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Original Article

Inflammation-related biomarkers across Alzheimer disease severity in older adults: A retrospective single-center study

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Abstract

Aim: We examined how routine inflammation-related biomarkers vary across Alzheimer disease (AD) severity and whether they are independently associated with moderate-to-severe disease.

Materials and Methods: This retrospective cross-sectional study included outpatients aged ≥ 65 years with clinically diagnosed AD. Severity was staged (Clinical Dementia Rating) as mild, moderate, or severe. We evaluated 6 biomarkers: red cell distribution width-to-albumin ratio (RAR), C-reactive protein-to-albumin ratio (CAR), C-reactive protein-albumin-lymphocyte index (CALLY), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII). Groups were compared using nonparametric tests with multiple-comparison corrections. Cross-sectional separation was assessed using the area under the receiver operating characteristic curve (AUC). We used Firth penalized logistic regression with multiple imputation, adjusting for age, body mass index, sex, malnutrition risk, and multimorbidity.

Results: Among 151 patients (90 mild, 53 moderate, 8 severe), only CAR differed across severity in unadjusted tests ($p = .03$); no biomarker remained significant after multiple-comparison correction (Holm-adjusted $p \geq .18$). Cross-sectional separation for moderate-to-severe disease was weak (all AUCs < 0.60). In adjusted models, no biomarker was independently associated with moderate-to-severe disease (SII [per 100-unit increment]: odds ratio [OR], 1.06 [95% confidence interval (CI), 0.95 – 1.17]; CAR: OR, 0.90 [95% CI, 0.64 – 1.08]; CALLY: OR, 0.99 [95% CI, 0.96 – 1.03]). Multimorbidity was inversely associated with severity.

Conclusion: Routine inflammation-related biomarkers were not independently associated with AD severity. Frailty and functional status, rather than blood biomarkers, most clearly indicated severity. These hypothesis-generating findings require validation in larger cohorts.

Keywords: Alzheimer disease, inflammation, biomarkers, C-reactive protein, geriatric assessment

INTRODUCTION

Dementia is a leading cause of disability and loss of independence among older adults, with a worldwide prevalence that continues to rise as populations age. In 2021, dementia affected approximately 57 million people globally, with an estimated 10 million new diagnoses annually (1). Alzheimer disease (AD) is the predominant form, accounting for roughly 60%–70% of cases worldwide, including in Türkiye (2). Beyond cognitive decline, AD is a multisystem condition involving functional impairment, frailty, nutritional compromise, and substantial caregiving demands (3). Inflammatory processes are implicated in both the initiation and clinical progression of AD (4). Peripheral immune activation and persistent low-grade systemic inflammation may amplify neuroinflammatory cascades, compromise blood-brain barrier integrity, and aggravate neuronal injury (5,6). Consequently, inflammation-related biomarkers derived from routine hemogram and biochemistry panels have attracted

interest as inexpensive, widely available adjuncts for clinical evaluation.

Among these indices, the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) have been studied in AD cohorts, with some data suggesting that higher values accompany greater disease severity (5,7). More recently developed composite markers that jointly capture inflammatory and nutritional dimensions, such as the C-reactive protein-to-albumin ratio (CAR), C-reactive protein-albumin-lymphocyte index (CALLY), and red cell distribution width-to-albumin ratio (RAR), carry prognostic information; however, their relationship with AD severity remains insufficiently characterized (8-10). Population-level analyses also link higher RAR to poorer cognitive performance in older adults (11).

Given this uncertainty, we examined how a panel of routinely obtainable inflammation-related biomarkers (RAR, CAR, CALLY, NLR, the monocyte-to-lymphocyte ratio (MLR), and SII) varies across AD severity stages, and whether any biomarker is independently associated with moderate-to-severe disease after accounting for relevant geriatric covariates.

MATERIALS AND METHODS

Study design and ethical approval

This retrospective, single-center, cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The institutional ethics committee approved the study and waived the requirement for informed consent.

We reviewed electronic health records (January 2020 to December 2024) of community-dwelling adults aged ≥ 65 years with clinically diagnosed Alzheimer disease followed in our university geriatric outpatient clinics. Alzheimer disease was diagnosed on clinical criteria by geriatric medicine specialists in the dementia outpatient clinic; the Clinical Dementia Rating (CDR) was applied for severity staging only. We excluded patients with non-Alzheimer dementias, active malignancies undergoing treatment, delirium, active infections (including COVID-19), systemic inflammatory disorders, or acute confounding illnesses. Patients with a remote history of cancer in remission were retained. For patients with multiple visits, the a priori index encounter was the visit with the most complete biomarker panel, breaking ties with the most recent date.

Severity was staged using the global CDR (stages 1, 2, and 3 corresponding to mild, moderate, and severe disease, respectively) (12). Staging was performed by a single geriatric medicine specialist on the basis of the patient examination together with informant (caregiver) history obtained at the clinic visit, in keeping with the standard CDR protocol. The primary multivariable outcome was moderate-to-severe dementia (CDR stages 2–3) compared with mild dementia (CDR stage 1). Because severe dementia was rare ($n = 8$), the combined outcome comprised predominantly moderate cases (53 of 61 [87%]).

Data collection and comprehensive geriatric assessment

We extracted data on age, sex, marital and cohabitation status, smoking history, body mass index (BMI), and education (dichotomized as ≤ 8 vs ≥ 9 years (13)). Recorded comorbidities included hypertension, diabetes, coronary artery disease, heart failure, atrial fibrillation, chronic kidney disease, cerebrovascular disease, Parkinson disease, cancer history, chronic pulmonary disease, asthma, and hypo- or hyperthyroidism. We defined multimorbidity as ≥ 2 of these 13 conditions; comorbidity data were 100% complete. Polypharmacy was defined as concurrent use of ≥ 5 medications (14).

Geriatric assessments included the Clinical Frailty Scale (analyzed continuously because all patients scored ≥ 5) (15), Katz Activities of Daily Living (ADL) (16), Lawton-Brody Instrumental ADL (17), Mini-Nutritional Assessment-Short Form (MNA-SF; scores < 12 indicate malnutrition risk) (18), Eating Assessment Tool-10 (scores ≥ 3 indicate abnormal swallowing) (19), and SARC-F (scores ≥ 4 indicate sarcopenia risk) (20). Probable sarcopenia was adjudicated using European Working Group on Sarcopenia in Older People 2 (EWGSOP2) criteria, with SARC-F as the screening instrument and low muscle strength defined by maximum handgrip strength < 27 kg (men) or < 16 kg (women), or a 5-repetition chair-stand > 15 seconds (21); because muscle mass was not measured (neither dual-energy x-ray absorptiometry nor bioimpedance analysis was available in this retrospective cohort), only probable, rather than confirmed, sarcopenia could be established. We recorded continence and falls within the preceding 12 months.

Laboratory measurements

Hematology differential counts ($\times 10^3/\mu L$), C-reactive protein (CRP; mg/L), and albumin (g/dL) were drawn from the index encounter or, where unavailable at that visit, from the closest documented result within a maximum window of ±30 days from the clinical assessment; this window was applied uniformly to all patients. We computed RAR (red cell distribution width / albumin); CAR (CRP / albumin); CALLY ([albumin × lymphocyte] / CRP) (9); NLR (neutrophil / lymphocyte); MLR (monocyte / lymphocyte); and SII ([platelet × neutrophil] / lymphocyte). The CALLY index was computed using laboratory-native units (lymphocytes $\times 10^3/\mu L$, CRP mg/L); this is mathematically equivalent to the $\times 10^4$ scaling constant in the original formulation (9), which reflects lymphocytes expressed in cells/μL and CRP in mg/dL. Because this scaling is identical for every patient, it does not affect rank-based comparisons or the regression estimates.

Statistical analysis

We used R version 4.6.0 for all analyses. Because we used nonparametric methods, we summarized continuous variables as medians (interquartile ranges [IQRs]) and compared them across severity groups using the Kruskal-Wallis test, followed by Bonferroni-adjusted Dunn post hoc tests (effect size: rank η^2). We applied Holm and Benjamini-Hochberg multiple-

comparison corrections to the 6 omnibus biomarker p values. Categorical variables were reported as frequencies (percentages) and compared using the χ^2 or Fisher exact test. The Jonckheere-Terpstra and Cochran-Armitage tests assessed monotonic trends.

Exploratory receiver operating characteristic (ROC) analyses assessed cross-sectional biomarker separation using 2000-replicate bootstrapped 95% confidence intervals (CIs) for the area under the ROC curve (AUC). We verified minimum sample size adequacy for the 6-parameter multivariable model using Riley criteria (using R package *pmsampsize*).

To account for sparse events and separation risk, we used Firth penalized logistic regression for the primary multivariable analysis. We modeled each biomarker (SII per 100-unit increment, CAR, or CALLY) separately, adjusting for a pre-specified, restricted covariate set: age, BMI, sex, malnutrition risk (MNA-SF), and multimorbidity. These covariates were selected a priori on clinical and literature-based grounds as established correlates of both systemic inflammation and geriatric disease burden; the set was deliberately restricted because the available cohort fell well below the size required for stable estimation of a larger model (see sample-size adequacy below). Functional status (Katz ADL, Lawton-Brody Instrumental ADL) was intentionally excluded from the primary models because functional decline is an integral constituent of CDR-based severity staging and is therefore collinear with the outcome by construction; it was instead examined in a separate sensitivity model. Missing laboratory values (CRP, 39%; platelets, 25%) were handled via multiple imputation by chained equations (m = 30) to passively derive the composite indices. Estimates were pooled using Rubin rules. Sensitivity analyses included standard complete-case logistic regression and additional adjustments for cholinesterase-inhibitor or memantine use, depression, and ADLs (interpreted cautiously due to collinearity with CDR staging). Disease duration was unavailable. Statistical significance was set at a 2-sided $p < .05$.

For the primary 6-parameter model, the Riley minimum sample size was 1795, 787, and 435 at anticipated C-statistics of 0.60, 0.65, and 0.70, respectively. This sample size adequacy benchmark, rather than a post hoc power calculation, indicates that the available cohort (n = 151) fell well below the size required for stable multivariable estimation; therefore, the regression estimates are imprecise and should be regarded as hypothesis-generating.

RESULTS

Cohort characteristics

The analytic cohort comprised 151 unique patients (collapsed from 180 encounters) (Figure 1). Among these, 90 (59.6%) had mild, 53 (35.1%) had moderate, and 8 (5.3%) had severe dementia. For multivariable modeling, 90 patients had mild dementia (no event) and 61 had moderate-to-severe dementia (the combined outcome).

Table 1 summarizes baseline demographic and clinical characteristics. The severity groups were similar in age (median, 77–78 years; p = .76), sex distribution (p > .99), education, smoking, BMI, and most comorbidities. Only 2 clinical variables differed significantly across severity stages: diabetes (35.6% [mild], 43.4% [moderate], and 0.0% [severe]; p = .04) and multimorbidity, which declined with increasing severity (70.0%, 60.4%, and 12.5%, respectively; p = .004).

Comprehensive geriatric assessment

Frailty and functional measures demonstrated clear gradients with dementia severity (Table 2). All patients had a Clinical Frailty Scale score ≥ 5 (median, 6; range, 5–9). Scores increased with severity (median, 6, 6, and 6.5 for mild, moderate, and severe groups, respectively; p < .001), with significant differences between the mild and moderate, and mild and severe groups. Functional dependence also increased with severity on both the Katz Activities of Daily Living (p = .02) and Lawton-Brody Instrumental ADL (p < .001) scales. Malnutrition risk (43.3%, 58.5%, and 87.5%; p = .03) and SARC-F-defined sarcopenia risk (36.7%, 43.4%, and 87.5%; p = .02) were more frequent in advanced disease. Probable sarcopenia by EWGSOP2 criteria increased across stages (71.1%, 79.2%, and 100%, respectively) but was not statistically significant (p = .15).

Inflammation-related biomarkers across severity

Among the 6 biomarkers, only CAR differed significantly across severity groups (median, 0.85 [mild], 0.72 [moderate], and 1.04 [severe]; p = .03). This pattern was nonmonotonic (the lowest value was in the moderate group), and no pairwise comparison survived Bonferroni correction. CALLY was borderline significant (median, 2.06, 2.45, and 1.44; p = .06) and similarly nonmonotonic. SII (p = .55), NLR (p = .37), MLR (p = .66), and RAR (p = .79) did not differ across groups (Table 3).

After correction for multiple comparisons across the 6-marker panel, no biomarker remained significant; the nominal CAR signal fell to a Holm-adjusted p = .18 (Benjamini-Hochberg p = .17), and CALLY fell to a Holm-adjusted *P* = .28. Effect sizes for all biomarkers were small (rank $\eta^2 \leq 0.034$), contrasting with the large effect for the Clinical Frailty Scale ($\eta^2 = 0.18$) and the moderate effect for the Lawton-Brody Instrumental ADL ($\eta^2 = 0.09$). Supplementary ordinal trend tests confirmed the absence of monotonic biomarker gradients across severity stages. Figure 2 displays biomarker distributions by severity.

Cross-sectional separation for moderate-to-severe dementia

Cross-sectional separation for the moderate-to-severe outcome was weak for every marker (Figure S1). The AUC was 0.41 (95% CI, 0.29 – 0.53) for CAR, 0.55 (95% CI, 0.44 – 0.66) for SII, and 0.43 (95% CI, 0.32 – 0.55) for CALLY. All AUCs were below 0.60, with CAR and CALLY at or below chance. A paired DeLong comparison was statistically significant for SII versus CAR but corresponded to a clinically meaningless difference because both AUCs remained below any useful threshold. The

Supplementary Material (Supplementary Note S1) contains this comparison, the optimal cutpoint derivation, and the bootstrap-validated operating characteristics for SII.

Multivariable regression

Figure 3 displays crude (univariable) and adjusted estimates as a forest plot. In the primary Firth penalized models, no biomarker was independently associated with moderate-to-severe dementia. The odds ratio (OR) for SII (per 100-unit increment) was 1.06 (95% CI, 0.95 – 1.17; p = .29); for CAR, 0.90 (95% CI, 0.64 – 1.08; p = .33); and for CALLY, 0.99 (95% CI, 0.96 – 1.03; p = .76). Crude biomarker estimates were likewise null.

Age, BMI, sex, and malnutrition risk were not independently associated with the outcome, although malnutrition risk showed a nonsignificant positive trend (adjusted ORs ranged from 1.78 to 1.95 across models). Multimorbidity was inversely associated with the outcome in every model (ORs ranged from 0.36 to 0.40; p = .02 – .03). Standard maximum-likelihood logistic regression yielded concordant estimates, and the separation algorithm indicated no separation (penalized and maximum-likelihood coefficients differed by ≤ 0.11 on the log-odds scale), confirming that the inverse multimorbidity association was not a numerical artifact.

Results remained unchanged after additional adjustment for depression and cholinesterase inhibitor or memantine use. In the functional status sensitivity model, lower Lawton-Brody Instrumental ADL scores were associated with the outcome (OR, 0.80 per point; p = .02), consistent with functional decline accompanying severity, while CAR remained nonsignificant (OR, 0.91; p = .32).

Table 1. Baseline demographic and clinical characteristics according to dementia severity

Variable	Mild (n = 90)	Moderate (n = 53)	Severe (n = 8)	p
Age, years	77.0 [73.0 – 82.0]	78.0 [73.0 – 82.0]	77.5 [71.8 – 83.5]	.76
Female sex	51 (56.7)	30 (56.6)	5 (62.5)	> .99
Marital status				.68
Single	1 (1.1)	1 (2.0)	0 (0.0)	
Married	47 (52.8)	29 (56.9)	3 (37.5)	
Widowed	38 (42.7)	21 (41.2)	5 (62.5)	
Divorced	3 (3.4)	0 (0.0)	0 (0.0)	
Living alone	12 (13.3)	7 (13.2)	1 (12.5)	> .99
Education ≤ 8 years	70 (77.8)	45 (84.9)	7 (87.5)	.64
Smoking status				.30
Never	67 (74.4)	42 (79.2)	4 (50.0)	
Current	22 (24.4)	11 (20.8)	4 (50.0)	
Former	1 (1.1)	0 (0.0)	0 (0.0)	
BMI, kg/m²	27.9 [25.2 – 31.4]	28.2 [25.4 – 31.0]	26.0 [24.6 – 27.1]	.30
Hypertension	63 (70.0)	32 (60.4)	3 (37.5)	.13
Diabetes	32 (35.6)	23 (43.4)	0 (0.0)	.04
Coronary artery disease	27 (30.0)	13 (24.5)	2 (25.0)	.87
Atrial fibrillation	8 (8.9)	10 (18.9)	1 (12.5)	.18
Pulmonary disease	7 (7.8)	0 (0.0)	0 (0.0)	.10
Hypothyroidism	15 (16.7)	3 (5.7)	0 (0.0)	.11
Chronic kidney disease	6 (6.7)	1 (1.9)	0 (0.0)	.49
Cerebrovascular disease	14 (15.6)	6 (11.3)	2 (25.0)	.45
Multimorbidity (≥ 2 conditions)	63 (70.0)	32 (60.4)	1 (12.5)	.004
Polypharmacy (≥ 5 medications)	80 (88.9)	43 (86.0)	5 (62.5)	.12
Cholinesterase inhibitor or memantine	16 (17.8)	14 (26.4)	2 (25.0)	.47
Antidepressant use	18 (20.0)	11 (20.8)	1 (12.5)	> .99
Depression diagnosis	34 (38.6)	18 (34.0)	3 (37.5)	.88

Data are presented as No. (%) or median [IQR]; p values are calculated using the χ^2 or Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables; BMI: body mass index, IQR: interquartile range

Table 2. Comprehensive geriatric assessment according to dementia severity

Variable	Mild (n = 90)	Moderate (n = 53)	Severe (n = 8)	p
Katz ADL	5.0 [4.0 – 6.0]	5.0 [3.0 – 6.0]	3.0 [0.8 – 4.2]	.02
Lawton-Brody Instrumental ADL	4.0 [2.0 – 7.0]	1.0 [0.0 – 5.0]	0.5 [0.0 – 1.0]	< .001
Clinical Frailty Scale	6.0 [5.0 – 6.0]	6.0 [6.0 – 7.0]	6.5 [6.0 – 7.0]	< .001
EAT-10	0.0 [0.0 – 0.0]	0.0 [0.0 – 1.0]	0.0 [0.0 – 0.2]	.40
Malnutrition risk (MNA-SF < 12)	39 (43.3)	31 (58.5)	7 (87.5)	.03
SARC-F	2.0 [0.0 – 4.0]	2.0 [0.0 – 5.0]	4.5 [4.0 – 6.2]	.06
Sarcopenia risk (SARC-F ≥ 4)	33 (36.7)	23 (43.4)	7 (87.5)	.02
Probable sarcopenia (EWGSOP2)	64 (71.1)	42 (79.2)	8 (100.0)	.15
Incontinence	47 (52.8)	29 (54.7)	7 (87.5)	.17
Falls in past year	36 (40.9)	23 (45.1)	5 (62.5)	.47

Data are presented as No. (%) or median [IQR]; ADL: activities of daily living, EAT-10: Eating Assessment Tool-10, EWGSOP2: European Working Group on Sarcopenia in Older People 2, IQR: interquartile range, MNA-SF: Mini-Nutritional Assessment-Short Form, SARC-F: sarcopenia screening questionnaire

Table 3. Inflammation-related biomarkers according to dementia severity

Marker	Mild (n = 90)	Moderate (n = 53)	Severe (n = 8)	p	p (Holm)[a]
RAR	3.22 [2.97 – 3.64]	3.22 [3.01 – 3.65]	3.49 [3.03 – 3.93]	.79	> .99
CAR	0.85 [0.70 – 1.81]	0.72 [0.67 – 0.80]	1.04 [0.89 – 1.78]	.03	.18
CALLY	2.06 [0.92 – 2.81]	2.45 [1.73 – 3.18]	1.44 [1.11 – 1.76]	.06	.28
NLR	2.33 [1.69 – 3.24]	2.41 [1.85 – 3.06]	2.84 [2.43 – 3.30]	.37	> .99
MLR	0.30 [0.24 – 0.41]	0.32 [0.25 – 0.37]	0.33 [0.27 – 0.39]	.66	> .99
SII	529 [380 – 702]	525 [383 – 743]	666 [491 – 808]	.55	> .99

[a] Holm-adjusted *P* value accounting for the 6 omnibus tests across the biomarker panel; The Benjamini-Hochberg false discovery rate adjustment yielded concordant results (CAR and CALLY both .17; all others ≥ .74); No biomarker remained significant after correction; Data are presented as median [IQR]; p values are calculated using the Kruskal-Wallis test; CALLY: C-reactive protein-albumin-lymphocyte index, CAR: C-reactive protein-to-albumin ratio, IQR: interquartile range, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, RAR: red cell distribution width-to-albumin ratio, SII: systemic immune-inflammation index

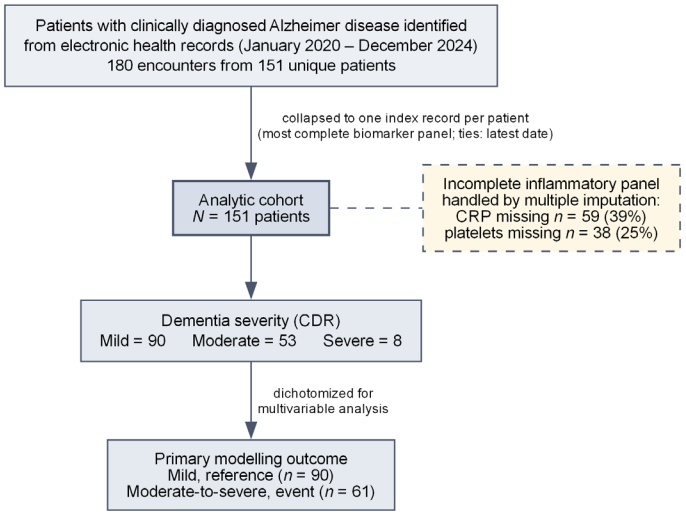

Figure 1. STROBE flow diagram; Source records (180 encounters across 151 unique patients) were collapsed to 1 index record per patient, defined as the encounter with the most complete inflammatory biomarker panel (ties broken by the most recent admission date); This yielded an analytic cohort of 151 patients (90 with mild, 53 with moderate, and 8 with severe dementia; 90 vs 61 for the combined moderate-to-severe outcome); STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

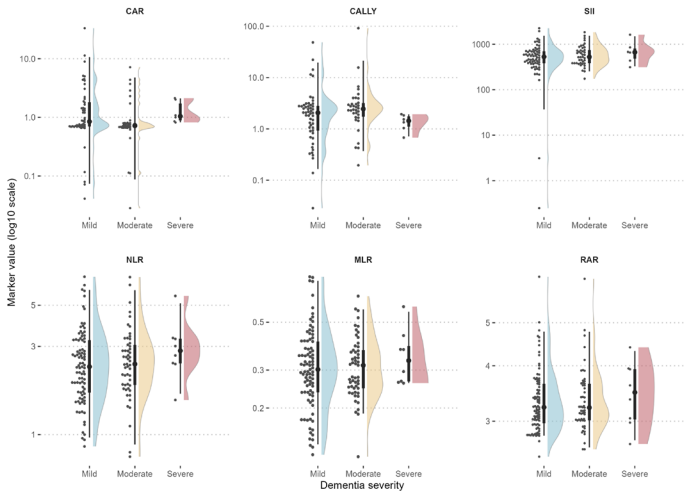

Figure 2. Distribution of inflammation-related biomarkers by dementia severity; Data are displayed as raincloud plots; For each severity group, a half-eye density plot (the "cloud") shows the median and 50% and 95% intervals, alongside the raw data plotted as individual points (the "rain"); The *y*-axis is presented on a $\log_{10}$ scale because all 6 markers are ratio-based indices; CALLY: C-reactive protein-albumin-lymphocyte index, CAR: C-reactive protein-to-albumin ratio, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, RAR: red cell distribution width-to-albumin ratio, SII: systemic immune-inflammation index

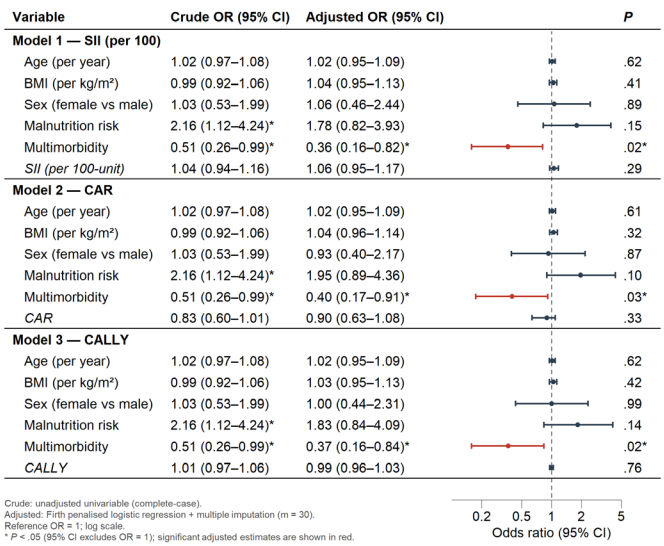

Figure 3. Forest plot of crude and adjusted ORs for moderate-to-severe dementia; Estimates are grouped by the 3 primary models; Each model contains 1 inflammation-related biomarker (SII per 100-unit increment, CAR, or CALLY) and the pre-specified covariate set (age, BMI, sex, malnutrition risk, and multimorbidity); Plotted points and horizontal bars represent the point estimates and 95% CIs from the primary Firth penalized logistic regression with multiple imputation (adjusted ORs); The adjacent column lists the corresponding crude (unadjusted univariable) ORs (complete-case per variable: n = 151 for age, BMI, sex, malnutrition risk, and multimorbidity; n = 113 for SII; n = 92 for CAR and CALLY); The dashed vertical line marks the null value (OR = 1), and the *x*-axis is on a log scale; An asterisk indicates estimates whose 95% CI excludes 1 ($p < .05$), and significant adjusted intervals are drawn in red; BMI: body mass index, CALLY: C-reactive protein-albumin-lymphocyte index, CAR: C-reactive protein-to-albumin ratio, CI: confidence interval, OR: odds ratio, SII: systemic immune-inflammation index

DISCUSSION

In this retrospective cohort of older outpatients with Alzheimer disease, routinely available inflammation-related biomarkers were not independently associated with disease severity and demonstrated weak cross-sectional separation between mild and moderate-to-severe stages. Only CAR differed across severity in unadjusted comparisons, but the pattern was nonmonotonic, did not survive correction for multiple comparisons, and lost significance after multivariable adjustment.

Conversely, frailty and functional measures demonstrated the strongest and most consistent gradients with severity. These findings suggest that hemogram- and biochemistry-derived inflammatory indices may not serve as practical markers of AD severity, at least in cohorts of this size and case mix.

Our results contrast with several prior reports. Algül et al (7) described a significant relationship between SII and AD severity, and Bolayır et al (22) reported a trend toward higher SII with greater clinical severity. Elevated NLR has likewise been linked to AD and cognitive decline in a meta-analysis (5), and another cross-sectional analysis associated systemic inflammatory markers with AD (23). We did not replicate these associations; SII, NLR, and MLR did not differ across severity stages, and SII was not independently associated with severity after adjustment.

Several factors may explain these discrepancies. First, our cohort was small; the sample fell below the minimum required for stable multivariable estimation, increasing the risk of missing modest true associations and yielding imprecise estimates. Second, relying on a single laboratory measurement per patient makes this cross-sectional study vulnerable to short-term biological variation in acute-phase markers. Third, excluding active malignancies, active infections, and acute inflammatory states (although appropriate for isolating chronic inflammatory signals) may have removed much of the between-patient variance in these markers. Finally, ambulatory geriatric clinics preferentially capture patients well enough to attend, potentially attenuating severity-related differences in systemic inflammation.

The composite CAR and CALLY indices behaved inconsistently across stages. Although CAR reached nominal significance overall and CALLY approached it, both followed nonmonotonic patterns, and neither was independently associated with the outcome. CRP itself has been reported to be paradoxically lower in AD (24), which may contribute to the inconsistent behavior of CRP-based indices.

CAR and CALLY integrate CRP, albumin, and (for CALLY) lymphocyte counts. In the broader geriatric literature, they have been linked to frailty, malnutrition, sarcopenia, and mortality (25-30). Their behavior in our study likely reflects a generalized state of immunonutritional and systemic vulnerability accompanying advanced age and frailty, rather than a specific signal of AD severity. This interpretation aligns with our finding that frailty (Clinical Frailty Scale) and functional status (Katz and Lawton-Brody scales), alongside malnutrition and sarcopenia risk, were the variables most clearly associated with severity.

A counterintuitive finding was the inverse association between multimorbidity and severity: multimorbidity prevalence fell from 70% in mild disease to 13% in severe disease, and the adjusted odds ratio remained consistently below 1. Formal diagnostics excluded quasi-complete separation, indicating that this association reflects real cohort composition rather than a modeling artifact. The most plausible mechanism is selection bias. Patients with severe AD and a high comorbidity burden are disproportionately bedbound, institutionalized, or hospitalized. They are therefore underrepresented in ambulatory geriatric clinics, leaving a comparatively healthier severe subgroup. This pattern underscores the susceptibility of single-center outpatient cohorts to selection bias and cautions against causal interpretation of the multimorbidity result.

This study has several limitations. The retrospective, single-center, cross-sectional design limits causal inference and generalizability, and the protocol was not prospectively registered. The cross-sectional design also precludes determination of temporality: any biomarker differences observed in more

advanced AD may equally reflect consequences of advanced disease (nutritional deterioration with falling albumin, reduced oral intake, immobility-related low-grade inflammation, and intercurrent subclinical infection) rather than contributors to disease progression. The direction of association therefore cannot be inferred from these data, and this bidirectional uncertainty applies even to the markers that approached nominal significance. The overall sample size, including the small severe subgroup (n = 8), fell below the threshold required for stable multivariable estimation, meaning null biomarker findings cannot definitively exclude modest true effects. Reliance on a single measurement of volatile acute-phase markers introduces non-differential measurement error expected to bias associations toward the null, potentially obscuring modest true effects. Furthermore, clinical diagnoses lacked confirmatory cerebrospinal fluid or imaging biomarkers, risking the inclusion of mixed or non-AD dementias that could dilute inflammatory signals.

Additionally, although acute infections were excluded, the study overlapped with the COVID-19 pandemic. Unrecorded vaccination status or recent asymptomatic infections (which can transiently elevate CRP and SII) could not be accounted for. Standardized data on as-needed nonsteroidal anti-inflammatory drug and short-course corticosteroid use (which directly influence CRP, NLR, and SII) were also not consistently documented, leaving potential residual confounding that the a priori exclusion of active infections and systemic inflammatory disorders only partially mitigates. Disease duration was likewise unavailable. Retrospective electronic health records also risk under-capturing comorbidity prevalence. Finally, CRP and platelet data were incomplete and handled via multiple imputation. Although sensitivity analyses and baseline comparisons support the missing-at-random assumption (with CRP more often measured in frailer patients; Supplementary Table S1), unmeasured informative missingness cannot be entirely excluded.

Strengths of this study include the simultaneous evaluation of 6 low-cost, widely available markers, the incorporation of comprehensive geriatric assessment covariates, and a robust analytic strategy combining penalized regression with multiple imputation, family-wise error control, and formal separation diagnostics.

CONCLUSION

In conclusion, frailty and functional status track AD severity more reliably than blood-based inflammatory indices in this geriatric outpatient setting. Adequately powered, prospective, multicenter studies with serial biomarker sampling and biomarker-confirmed diagnoses are needed to determine whether these indices carry clinically meaningful information about AD progression.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
The study protocol adhered to the principles of the Declaration of Helsinki. The local ethics committee of Hacettepe University (decision no: 2024/13-04, date: July 30, 2024) approved the study protocol.

Informed Consent
Because of the retrospective nature of the study, the ethics committee waived the requirement for individual informed consent.

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