforated viscus, pancreatitis, cholecystitis, peritonitis, etc) and other.

Data Analysis

We compared subject characteristics between sepsis cases and non-sepsis controls using paired t-tests and McNemar's Q. We evaluated the associations between baseline biomarker levels and sepsis using conditional logistic regression, dividing each biomarker level into quartiles. For multivariable adjustment, we selected demographics, health behaviors and conditions found to be statistically significant on univariable analysis. Because they are more likely effect modifiers than true confounders, in a sensitivity analysis, we examined the additional effect of infection type upon the associations between each biomarker and sepsis, adding a main and [infection type X biomarker] interaction term to the multivariable model.

RESULTS

Among the 30,239 REGARDS participants, from February 5, 2003 through October 14, 2011 we identified 1,677 hospitalizations for serious infection, of which 940 met sepsis criteria. We included 162 sepsis cases and 162 matched non-sepsis controls (individuals hospitalized for a serious infection but not meeting sepsis criteria). There were no differences in baseline race, education, and income between cases and controls. (Table 1) While cases and controls reported similar frequencies of alcohol use, cases were nearly twice as likely to be current smokers. While the prevalence of most conditions were similar between cases and controls, cases were more likely to have hypertension and chronic kidney disease. Baseline levels of IL-6, TNF-α, E-Selectin and VCAM-1 were higher for cases than controls. (Table 2)

When examining the associations between baseline biomarker levels and sepsis, after adjusting for smoking status, hypertension and chronic kidney disease, higher baseline IL-6 levels were associated with increased odds ratios for sepsis. (Table 3) Higher E-Selectin and ICAM-1 levels were also associated with adjusted increased odds ratios for sepsis. Baseline TNF-α and VCAM-1 levels were not associated with sepsis.

In the sensitivity analysis, we added infection type and an [infection type X biomarker] term to each multivariable model. (Appendix) The relationship between each biomarker and sepsis were similar, although the association with ICAM-1 was no longer statistically significant.

DISCUSSION

Inflammation and endothelial cell activation may play important roles in sepsis pathophysiology.[4–6] The results of our preliminary study suggest that select biomarkers measured at baseline are potentially associated with future sepsis episodes. While pilot in nature, our findings suggest that biomarkers may play an important role in facilitating pre-illness risk detection, differentiating those who will develop a mild response to infection from those who will develop frank sepsis. If validated, these findings may lead to strategies that may allow for measures to mitigate or prevent the effects of sepsis. For example, the biomarkers might be used for heightened surveillance or monitoring, limitation of exposure to bacterial pathogens, earlier antimicrobial therapy at the initial stages of infection, or aggressive resuscitative care at the earliest signs of sepsis. Certain biomarkers might also prove viable as therapeutic targets.[6]

In this study, we observed associations between baseline levels of IL-6 and the risk of sepsis. One possible explanation is that baseline elevation of IL-6 may indicate individuals prone to developing a hyper-inflammatory or dysfunctional response to microbial infection. This connection is plausible given that IL-6 is a marker of inflammation in sepsis, and prior studies have linked this biomarker with infection risk.[4] For example, in a study utilizing the Health ABC cohort, Yende, et al. observed associations between pre-infection circulating IL-6 and TNF-α and subsequent pneumonia.[10] The biomarkers may also reflect behavioral, environmental or chronic medical conditions that collectively weaken or alter immune response. For example, Sunyer, et al. identified an interaction between smoking tobacco use and the gene for IL-6.[13] The biomarkers may also signal individuals at risk for a range of illnesses, of which sepsis is one condition.

We also observed associations between E-selectin and ICAM-1 and the subsequent risk of sepsis. The endothelium plays a prominent role in immune response and sepsis pathophysiology, facilitating leukocyte trafficking, activation of coagulation and increased vascular leakage.[5,7] Elevation of these endothelial cell activation biomarkers have been observed during acute sepsis. Shapiro, et al. previously demonstrated elevation of endothelial cell activation markers in proportion to the severity of acute sepsis.[7] However, the serum samples in this study were obtained while individuals were in a stable phase of health, prior to the onset of sepsis. In this context the elevated biomarkers may indicate individuals that are prone to endothelial dysfunction in the face of acute infection. In the Atherosclerosis Risk in Communities (ARIC) Study, Hwang, et al. found that baseline plasma E-Selectin and ICAM-1 were associated with increased risk of coronary heart disease, supporting the potential connection between baseline endothelial activation biomarker levels and future disease episodes.[14]

The findings of this study highlight unanswered questions regarding sepsis pathophysiology. In general, biomarkers may act as diagnostic or prognostic markers or as targets for therapy.[15] An important question is whether blocking the production of these cytokines could attenuate sepsis risk. Genetic polymorphisms have been identified for the secretion of IL-6 and TNF-α; these polymorphisms may prove useful for screening or as therapeutic targets for altering host response to infection and sepsis.[16] Teoh, et al. demonstrated attenuation of sepsis response using BRCA1 adenovirus therapy.[17] We note that we did not observe associations between baseline TNF-α and VCAM-1 and future sepsis events. An enhanced understanding of these and other aspects of sepsis pathophysiology could lead to new strategies influencing sepsis care.

Limitations

Because of limited resources, we focused upon a select array of biomarkers involving only a portion of the full REGARDS person cohort. An ideal study would encompass biomarker analysis of all 30,329 subjects in the cohort. However, our preliminary study lays the foundation for a more comprehensive examination of a broader range of biomarkers and mechanisms. There are other important markers of inflammation and endothelial cell activation such as fms-like tyrosine kinase (sFlt-1) and plasminogen activator inhibitors (PAI-1).[5] Other potentially important markers of general inflammation such as C-reactive protein may also play an important role.[18] Genomic analysis is also a natural target for future investigation, potentially identifying polymorphisms leading to the aberrant cellular response. Our study examined only a single biomarker level at the beginning of the REGARDS study. Repeat blood and serum samples are not yet available for REGARDS participants.

While we did not examine sepsis severity variants (-e.g., severe sepsis, septic shock, sepsis death), our study is relevant to these more advanced stages because it identifies individuals at the earliest stages of disease. We also did not study the hospital course of sepsis or repeat sepsis events. Community level factors such as quality of care or antimicrobial resistance may potentially influence sepsis risk, but these factors were beyond the scope of this analysis. Due to the limited available sample size, we did not examine other potential confounders such as medication use. Our observations demonstrate associations between baseline biomarkers and future sepsis events, but do not indicate relevant clinical actions or therapeutic strategies.

Because we relied on participant reports of hospitalizations, recall or reporting biases may have resulted in under-identification of sepsis events. However, our approach utilized prospective, systematic, dual review of hospital records using consensus definitions. By design, the REGARDS cohort contains only African Americans and whites, and thus we could not examine or account for associations with other racial groups or Hispanic ethnicity.

CONCLUSION

In this study we observed that episodes of sepsis were associated with baseline levels of select inflammatory and endothelial cell signaling biomarkers. Biomarkers at healthy baseline may potentially play a role in the characterization, mitigation or prevention of sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FINANCIAL SUPPORT AND ACKNOWLEDGEMENTS

This study was supported by R01-NR012726 from the National Institute for Nursing Research, UL1-RR025777 from the National Center for Research Resources, and grants from the Center for Clinical and Translational Science and the Lister Hill Center for Health Policy of the University of Alabama at Birmingham.

The parent REGARDS study was supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health. Representatives of the funding agency have been involved in the review of the manuscript but not directly involved in the collection, management, analysis or interpretation of the data.

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

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TABLE 1

Comparison of demographic, substance use, and comorbidity characteristics between sepsis cases and matched controls. Cases and controls were matched by age (±5 years), sex and follow-up time (2-year epochs).

Characteristic	Sepsis Cases (N=162)	Non-Sepsis Controls (N=162)	p-value†
DEMOGRAPHICS			
Age (mean ± SD)	70.3 ± 9.3	70.3 ± 9.2	0.18
Gender (%)			
Male	50.6	46.9	0.51
Female	49.4	53.1	
Race (%)			
White	73.5	77.2	0.44
Black	26.5	22.8	
Education (%)			
Less than high school	22.2	14.8	0.19
High school graduate	22.2	30.9	
Some college	29.0	29.6	
College or higher	26.5	24.7	
Income (%)			
<$20k	31.6	20.4	0.93
$20k–$34k	29.0	33.3	
$35k–$74k	28.4	25.3	
≥$75k	8.6	9.3	
Refused	12.3	11.7	
SUBSTANCE USE			
Tobacco Use (%)			
Current	21.6	8.6	0.005
Past	47.5	51.2	
Never	30.9	40.1	
Alcohol Use (%)			
Heavy	4.5	3.8	0.21
Moderate	33.1	24.5	
None	62.4	71.7	
MEDICATIONS			
Statins	40.1	47.5	0.18
Aspirin	53.1	46.3	0.21
CHRONIC MEDICAL CONDITIONS			
Hypertension (%)	69.4	59.0	0.05
Diabetes (%)	31.3	27.0	0.41
Dyslipidemia (%)	47.8	41.4	0.25
Coronary Artery Disease (%)	32.3	36.3	0.45
Atrial Fibrillation (%)	14.5	11.9	0.51

Characteristic	Sepsis Cases (N=162)	Non-Sepsis Controls (N=162)	p-value†
Myocardial Infarction (%)	18.0	19.5	0.73
Stroke (%)	11.1	10.6	0.89
Deep Vein Thrombosis (%)	8.1	9.3	0.71
Peripheral artery disease (%)	6.2	3.1	0.19
Chronic Kidney Disease (%)	44.4	31.1	0.01
INFECTION TYPE			
Lung	66.5	45.3	0.004
Kidney	11.4	18.6	
Abdominal	10.1	13.1	
Other	12.0	23.0	

† Estimated from paired t-test and McNemar's Q for continuous and categorical variables, respectively.

TABLE 2

Baseline inflammatory and endothelial activation biomarker levels. Cases and controls were matched by age (±5 years), sex and follow-up time (2-year epochs).

Characteristic	Sepsis Cases (N=162)	Non-Sepsis Controls (N=162)	p-value*
IL-6 (pg/mL)	4.3 ± 2.6	3.5 ± 2.3	0.009
TNF-α (pg/mL)	6.9 ± 5.3	5.8 ± 3.6	0.0498
E-Selectin (ng/mL)	51.7 ± 25.5	43.9 ± 17.4	0.003
ICAM-1 (ng/mL)	165.1 ± 71.1	151.9 ± 59.0	0.08
VCAM-1 (ng/mL)	1236.2 ± 300.7	1165.7 ± 288.3	0.04

*Estimated from paired t-test.

TABLE 3

Odds ratios and 95% confidence intervals for the associations between baseline biomarker levels and sepsis. Cases and controls were matched by age (±5 years), sex and follow-up time (2-year epochs).

Biomarker	Sepsis Cases (%) N=162	Non-Sepsis Controls (%) N=162	Crude Odds Ratio (95% CI)	Odds Ratio Adjusted for Smoking (95% CI)	Odds Ratio Adjusted for Smoking, Hypertension and Chronic Kidney Disease (95% CI)	p-value for trend
IL-6						
≤ 1.92 pg/mL	12.2	27.7	Ref	Ref	Ref	0.02
>1.92 to 3.02	25.0	23.0	2.96 (1.34–6.51)	2.70 (1.19–6.11)	2.31 (1.01–5.30)	
>3.02 to 4.73	32.1	24.3	3.07 (1.45–6.47)	2.74 (1.28–5.86)	2.40 (1.11–5.19)	
>4.73	30.8	25.0	3.60 (1.65–7.87)	3.21 (1.44–7.14)	2.84 (1.26–6.43)	
TNF-α						
≤ 3.99 pg/mL	21.0	31.1	Ref	Ref	Ref	0.29
>3.99 to 5.19	26.8	21.6	1.66 (0.85–3.27)	1.90 (0.93–3.89)	1.70 (0.82–3.55)	
>5.19 to 7.31	19.7	27.7	0.89 (0.46–1.74)	0.92 (0.46–1.85)	0.80 (0.38–1.65)	
>7.31	32.5	19.6	2.21 (1.17–4.17)	2.24 (1.16–4.33)	1.84 (0.93–3.67)	
E-Selectin						
≤ 34.52 ng/mL	22.3	29.9	Ref	Ref	Ref	0.02
>34.52 to 44.15	23.6	26.5	1.15 (0.61–2.19)	1.12 (0.58–2.15)	1.04 (0.53–2.05)	
>44.15 to 56.22	22.9	27.2	1.16 (0.60–2.26)	1.20 (0.60–2.39)	1.16 (0.57–2.34)	
> 56.22	31.2	16.3	2.57 (1.31–5.05)	2.58 (1.28–5.21)	2.29 (1.11–4.71)	
ICAM-1						
≤ 123.26 ng/mL	22.9	29.1	Ref	Ref	Ref	0.04
> 123.26 to 149.56	21.6	29.1	0.84 (0.43–1.65)	0.95 (0.48–1.90)	1.16 (0.56–2.39)	
> 149.56 to 177.1	23.6	24.3	1.07 (0.57–2.01)	1.16 (0.61–2.23)	1.27 (0.64–2.51)	
> 177.1	31.8	17.6	2.12 (1.13–3.99)	1.88 (0.97–3.64)	2.09 (1.05–4.15)	
VCAM-1						
≤ 1003.65 ng/mL	18.5	29.1	Ref	Ref	Ref	0.33
>1003.65 to 1173.66	29.9	24.3	1.71 (0.86–3.41)	1.60 (0.79–3.25)	1.65 (0.79–3.42)	
>1173.66 to 1348.53	24.8	23.6	1.40 (0.74–2.67)	1.21 (0.62–2.36)	1.16 (0.58–2.29)	
> 1348.53	26.8	23.0	1.72 (0.88–3.34)	1.75 (0.87–3.54)	1.65 (0.80–3.44)	