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An increased Neutrophil-Lymphocyte ratio in Alzheimer’s disease is a function of age and is weakly correlated with neocortical amyloid accumulation.

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Abstract

Inflammation is a hallmark of Alzheimer’s disease (AD). Whether directly involved in the pathogenesis, or a downstream consequence of neuronal death, the blood neutrophil-lymphocyte ratio (NLR) is reported to be a putative, non-invasive peripheral biomarker for AD. The aim of this study was to re-evaluate the diagnostic utility of longitudinal measures of the NLR in participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Healthy controls (HC), AD and mild cognitively impaired (MCI) participants were screened by clinical pathology blood count analysis for neutrophils and lymphocytes over 4 time points, 18 months apart. The NLR was stable across all time-points and weakly correlated with neocortical amyloid burden (R=0.21 at baseline, 0.27 at 18 months, 0.20 at 36 months and 0.10 at 54 months). Cross-sectionally, the NLR was significantly elevated in AD participants as compared to HC participants at baseline (p<0.0001), 18
months ($p<0.0001$), 36 months ($p=0.002$) and at 54 months ($p=0.007$), however only prior to adjustment for age, sex and $APOE\varepsilon 4$ allele status ($p>0.05$ at all time-points except for 18 months; $p<0.0001$). Longitudinally, the NLR was not significantly different between HC and AD participants ($p>0.05$) adjusted for age, sex and $APOE\varepsilon 4$ allele status. Comparing the NLR between cognitive transition groups over time (transition towards an AD type dementia), there was no significant difference in the NLR levels between those participants, who did not transition and those participants who did transition, or those in the stable AD group after adjusting for age, sex and $APOE\varepsilon 4$ allele status ($p>0.05$). Despite inflammation being a hallmark in AD and previous reports showing that the NLR can discriminate HC from AD patients, our results suggest that the sensitivity of the NLR itself is not robust enough for diagnostic utility. We identified significant relationships cross sectionally ($p<0.05$ at baseline, 18 months and 36 months) between the NLR and neocortical amyloid burden, but this relationship was lost after longitudinal analyses ($p>0.5$). The NLR also had limited association with cognitive decline, although in our cohort, the number of participants transitioning was relatively small. In conclusion, the NLR may reflect AD-related inflammatory processes in the periphery, but age and sex are dominant covariates which need to be controlled for in population-based screening.
Introduction

The growing prevalence of Alzheimer’s disease (AD) represents one of the major unmet medical challenges of the 21st century. In 2010, there were an estimated 35.6 million individuals diagnosed with dementia bringing with them an estimated annual cost in excess of $604 billion [1]; a figure that far surpasses the costs of cancer, heart disease and stroke in a number of developed countries [2]. It is projected that without an effective therapy, the prevalence of AD will nearly double every 20 years; reaching 65.7 million affected individuals in 2030 and 115.4 million by 2050 [3, 4]. To date, efforts to treat mild-to-moderate AD have been unsuccessful [5, 6] and have led to a growing realisation within the field that treating it within the mild to moderate stages is too late [7, 8]. Rather, it is recognised that to be effective, disease-specific therapeutic interventions should be implemented within the pre-symptomatic or preclinical stages of the disease, before synaptic loss and neuronal degeneration is largely irreversible [7, 9]. However, in order to implement such a strategy, a panel of biomarkers allowing the preclinical identification of those individuals most at risk of developing AD must first be identified.

The amyloid-centric theory purports that AD arises from a disequilibrium between amyloid-β (Aβ) production and clearance, resulting in increased accumulation of Aβ in the brain and a subsequent cascade of downstream processes, including gliosis, excitotoxicity, neurofibrillary tangle formation, oxidative stress and inflammation [10]. With underlying Aβ pathology preceding the clinical onset of AD by upwards of 20 years [11-13] it is not surprising that efforts to identify peripheral markers for AD have thus far focused on plasma Aβ levels [14-17]. However, despite the inherent promise of Aβ, peripheral levels of the peptide have thus far failed to provide the prognostic power necessary to identify asymptomatic individuals at-risk for AD. As a result of these findings many researchers have turned their attention towards biomarkers of the downstream processes of Aβ dysregulation, such as markers of peripheral inflammation.
Inflammation is a well-established hallmark of a number of neurodegenerative diseases, including AD [18-23]. In AD, proinflammatory cytokines have been detected in both the central nervous system (CNS) [24] and the periphery [25, 26] indicating that a strong innate immune response and systemic immune recruitment are occurring throughout disease progression. Furthermore, these innate immune host-defence responses are reported to be triggered by the upstream dysregulation in the production and degradation of the Aβ peptide [27-29]. In the broader literature, circulating peripheral cells such as leukocytes, lymphocytes and neutrophils, are widely utilised as markers of systemic inflammation [30-32]. Studies have reported that peripheral leukocytes are altered in AD patients, compared to controls [33] and in models of systemic inflammation, such leukocytes have been reported to traverse the blood brain barrier and accumulate in neuronal tissue in a process that is mediated by interleukin-1β (IL-1β) [34]. Other studies have investigated the functional state of lymphocytes in AD and have reported that increased mitochondrial oxidative stress is evident in the lymphocytes of patients in the progression towards AD [35]. Additionally, elevations in oxidative stress markers are also evident in neutrophils of patients with either AD or Parkinson’s disease when compared to aged matched healthy controls [36]. Neutrophils have been observed to contain Aβ peptides in their phagocytic granules [37] and Aβ clearance is not thought to be limited to parenchymal microglia, but also to innate immune macrophages; however, perturbations in these phagocytic processes have been reported to occur in AD-affected tissue [38, 39].

There is overwhelming evidence to suggest that systemic inflammation is a central tenet of AD progression and the reported perturbations in circulating peripheral fluids [40-42] suggest that further investigations are warranted to determine whether such markers may be utilised in a diagnostic or even prognostic setting. At present one of the most economical and widely available clinical markers of peripheral inflammation is the neutrophil to lymphocyte ratio (NLR). Whilst the NLR is a broad-based measure, it has the distinct advantage of being generated from markers that are readily measurable in a standard full blood examination (FBE). Disequilibrium in the NLR has previously been reported to be predictive of poorer prognosis in a colorectal cancer [30], lung cancer [31], cardiovascular disease [43], diabetes [44] and recently, a significant increase in the NLR has been
observed in AD patients when compared to healthy controls [45]. However, whilst this study demonstrated that the NLRs of AD patients were significantly elevated, it did not establish whether the marker would be an effective and reliable diagnostic or even prognostic measure for AD. The aim of the present study therefore was to re-evaluate the diagnostic utility of standard clinical pathology testing of neutrophil and lymphocyte levels over 4 time-points, coupled with amyloid imaging modalities in a large, well characterised cohort.

Methods

Population sample

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study is a longitudinal prospective study of aging and Alzheimer’s disease. The study methodology has been previously described [46]. In brief, participants fluent in English and over the age of 65 years were divided into three clinical classifications, healthy control (HC), mild cognitive impairment (MCI) based on the established criteria [47, 48], and participants diagnosed with possible or probable AD as defined by NINCDS-ADRDA criteria [49]. Participants that transitioned between clinical classifications were classed as previously described [16]. Informed consent was obtained from all participants in writing and the study was approved by the appropriate institutional ethics committees.

Overnight fasted participants had blood collected into Sarstedt 2.6 mL K3E Ethylenediaminetetraacetic acid (EDTA) tubes (04.1901.001) with a 27 gauge phlebotomy needle, tubes were kept on a low speed laboratory rocker at room temperature and analysed within 2 hours.

Participants were screened by standard clinical pathology haematology (bulk counts only) for total neutrophil and lymphocyte levels over 4 time points, 18 months apart using a Coulter LH 700 series automated haematology analyser. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.
Neuroimaging methodology

Neocortical amyloid imaging was assessed by $^{11}$C-Pittsburgh compound B (PiB)-positron emission tomography (PET) (as calculated by the Standardized Uptake Value Ratio (SUVR)) as described previously [50].

Statistical methodology

Descriptive statistics including means, standard deviations and frequencies were calculated across clinical classification. Sex and $APOE\varepsilon 4$ allele comparisons were assessed using Chi squared ($\chi^2$) test and Fisher’s Exact where necessary. Ordered Polynomial Logistic Regression (PLR) was used to assess biomarker significance across HC, MCI and AD groups, and non-transition, transition and stable AD groups. Generalised Linear Modelling (GLM) and Generalised Linear Mixed Modelling (GLMM) were used to assess relationships between HC and AD groups, and non-transition and transition groups and biomarkers, adjusted for age, sex and $APOE\varepsilon 4$ allele status. Tobit regression and GLMs were used to investigate MMSE and memory composite scores respectively. Pearson’s Correlation coefficients were calculated to describe the relationship between the NLR and SUVR and hippocampal volume.

Episodic memory composites were calculated as the average of the $z$ score for California Verbal Learning Test Second Edition long delayed recall and Rey Complex Figure Test 30 minute delayed recall. Non-memory cognition composites were calculated the average of the $z$ scores for Rey Complex Figure Test copy, Digit Symbol Coding, Boston Naming Test, Letter Fluency, Category Fluency, Digit Span (forwards), and Digit Span (backwards). $^a$ $p$-value unadjusted. $^b$ $p$-value adjusted for age, sex, $APOE\varepsilon 4$ genotype and site. $p$-values represent the differences across HC, MC and AD classifications.

The R statistical software environment, version 3.0.2 was utilised for all statistical analyses (Team, R Development Core. 2009. R: A Language and Environment for Statistical Computing Manual). $p$-values were compared against a Bonferroni adjusted alpha of 0.017 (0.05/3).
Results

Population demographics

From an overall cohort of 1,112 participants, NLR data was available for 98.4% of participants at baseline (N=1,094) whilst follow-up NLR data collected at 18, 36, and 54 months was available from >98% of baseline participants at each time point (Table 1). As expected, there were significant differences across the diagnostic group for age, APOEε4 status and cognitive functioning, with AD patients being older, having higher percentages of APOEε4 carriers and poorer performance on cognitive assessments. There were no significant differences in sex across the clinical groups, regardless of time point.

Neutrophil and Lymphocyte comparisons

Neutrophil and lymphocyte levels were compared across clinical classifications (HC, MCI and AD) in addition to cognitive transition groups (non-transition, transition, stable AD) at each time point. Unadjusted p-values (a) were presented alongside p-values (b) adjusted for age, sex and APOEε4 allele status (Table 1 and Supplementary Table 2). Post adjustment and comparing individual classifications (data not shown), neutrophil levels were significantly higher in AD subjects compared to HC at both the 18 and 36 month time points (p<0.0001). However, no significant differences were observed at baseline or 54 months for neutrophil or lymphocyte levels between AD patients and HCs, regardless of time point. Comparisons between the HC and MCI groups did not reveal any significant differences in either neutrophil or lymphocyte levels, regardless of time point and / or statistical adjustments.

Similar findings were made when neutrophil and lymphocyte levels were compared across the three cognitive transition groups, again regardless of time point (Supplementary Table 2). Comparing individual groups (data not shown), elevated neutrophil levels were observed in the stable AD group at 18 (p<0.0001), 36 (p=0.0001) and 54 months (p=0.007) when compared with the non-transition group post adjustment for age, sex and APOEε4 allele status. However, a significant difference was
not observed at baseline ($p=0.06$). Furthermore, no significant differences were observed between non-transition and transition groups for either neutrophil or lymphocyte levels, regardless of time point or adjustment.

**Cross sectional NLR comparisons**

NLR data was compared across diagnostic groups, and cognitive transition groups at each time point (Table 1 and Supplementary Table 2). Comparison of the marginal unadjusted means across diagnostic groups revealed significant increases in the NLR for AD participants, when compared to HC participants at baseline ($p<0.0001$), 18 months ($p<0.0001$), 36 months ($p=0.002$) and 54 months ($p=0.007$; Figure 1). However, this significance at baseline, 36 and 54 months was abrogated after adjustments were made for age, sex and $APOE\epsilon4$ allele status, whilst at 18 months the significant elevation was retained ($p<0.0001$). Significant differences in the NLR ratios were also observed between MCI and HC participants; however, only prior to adjustment, and only for the baseline and 18 month time points ($p=0.01$ & $p=0.002$ respectively).

Comparing the NLR marginal means across transition groups, we identified a significant elevation in both transition and stable AD groups compared with the non-transition group at baseline (non-transition vs transition: $p=0.01$, non-transition vs stable AD: $p<0.0001$), 18 months (non-transition vs transition: $p=0.0001$, non-transition vs stable AD: $p<0.0001$), 36 months (non-transition vs transition: $p=0.033$, non-transition vs stable AD: $p=0.006$) and at 54 months, except for non-transition vs transition (non-transition vs transition: $p=0.262$, non-transition vs stable AD: $p=0.004$). Adjusting for age, sex and $APOE\epsilon4$ allele status abrogated these significant differences at all time points ($p>0.05$), except at the 18 month time point ($p=0.0001$).

**Longitudinal NLR comparisons**

NLR levels were found to significantly increase with age over time ($p<0.0001$) and were significantly elevated in $APOE\epsilon4$ carriers ($APOE\epsilon4$ negative: NLR=1.71 (SD±0.50), $APOE\epsilon4$ positive: NLR=1.64 (SD±0.49) $p=0.005$ respectively). The NLR appeared to be elevated in male participants when
compared to female participants (males NLR= 2.68 (SD±1.38), females NLR= 2.30 (SD±1.30); however, this comparison did not reach statistical significance (p>0.05).

Generalised Linear Mixed Modelling (GLMM) was used to assess the NLR levels across the diagnostic groups over time. Post adjustment for age, sex and APOE\(\varepsilon4\) allele status, we found no significant elevation in the NLR levels over the 54 months (p=0.16; data not shown). Analysis of the transition groups also revealed no significant differences between the NLR levels over time for either transition or stable AD participants when compared to those of non-transition participants (p>0.05).

**NLR vs MMSE, memory and non-memory composite scores**

Pearson’s correlations were used to ascertain the level of overlap between the clinical presentations of AD and observable peripheral inflammatory processes. These analyses revealed that NLR levels did not correlate with cognitive function as measured by the MMSE, regardless of time point (p>0.05). However, weak negative correlations were observed between the NLR and both composite episodic memory scores and non-memory cognitive scores (p=0.05 and p=0.02 respectively).

**NLR vs neocortical amyloid burden**

Overall, the NLR levels were found to positively correlate with neocortical amyloid burden as measured by PiB-PET SUVR (Figure 2; Baseline: R=0.21 (p=0.001), 18 months: R=0.27 (p<0.0001), 36 months: R=0.20 (p=0.01) and 54 months: R=0.10, (p=0.26)); however, relationships were noticeably subtle. Further investigation using GLM revealed a significant positive association between the NLR and amyloid burden was also evident at baseline (unadjusted, p=0.002, adjusted p=0.007), 18 months (unadjusted p=0.0001, adjusted p=0.006) and 36 months (unadjusted p=0.03, adjusted p=0.03), but not at 54 months (unadjusted p=0.21, adjusted p=0.39), even after adjustment for age, sex and APOE\(\varepsilon4\) allele status (p>0.05). Longitudinal analyses via GLMM revealed no significant association between the NLR and amyloid burden both prior to and post adjustment for
age, sex and \textit{APOE}\textsubscript{ε4} allele status ($p=0.82$ and $p=0.79$ respectively), with the association abrogated due to the age and time point associations.

\textbf{Discussion}

The peripheral immune system has long been interrogated as a source of biomarkers for various disease states including AD [30-32, 35, 51]. Recently, the NLR was proposed to be informative as a non-invasive, peripheral biomarker for AD [45]. This notion was re-evaluated in the current study through the analysis of the NLR in the AIBL cohort and whilst some significant differences were observed the sensitivity of the NLR was limited for the detection of AD and inadequate for predicting which participants would transition through to MCI or AD. Significant correlations were observed between the NLR and neocortical amyloid burden; however, these correlations were weak and were likely driven by the large sample size of the cohort. The initial findings that the NLR was elevated in AD compared to HCs were consistent with the results reported by [45]; however, adjustments for age, sex and \textit{APOE}\textsubscript{ε4} allele status, in the current study, indicate that it was these covariates, rather than the underlying disease process, that were driving the changes observed in this ratio.

In the current study, cross-sectional neutrophil levels, but not lymphocyte levels, were significantly elevated in both AD participants and stable AD participants compared with controls and non-transitioners respectively. However, this significance was abrogated through the longitudinal analysis, both before and after statistical adjustments were made. As lymphocyte levels were not significantly different across the diagnostic groups, it was postulated that the observable differences in the NLR were being driven primarily by the elevated neutrophil levels observed in the AD patients in addition to covariates such as age rather than AD pathogenesis.

Aging subjects often have concomitant disease processes that may act to mask or trigger immune responses, which can subsequently modulate the relative ratios of immune cell proliferation or expression. Whilst the CNS is largely thought of as an immune privileged tissue, systemic immune cross-talk and infiltration can occur, between the CNS and the peripheral system, under certain conditions [52, 53]. During inflammation, it is thought that impediments in the Aβ clearance
pathways, in addition to signals from distressed / dying neurons, result in the relay of signals from the CNS to the systemic immune system that could stimulate peripheral inflammation. It has been postulated that this local recruitment may be responsible for a number of subtle changes in immune cell dynamics and eventually lead to aberrations in peripheral immune expression [18, 54].

The activation of the peripheral immune response in AD [19] coupled with the knowledge that biomarkers of this response have previously been detected in the disease indicate that such markers may have utility in the diagnostic setting [55]. This notion is further aided by the non-invasive, economical and expedient nature of standard clinical pathology haematological screening techniques. However, whilst promising, these markers remain largely non-specific and our results suggest that they are also readily influenced by covariate factors such as age and sex.

Moving forward, investigations examining the activation and maturation phenotype of such immune cells will better elucidate what role these biomarkers will serve in the diagnostic processes. Additionally, the analysis of cell surface markers and intracellular markers, would provide researchers with a more thorough understanding of the contributions that changes in these peripheral systems make to the pathogenesis of AD and whether they can be utilised as surrogate markers for neocortical amyloid burden or other underlying pathogenic processes.

In conclusion, differences in the NLR were found to be driven by covariates including age, sex and \( APOE^\varepsilon4 \) status and offered inadequate diagnostic or prognostic utility. Future studies utilising broad-based measures for AD biomarkers, such as the NLR, should be mindful to adjust for these covariates in order to ensure that the clinical utility of such measures are not over extrapolated.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>18 months</th>
<th>36 months</th>
<th>54 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>MCI</td>
<td>AD</td>
<td>p-value&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>759</td>
<td>130</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>70.57 (6.98)</td>
<td>76.25 (7.5)</td>
<td>78.99 (8.4)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>436/323</td>
<td>74/56</td>
<td>125/80</td>
<td>0.637</td>
</tr>
<tr>
<td><strong>APOE&lt;sub&gt;ε4&lt;/sub&gt;</strong></td>
<td>552/207</td>
<td>65/65</td>
<td>78/127</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29 (1.19)</td>
<td>26.5 (2.66)</td>
<td>20 (5.27)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Composite score&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td>0.06 (0.58)</td>
<td>-1.3 (0.56)</td>
<td>-1.84 (0.57)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Composite score&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>0.05 (0.68)</td>
<td>-0.95 (0.77)</td>
<td>-1.86 (0.7)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>3.49 (1.19)</td>
<td>3.73 (1.39)</td>
<td>3.9 (1.54)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>1.62 (0.51)</td>
<td>1.6 (0.73)</td>
<td>1.58 (0.59)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>NLR</strong></td>
<td>2.34 (1.07)</td>
<td>2.69 (1.42)</td>
<td>2.76 (1.37)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>SUVR (N)</strong></td>
<td>171</td>
<td>53</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td><strong>SUVR mean(sd)</strong></td>
<td>1.42 (0.4)</td>
<td>1.86 (0.4)</td>
<td>2.32 (0.4)</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>
Table 1. Shows the demographics of the cohort analysed in this study, means and standard deviation (sd), neuropsychological performance based on MMSE and Neutrophil, Lymphocyte counts and their relative ratios at baseline, 18, 36 and 54 months, divided by clinical classification at each time point.

AD Alzheimer's disease, MCI, mild cognitive impairment, HC healthy control, APOEε4 Apolipoprotein ε4, MMSE mini-mental state examination, NLR Neutrophil-Lymphocyte ratio, SUVR Standardized Uptake Value Ratio. ¹ Calculated as the average of the z score for California Verbal Learning Test (Second Edition) long delayed recall and Rey Complex Figure Test, 30 minute delayed recall. ² Calculated as the average of the z scores for Rey Complex Figure Test copy, Digit Symbol Coding, Boston Naming Test, Letter Fluency, Category Fluency, Digit Span (forwards), and Digit Span (backwards). ᵃ p-value unadjusted. ᵇ p-value adjusted for age, sex, APOEε4 genotype and site. p-values represent the differences across HC, MC and AD classifications.
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References


Figure 1.
Figure 2.
Figure 1: Box and whisker plots of the Neutrophil to Lymphocyte ratio between clinical classification and time points; A) baseline, B) 18 C) 36 and D) 54 months. Box and whisker plots show the range, interquartile range and median values.

Figure 2: The Neutrophil to Lymphocyte versus neocortical amyloid burden (NAB) as assessed by standardized uptake volume ratio (SUVR) by clinical classification and time points; A) baseline, B) 18, C) 36 and D) 54 months. Correlation coefficients for baseline; (HC): R=0.152, (MCI): R=0.163, (AD): R=0.006. 18 months; (HC): R=0.222, (MCI): R=0.053, (AD): R=0.134. 36 months; (HC): R=0.076, (MCI): R=0.261, (AD): R=0.204. 54 months; (HC): R=0.068, (MCI): R=0.071, (AD): R=0.206.
**Highlights**

The neutrophil to lymphocyte ratio was analysed in a comprehensive study of aging.

The neutrophil to lymphocyte ratio was elevated in subjects with Alzheimer’s disease.

The neutrophil to lymphocyte ratio also correlated with neocortical amyloid burden.

Age and sex are dominant covariates that need to be considered when interpreting these findings.
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