

Predicting risk of Alzheimer's disease using trajectories of systemic inflammation markers prior to initial emergency department utilization

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BACKGROUND

- Systemic inflammation is linked to Alzheimer's disease and related dementias (AD/ADRD)
- Markers like neutrophil- and monocyte-to-lymphocyte ratios (NLR, MLR) are associated with AD/ADRD risk¹
- In the emergency department (ED), these markers are often transiently elevated due to acute illness, biasing their predictive value

HYPOTHESIS

Incorporating pre-ED trajectories of NLR and MLR will improve AD/ADRD risk prediction

METHODS

- Outcomes were assessed starting 3 months post-ED visit over 3–7-year windows.
- ED-SIM model using NLR and MLR measurements obtained up to 2 years before the ED visit.
- For each patient, μ_0 (mean NLR/MLR prior to ED), μ_1 (NLR/MLR at ED visit), and θ (time-trend in NLR/MLR up to baseline) were derived
- Weighted pre-ED trends (θ) and mean systemic inflammation marker (SIM) levels, before and during ED, (μ) were combined via outer product and input into a logistic regression with age, sex, and race/ethnicity covariates to predict AD/ADRD incidence.

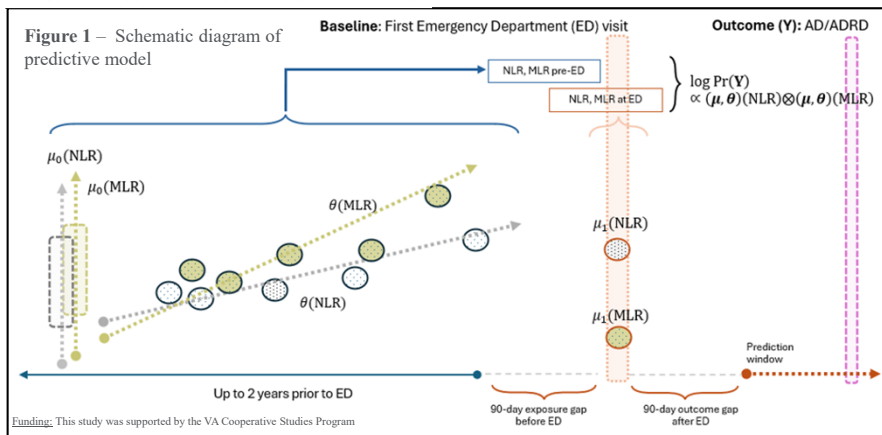
SAMPLE

- Patients in Veteran's Health Administration (VA) with emergency department (ED) utilization from 2011 to 2020, age 60–85, no prior AD/ADRD history, and at least one NLR/MLR.
- Split into 80/20% training/validation sets

Table 1 – Cohort Characteristics at Baseline

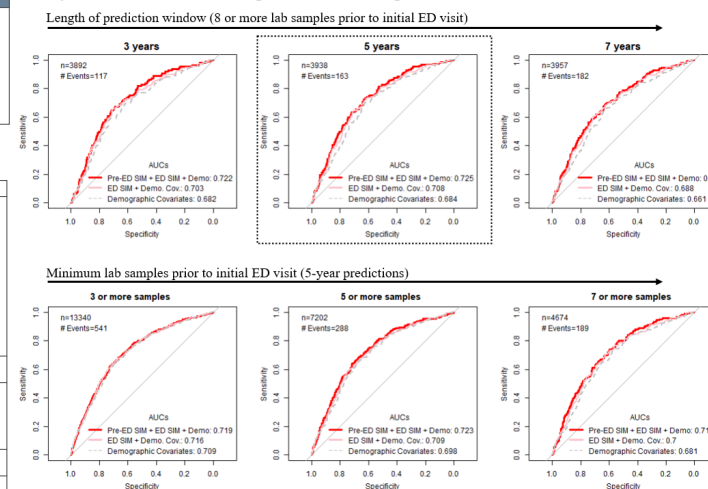
	no AD/ADRD	AD/ADRD	Total
	n=49,799 (94.3%)	n=3,017 (5.6%)	n=52,816
Female sex, n (%)	1134 (2.3%)	53 (1.8%)	1187 (2.2%)
Age, median [IQR]	69.4 [64.7, 76.7]	76.7 [69.7, 80.8]	69.8 [64.8, 77.2]
Race/ Ethnicity			
Black, n (%)	8256 (16.6%)	651 (21.6%)	8907 (16.9%)
Hispanic, n (%)	3269 (6.6%)	403 (13.4%)	3672 (7.0%)
White, n (%)	34424 (69.1%)	1799 (59.6%)	36223 (68.6%)
Exposures: Systemic inflammation markers (SIMs) during initial ED visit			
NLR at ED, median [IQR]	3.52 [2.26, 5.85]	3.17 [2.06, 4.87]	3.48 [3.25, 5.75]
MLR at ED, median [IQR]	0.46 [0.32, 0.70]	0.43 [0.31, 0.62]	0.46 [0.32, 0.68]
SIMs (prior to initial ED visit)			
NLR pre-ED, median [IQR]	2.99 [2.12, 4.31]	2.88 [2.05, 4.05]	2.98 [2.11, 4.29]
MLR pre-ED, median [IQR]	0.42 [0.31, 0.57]	0.41 [0.31, 0.54]	0.42 [0.31, 0.57]
Number of SIMs pre-ED, median [IQR]	8 [6, 13]	7 [5, 11]	8 [6, 13]
Follow-up (years), median [IQR]	2.86 [0.78, 7.18]	3.28 [1.49, 5.67]	2.9 [0.81, 7.04]
Death, n (%)	3089 (6.2%)	229 (7.6%)	3318 (6.3%)

Means (μ) and trend (θ) of NLR, MLR up to baseline predicts AD/ADRD (Y):



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Figure 2 – ROC curves comparison of AD/ADRD prediction models from ED



RESULTS

- Cohort:** 52,816 patients; 3,017 (5.6%) developed AD/ADRD. Median NLR 3.48 [3.25–5.75] and MLR 0.46 [0.32–0.68] at initial ED visit, with slightly lower pre-ED values across 8 [6–13] samples.
- Main Result:** In the 20% validation set, the 5-year prediction model incorporating ≥ 8 pre-ED SIM values achieved an AUC of 0.725, outperforming ED-only SIMs (AUC 0.708) and demographics alone (AUC 0.684). Similar relative gains were observed in sub-cohorts with fewer SIM measurements.
- Model Comparison** (Figure 2): ROC curves stratified by prediction window (3, 5, 7 yrs) and minimum lab samples (3, 5, 7 pre-ED). The full ED-SIM trajectory model (Pre-ED + ED SIM + Demographics) outperformed the ED SIM + Demographics model and the demographics-only model. All models adjusted for age (linear/quadratic), sex, and race/ethnicity (Figure 2).

CONCLUSIONS AND FUTURE WORK

- Incorporating markers of systemic inflammation (NLR, MLR) measured during and prior to an initial ED visit substantially improves AD/ADRD risk prediction. While SIMs from a single ED visit demonstrate strong predictive performance, inclusion of prior values provides additional improvement, substantiating the role of systemic inflammation in AD/ADRD.

REFERENCES

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