Online Data Supplement to:

Inflammation and Coagulation during Critical Illness and Long-Term Cognitive Impairment and Disability

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1. Methods

a. Inclusion and exclusion criteria for the BRAIN-ICU and MIND-ICU studies

Inclusion Criteria

Patients were eligible for inclusion if they were treated in the medical or surgical intensive care units (ICU) at Vanderbilt University Medical Center (Nashville, TN, USA), Saint Thomas Hospital (Nashville, TN, USA), Department of Veterans Affairs (VA) Tennessee Valley Healthcare System (Nashville, TN, USA), the George E. Wahlen Department of Veterans Affairs Medical Center (Salt Lake City, UT, USA), and the VA Puget Sound Health Care System (Seattle, WA, USA) for respiratory failure or shock.

Respiratory failure was defined as receiving any of the following treatments: invasive mechanical ventilation, noninvasive positive pressure ventilation, continuous positive airway pressure, supplemental oxygen via a nonrebreather mask, or nasal cannula delivering heated high-flow oxygen.

Cardiogenic shock was defined as treatment with an intra-aortic balloon pump or any of the following medications administered for acute cardiac dysfunction: dopamine ≥ 7.5mcg/kg/min, dobutamine ≥ 5 mcg/kg/min, norepinephrine ≥ 5 mcg/min, phenylephrine ≥ 75 mcg/min, epinephrine at any dose, milrinone at any dose (if used with another vasopressor), or vasopressin ≥ 0.03 units/min (if used with another vasopressor).

Septic shock was defined as treatment for suspected or proven infection

documented in the medical record in the setting of hypotension being treated with any of the above medications.

Patients who were on long-term ventilatory support prior to their acute illness that resulted in the hospitalization qualified for enrollment in this study if they met criteria for shock (as defined above) or they had a new onset of respiratory failure, defined as either an increase of pressure support of 5 cms H_2O or positive end expiratory pressure of 2 cms H_2O from the patient's baseline ventilatory settings.

Exclusion Criteria

Patients who met inclusion criteria were excluded if they meet any of the following criteria:

i. Cumulative ICU time > 5 days in the past 30 days, not including the current ICU stay, as this might create a state of flux regarding patients' cognitive baseline

ii. Severe cognitive or neurodegenerative diseases that prevent a patient from living independently at baseline, including mental illness requiring institutionalization, acquired or congenital mental retardation, known brain lesions, traumatic brain injury, cerebrovascular accidents with resultant moderate to severe cognitive deficits or ADL disability, Parkinson's disease,

Huntington's disease, severe Alzheimer's disease or dementia of any etiology

iii. ICU admission post cardiopulmonary resuscitation with suspected anoxic injury

iv. An active substance abuse or psychotic disorder, or a recent (within the past 6 months) serious suicidal gesture necessitating hospitalization. This exclusion will enrich follow-up rates by avoiding patients with whom it is particularly challenging to maintain long-term contact

v. Blind, deaf, or unable to speak English, as these conditions would preclude our ability to perform the follow-up evaluation interviews.

vi. Moribund and not expected to survive for an additional 24 hours and / or withdrawing life support to focus on comfort measures only.

vii. Prisoners

viii. Patients who live further than 200 miles from an enrolling center and who do not regularly visit the center.

ix. Patients who are homeless and have no secondary contact person available. This exclusion will enrich follow-up rates by

avoiding patients with whom it is particularly challenging to maintain long-term contact

x. The onset of the current episode of respiratory failure, cardiogenic shock, or septic shock was > 72 hours ago.

xi. Patients who have had cardiac bypass surgery within the past 3 months (including the current hospitalization)

b. Summary of the BRAIN-ICU and MIND-ICU protocols

i. Each day, study personnel screened the census of the medical and surgical ICUs at the 5 enrolling sites (Vanderbilt University Medical Center, Nashville, TN, USA; Saint Thomas Hospital, Nashville, TN, USA; Tennessee Valley Veterans Affairs Medical Center, Nashville, TN, USA; George Whalen Veterans Affairs Medical Center, Salt Lake City, UT, USA; and Puget Sound Veterans Affairs Medical Center, Seattle, WA, USA).

ii. At enrollment, study personnel collected baseline information including sociodemographics, comorbid medical conditions, and baseline cognitive function. Enrolled patients were followed daily in the hospital until they were discharged (or for up to 30 days). Each day, study personnel collected detailed physiologic and medication data used to calculate the covariates described below including corticosteroid prescriptions, severe sepsis, daily severity of illness scores, and mean daily doses of sedatives and opiates.

c. Cognitive screening at enrollment in BRAIN-ICU and MIND-ICU studies

i. To assess pre-existing cognitive impairment, we used the validated Short Form Informant Questionnaire On Cognitive Decline in the Elderly (Short IQCODE) for patients >50 years of age and for patients <50 years but with known memory problems. The IQCODE is a questionnaire that was developed to identify and quantify cognitive decline using an informant, and it has been repeatedly shown to be effective in identifying the presence of significant cognitive impairment in medical populations and in elderly populations. The Short IQCODE consists of a series of 16 questions that are answered by a surrogate with intimate knowledge of the participant. The questions prompt the surrogate to compare the participant's present (or, in the case of this study, pre-ICU) cognitive abilities with those 10 years prior. A score of 1 on a question denotes much improvement, a 3 denotes not much change, and a 5 denotes much worse performance. The total score on the 16 questions is then divided by 16 to generate a score ranging from 1 to 5, with higher scores denoting worsening cognitive function. Participants who scored > 3.3 on the Short IQCODE, and therefore had suspected cognitive impairment, were also assessed with the Clinical Dementia Rating (CDR) Scale.

The CDR is a numeric rating scale used to quantify the severity of dementia symptoms via the use of a structured clinical interview. Individuals are classified across a total of 5 stages (0, 0.5, 1, 2, 3) ranging from "no impairment" to "severe dementia" based on cognitive and

functional performance in areas including memory, orientation/judgment and problem solving, community affairs, home and hobbies, and personal care. Those with a CDR score >2, suggestive of severe dementia, were excluded, while those with a CDR of <2, suggestive of mild to moderate pre-existing cognitive impairment, were included in the study.

d. Description of markers of inflammation and endogenous anticoagulant activity

1) C-reactive protein (CRP): an acute phase reactant that stimulates the production of proinflammatory cytokines, activates complement, and acts as an opsonin for various pathogens (1). Measured using enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN, USA).

2) Interferon-gamma (IFN-γ): a type II interferon secreted in response to cytokines produced by antigen presenting cells that coordinates a diverse array of immunologically relevant genes (2). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

3) Interluekin-1 beta (IL-1β): a pro-inflammatory cytokine produced by monocytes, macrophages, skin dendritic cells and brain microglia in response to toll-like receptor activation, activated complement components, and other inflammatory cytokines (3). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

4) Interluekin-6 (IL-6): a multifunctional cytokine involved in regulation of immune responses, acute-phase responses, hematopoiesis, and

inflammation (4). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

5) Interleukin-8 (IL-8): a member of the CXC chemokine family responsible for activation and recruitment of neutrophils to a site of infection or injury(4). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

6) Interleukin-10 (IL-10): an anti-inflammatory cytokine that inhibits the expression of many pro-inflammatory cytokines, chemokines, and chemokine receptors (4). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

7) Interleukin-12 (IL-12): a pro-inflammatory cytokine that stimulates production of IFN-γ induces T-helper 1 cell development, and augments proliferation and colony formation of Natural Killer, Natural Killer T-cells, and T-cells (5). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

8) Matrix metalloproteinase 9 (MMP-9): an enzyme that regulates cell-matrix composition and is released from neutrophils after activation by inflammatory mediators (6). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

9) Tumor Necrosis Factor-alpha (TNF-α): a pleiotropic cytokine that acts as a pro-inflammatory mediator, an immunosuppressive mediator, and plays a role

in maintenance of immune homeostasis by limiting the extent and duration of inflammatory processes (4). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

10) Tumor necrosis factor receptor 1 (TNFR1): a molecule widely considered a marker of a proinflammatory state, though its mechanism is actually anti-inflammatory in that it neutralizes the effects of TNF-alpha (7). Measured using electrochemiluminescent assay (Meso Scale Discovery, Rockville, MD, USA).

11) Protein C: a plasma glycoprotein that exhibits endogenous anticoagulation activity by promoting fibrinolysis and inhibiting thrombosis and inflammation (8). Measured using enzyme-linked immunosorbent assay (Helena Laboratories, Beaumont, TX, USA).

e. Description of Covariates

i. Charlson comorbidity index

Charlson comorbidity index is a score that predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Clinical conditions and associated scores are as follows: 1 point each for: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease and diabetes; 2 points each for: hemiplegia, moderate or severe kidney disease, diabetes with complication, tumor,

leukemia, lymphoma; 3 points for moderate or severe liver disease; and 6 points each for malignant tumor, metastasis, AIDS. Scores are summed to provide a total score to predict mortality. The range of the score is 0-33 (since some categories above are exclusive), with scores of 1-2 associated with approximately a 25% 10-year mortality.

ii. The Short Version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

The IQCODE consists of a series of 16 questions that are answered by a surrogate with intimate knowledge of the patient, who compares the participant's present cognitive abilities to those 10 years prior. A score of 1 on a question denotes much improvement, a 3 denotes not much change, and a 5 denotes much worse performance. Total score on the 16 questions is then divided by 16 to generate a score ranging from 1 to 5, with higher scores denoting worsening cognitive function.

iii. Framingham Stroke Risk Profile

Framingham Stroke Risk Profile is a widely used clinical score based on the prediction of stroke events observed over a 10-year follow-up period in the Framingham Heart Study. The Framingham Stroke Risk Score is based on the following risk factors: age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy as determined by an electrocardiogram. The range of the score is 0-30, with most studies showing

worsening outcomes in patients with >10 points as compared to those with lower scores.

iv. Katz Activities of Daily Living Index (Katz ADL)

The Katz ADL measures 6 basic activities of daily living: bathing, dressing, toileting, transferring, continence, and feeding. Each question is scored from 0 (independent) to 2 (disabled). Thus, scores range from 0 to 12; scores other than 0 indicate disability in basic ADLs.

v. Functional Activities Questionnaire

The Functional Activities Questionnaire assess 10 Instrumental Activities of Daily Living: paying bills, assembling papers/business affairs, shopping, playing a game/hobby, cooking, preparing a balanced meal, keeping track of current events, paying attention to a book/movie/TV show, remembering appointments, traveling out of neighborhood. Patients are given 0 points if they reported no difficulty completing an IADL, 1 point if they reported difficulty doing the IADL but could do it without assistance, 2 points if they reported requiring assistance with the IADL, and 3 points if the patient reported complete dependency in the IADL. Thus, scores range from 0 to 30, with higher scores indicating worse disability.

f. Inverse Probability of Attrition Weighting models

i. We estimated the probability that each enrolled participant would contribute to follow-up in each of the four potential outcomes models: cognitive outcomes

at 3 months, cognitive outcomes at 12 months, disability outcomes at 3 months, and disability outcomes at 12 months. In each of these models, we included age, Charlson comorbidity index score, years of education, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score, Framingham stroke risk score, mean 24-hour doses of benzodiazepines, opioids, propofol, dexmedetomidine, and haloperidol, duration of severe sepsis, duration of delirium, duration of coma, and mean modified SOFA score (with the neurological component removed because we included the duration of delirium and coma in models).

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Table E1. Demographics and Clinical Characteristics of Enrolled Participants and Participants who Participated in Follow-up.

	Enrolled Cohort (N=991)	Follow-up Cohort (N=548)
Age	62 (53-72)	61 (52-70)
Male Sex, %(N)	61% (605)	60% (328)
Caucasian Race, %(N)	91% (899)	89% (488)
Years of Education	12 (12-14)	12 (12-14)
IQCODE Score at enrollment	3.0 (3.0-3.1)	3.0 (3.0-3.1)
Katz ADL Score	0 (0-1)	0 (0-1)
Functional Activities Questionnaire Score	0 (0-3)	0 (0-2)
Charlson Comorbidity Index Score	2 (1-4)	2 (1-4)
APACHE II score at admission	24 (18-30)	23 (17-29)
SOFA at ICU admission	9 (7-11)	8 (7-11)
Diagnosis at admission, % (N)		
Sepsis	32% (314)	30% (166)
Acute respiratory failure	17% (164)	16% (90)
Cardiogenic shock, myocardial infarction, or arrhythmia	17% (168)	17% (96)
Airway protection/Upper airway obstruction	10% (103)	10% (55)
Surgical Procedure*	16% (163)	18% (99)
Neurologic disease or seizure	1% (12)	1% (7)
Other diagnosis	7% (67)	6% (35)
Enrolling Center		

Academic	51% (501)	54% (295)
Community	28% (274)	25% (135)
Veterans Affairs	22% (216)	22% (118)
Mechanical Ventilation		
Patients, %(N)	89% (883)	88% (483)
Days of mechanical ventilation†	3 (1-9)	2 (1-6)
Delirium		
Patients, %(N)	71% (708)	71% (389)
Days of delirium†	4 (2-8)	3 (2-7)
Coma†		
Patients, %(N)	61% (603)	53% (288)
Days of coma†	3 (1-6)	2 (1-5)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment

* Includes gastric, colonic, vascular, urologic, orthopedic, obstetric/gynecologic, hepatobiliary/pancreatic, otolaryngologic, or transplant.

†Among participants who had the clinical condition.

Table E2. Concentrations of Markers According to Study Day

Marker	Study Day 1*	Study Day 3*	Study Day 5*
CRP (μg/mL)	143.6 (75.2 to 230.8)	121.4 (52.9 to 191.4)	88.6 (32.7 to 162.7)
IFN-γ (pg/mL)	1.11 (0.43 to 3.46)	0.89 (0.43 to 2.55)	0.91 (0.42 to 2.44)
IL-1β (pg/mL)	0.47 (0.21 to 1.01)	0.44 (0.22 to 0.83)	0.41 (0.22 to 0.68)
IL-6 (pg/mL)	36.3 (11.0 to 115.2)	17.9 (6.2 to 57.5)	15.1 (5.3 to 37.5)
IL-8 (pg/mL)	7.5 (3.7 to 16.9)	7.0 (3.6 to 12.7)	7.2 (4.0 to 14.4)
IL-10 (pg/mL)	10.6 (4.4 to 30.5)	8.4 (3.4 to 20.3)	7.3 (3.2 to 18.2)
IL-12 (pg/mL)	1.3 (0.49 to 4.21)	1.25 (0.48 to 3.94)	1.24 (0.47 to 3.76)
MMP-9 (μg/mL)	145.4 (66.5 to 284.6)	148.5 (68.3 to 291.6)	163.7 (81.4 to 337.2)
TNF-α (pg/mL)	8.9 (5.1 to 16.1)	8.0 (4.9 to 13.7)	8.0 (5.0 to 13.9)
TNFR1 (pg/mL)	8291 (4098 to 16730)	8042 (4026 to 15565)	8560 (4418 to 16735)
Protein C (% control)	80 (53 to 119)	88 (59 to 127)	93 (64 to 137)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor

*Median (interquartile range)

Table E3. Associations between First Day Biomarker Level and Long-Term Cognitive Outcomes

	RBANS Score				Trails B Score			
	3 Months		12 Months		3 Months		12 Months	
Marker	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI
CRP	0.2	(-1.4 to 1.8)	-0.8	(-2.7 to 1.1)	1.3	(-0.5 to 3.0)	0.2	(-1.7 to 2.1)
IFN-γ	-0.6	(-2.0 to 0.8)	-1.3	(-2.9 to 0.4)	-0.3	(-1.9 to 1.2)	0.2	(-1.4 to 1.7)
IL-1β	-0.6	(-1.9 to 0.7)	0.3	(-1.2 to 1.8)	-0.4	(-1.7 to 1.0)	0.0	(-1.4 to 1.4)
IL-6	-0.5	(-2.0 to 1.0)	-0.6	(-2.3 to 1.1)	0.6	(-1.1 to 2.2)	0.4	(-1.2 to 2.0)
IL-8	-0.2	(-1.6 to 1.2)	-1.1	(-2.8 to 0.7)	-0.3	(-1.8 to 1.3)	0.1	(-1.6 to 1.9)
IL-10	-0.6	(-2.3 to 1.0)	-1.0	(-2.9 to 1.0)	0.3	(-1.5 to 2.1)	1.4	(-0.5 to 3.3)
IL-12	-0.1	(-1.5 to 1.4)	0.9	(-0.7 to 2.6)	-0.2	(-1.8 to 1.4)	0.8	(-0.7 to 2.3)
MMP-9	0.1	(-1.4 to 1.5)	-0.3	(-2.0 to 1.5)	-0.2	(-1.8 to 1.5)	0.5	(-1.3 to 2.2)
TNF-α	-0.8	(-2.2 to 0.5)	-0.7	(-2.2 to 0.9)	-0.1	(-1.6 to 1.4)	0.6	(-0.9 to 2.2)
TNFR1	-0.9	(-2.5 to 0.7)	-1.4	(-3.2 to 0.4)	-0.4	(-2.1 to 1.3)	-0.4	(-2.3 to 1.4)
Protein C	-1.0	(-2.7 to 0.6)	-0.7	(-2.5 to 1.1)	-0.5	(-2.3 to 1.3)	-0.7	(-2.5 to 1.0)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; Trails B, Trail Making Test, Part B.

[a] The point estimate represents the adjusted difference in RBANS or Trails B score in a comparison between two patients, one with a biomarker concentration at 75th percentile (comparator) and the other with a biomarker concentration at the 25th percentile (reference), who are otherwise alike in all other ways (i.e., all covariates adjusted to the median or mode).

Table E4. Associations between Percent Change in Biomarker Level and Long-Term Cognitive Outcomes

	RBANS Score				Trails B Score			
	3 Months		12 Months		3 Months		12 Months	
Marker	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI
CRP	0.3	(-2.1 to 2.7)	0.5	(-2.0 to 2.9)	0.2	(-2.1 to 2.4)	-0.7	(-3.1 to 1.7)
IFN-γ	0.8	(-1.2 to 2.8)	3.5	(1.1 to 5.9)	-0.4	(-2.6 to 1.8)	1.3	(-1.1 to 3.7)
IL-1β	-0.3	(-2.4 to 1.8)	1.3	(-1.3 to 3.8)	-1.5	(-3.7 to 0.8)	0.6	(-1.9 to 3.0)
IL-6	-0.2	(-2.6 to 2.2)	2.1	(-0.7 to 4.9)	-1.9	(-4.6 to 0.8)	0.6	(-2.2 to 3.4)
IL-8	0.5	(-1.4 to 2.5)	1.4	(-0.8 to 3.6)	-0.8	(-2.9 to 1.2)	-1.6	(-3.8 to 0.5)
IL-10	0.8	(-1.3 to 2.8)	1.3	(-1.1 to 3.7)	0.6	(-1.6 to 2.9)	-0.9	(-3.4 to 1.6)
IL-12	-1.7	(-3.5 to 0.2)	0.2	(-1.9 to 2.3)	-1.2	(-3.2 to 0.8)	0.4	(-2.0 to 2.7)
MMP-9	0.3	(-2.0 to 2.7)	2.0	(-0.6 to 4.6)	0.5	(-2.1 to 3.1)	-0.1	(-2.7 to 2.5)
TNF-α	0.2	(-1.5 to 2.0)	0.0	(-2.1 to 2.1)	-0.3	(-2.1 to 1.6)	-0.1	(-2.4 to 2.2)
TNFR1	-1.4	(-3.1 to 0.4)	-1.1	(-3.1 to 0.9)	-0.7	(-2.5 to 1.2)	-1.0	(-3.0 to 1.0)
Protein C	0.9	(-1.0 to 2.7)	-0.3	(-2.5 to 2.0)	0.6	(-1.4 to 2.6)	0.7	(-1.5 to 2.8)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; Trails B, Trail Making Test, Part B.

[a] The point estimate represents the adjusted difference in RBANS or Trails B score in a comparison between two patients, one with a biomarker concentration at 75th percentile (comparator) and the other with a biomarker concentration at the 25th percentile (reference), who are otherwise alike in all other ways (i.e., all covariates adjusted to the median or mode).

Table E5. Associations between First Day Biomarker Level and Disability Outcomes

	Katz ADL Score				FAQ Score			
	3 Months		12 Months		3 Months		12 Months	
Marker	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI
CRP	1.1	(1.0 to 1.2)	1.1	(1.0 to 1.3)	1.0	(1.0 to 1.1)	1.2	(1.0 to 1.3)
IFN-γ	0.9	(0.8 to 1.0)	1.0	(0.8 to 1.1)	1.1	(0.9 to 1.2)	1.0	(0.9 to 1.1)
IL-1β	1.2	(1.0 to 1.3)	1.0	(0.8 to 1.1)	1.0	(1.0 to 1.1)	1.0	(0.9 to 1.2)
IL-6	1.1	(0.9 to 1.3)	1.1	(0.9 to 1.3)	1.0	(0.9 to 1.1)	1.0	(0.9 to 1.1)
IL-8	0.9	(0.8 to 1.1)	0.8	(0.7 to 1.0)	0.9	(0.8 to 1.1)	0.8	(0.7 to 1.0)
IL-10	0.8	(0.7 to 1.0)	1.0	(0.8 to 1.2)	1.0	(0.9 to 1.1)	1.0	(0.9 to 1.2)
IL-12	0.9	(0.8 to 1.0)	1.0	(0.8 to 1.1)	1.0	(0.9 to 1.0)	1.1	(1.0 to 1.2)
MMP-9	1.1	(0.9 to 1.2)	1.3	(1.1 to 1.5)	1.0	(0.9 to 1.2)	1.1	(1.0 to 1.3)
TNF-α	0.9	(0.8 to 1.1)	0.8	(0.7 to 1.0)	0.9	(0.8 to 1.0)	0.9	(0.8 to 1.0)
TNFR1	1.0	(0.8 to 1.2)	1.1	(0.9 to 1.3)	1.0	(0.8 to 1.1)	1.0	(0.9 to 1.1)
Protein C	1.0	(0.9 to 1.2)	0.9	(0.8 to 1.1)	1.0	(0.9 to 1.2)	0.9	(0.8 to 1.1)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; Katz ADL, Katz Index of Independence in Activities of Daily Living; FAQ, Functional Activities Questionnaire.

[a] The point estimate represents the adjusted incidence rate ratio in a comparison between two patients, one with a biomarker concentration at 75th percentile (comparator) and the other with a biomarker concentration at the 25th percentile (reference), who are otherwise alike in all other ways (i.e., all covariates adjusted to the median or mode value).

Table E6. Associations between Percent Change in Biomarker Level and Disability Outcomes

	Katz ADL Score				FAQ Score			
	3 Months		12 Months		3 Months		12 Months	
Marker	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI	Point Estimate[a]	95% CI
CRP	1.1	(1.0 to 1.2)	1.1	(1.0 to 1.3)	1.0	(1.0 to 1.0)	1.2	(1.0 to 1.3)
IFN-γ	1.3	(1.1 to 1.6)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	0.8	(0.7 to 0.9)
IL-1β	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	0.8	(0.7 to 1.0)	0.7	(0.6 to 0.9)
IL-6	1.0	(1.0 to 1.1)	1.0	(0.9 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)
IL-8	1.4	(1.1 to 1.7)	1.1	(1.0 to 1.1)	1.4	(1.1 to 1.7)	1.1	(1.0 to 1.1)
IL-10	1.3	(1.0 to 1.6)	0.8	(0.6 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)
IL-12	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)
MMP-9	1.2	(1.1 to 1.3)	1.0	(1.0 to 1.1)	1.1	(1.0 to 1.1)	1.0	(0.9 to 1.0)
TNF-α	1.2	(1.0 to 1.4)	1.0	(0.9 to 1.0)	1.1	(0.9 to 1.2)	1.0	(0.9 to 1.0)
TNFR1	1.0	(1.0 to 1.1)	0.9	(0.8 to 1.0)	1.1	(1.0 to 1.1)	1.0	(1.0 to 1.0)
Protein C	1.0	(0.9 to 1.1)	1.0	(1.0 to 1.1)	1.0	(0.9 to 1.1)	1.0	(1.0 to 1.1)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; Katz ADL, Katz Index of Independence in Activities of Daily Living; FAQ, Functional Activities Questionnaire.

[a] The point estimate represents the adjusted incidence rate ratio in a comparison between two patients, one with a biomarker concentration at 75th percentile (comparator) and the other with a biomarker concentration at the 25th percentile (reference), who are otherwise alike in all other ways (i.e., all covariates adjusted to the median or mode value).