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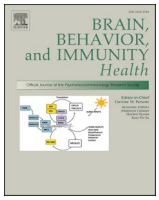

Structural and functional brain correlates of the neutrophil- and monocyte-to-lymphocyte ratio in neuropsychiatric disorders

Roger McIntosh [a,b]

[a] Department of Psychology, University of Miami, 5665 Ponce de Leon Blvd, Coral Gables, FL, 33146, USA
[b] Department of Medicine, University of Miami Miller School of Medicine, 1150 NW 14th Street, Miami, FL, 33136, USA

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ABSTRACT

Skews in the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) increasingly demonstrate prognostic capability in a range of acute and chronic mental health conditions. There has been a recent uptick in structural and functional magnetic responance imaging data corroborating the role of NLR and MLR in a cluster of neuropsychiatric disorders that are characterized by cognitive, affective, and psychomotor dysfunction. Moreover, these deficits are mostly evident in setting of acute and chronic disease comorbidity implicating aging and immunosenescent processes in the manifestation of these geriatric syndromes. The studies reviewed in this special edition implicate neutrophil and monocyte expansion relative to lymphocytopenia in the sequelae of depression, cognitive and functional decline, as well as provide support from a range of neuroimaging techniques that identify brain alteartions concommitant with expansion of the NLR or MLR and the sequelae of depression, dementia, and functional decline.

1. Introduction

The neutrophil-to-lymphocyte ratio (NLR) was first described in the medical setting at the cusp of the third millenium as an indicator of systemic inflammation and neuro-endocrine stress in critically ill hosptial admissions (Zahorec, 2001, 2021). Normative values of the NLR range from 0.78 to 3.53 with a mean of 1.65 with a range between 0.78 and 3.53, values which have been replicated in international cohorts (Forget et al., 2017; Luo et al., 2019). Prior to the establishment of the NLR as a marker of physiologic stress, scientists were aware that in vivo increases hydrocortisone resulted in a depletion in various sub-populations of human lymphocytes and to a lesser extent monocytes, while simultaneously increasing the neutrophil count (Fauci and Dale, 1974; Onsrud and Thorsby, 1981). In contrast to neutrophils which make up 40% to 60% of white blood cells monocytes constitute 2% to 8% of the pool resulting in a normal MLR range of .10 to .20. In response to an inflammatory-immune response extravasation of polymorphonuclear neutrophils is followed by a subsequent emigration of monocytes due to the chemotactic activity of lysates (Ward, 1968). Neuroendocrine responses are also implicated in the expansion of these ratios as the activation of β2-adrenoceptors transiently mobilizes lymphocyte subsets before they are subsequentially depleted (Benschop et al., 1996). Although elevated in response to MLR chronic infectious disease, i.e., bacterial and to a lesser extent viral pathogens, increase in physiologic stress may predominately skew neutrophils in a positive direction while driving down select leukocyte subsets, ultimately increasing neutrophil, monocyte, and platelet to lymphocyte ratios through mechanisms involving reciprocal activation (Ramirez et al., 2019) (see Table 1, Fig. 1).

The NLR is often elevated in conditions where there is an acute inflammatory response and a decrease in cell-mediated immunity such as infections, autoimmune diseases, and certain types of cancer (Zahorec, 2021; Bhat et al., 2013; Guthrie et al., 2013; Peng et al., 2018). On the other hand, MLR tends to be elevated in chronic inflammatory conditions (e.g., chronic infections, rheumatic conditions, and certain cancers where monocytes play a prominent role (Afari and Bhat, 2016; Gu et al., 2016; Nishijima et al., 2015; Quan et al., 2020; Stefaniuk et al., 2020). While both NLR and MLR are considered markers of inflammation, they are thought to be influenced by different underlying mechanisms. For example, high NLR is typically associated with acute inflammatory responses where neutrophils are rapidly recruited to the site of infection or injury, whereas the MLR is shown to expand where there is chronic tissue injury, repair or regeneration.

Skews in NLR and MLR aren't always in the same direction. For example, high NLR can be observed with lower MLR during early stages of infection (Fang et al., 2019; Hou et al., 2021). Whereas the NLR is

E-mail address: r.mcintosh@miami.edu.

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skewed down and MLR skewed up in chronic viral infections or autoimmune diseases that are characterized by prolonged inflammation. While different triggers are implicated in the expansion of neutrophil and monocyte pools, both ratios may be positively skewed in cancers (Cong et al., 2020) and a host of psychiatric conditions (Mazza et al., 2019; Yang et al., 2023). Age is common driver of a skewed neutrophil or monocyte ratio with both pre-clinical and clinical studies implicating cell-intrinsic mechanisms, pro-inflammatory signaling molecules, as well as local microenvironmental alterations (Kong et al., 2020). Amongst the other age-related changes in monocyte function that may impact the ratio with peripheral lymphocytes include variations in DNA methylation as well as co-inhibitory receptor density in lymphocyte and monocyte subsets, respectively (Cao et al., 2022; Reynolds et al., 2014).

Most recently, the scope of the NLR and MLR in human health and disease has expanded to include disorders of the central nervous system (Mazza et al., 2018; Su et al., 2022; Sunbul et al., 2016; Wei et al., 2022). Given that the NLR and MLR expand with increasing age a cluster of geriatric syndromes concomitant with immunosenescense, i.e., frailty, dementia, and depression have gained attention from a neuroimmune perspective (Bhikram and Sandor, 2022; Guan et al., 2022; Losada et al., 2019). Under normal conditions endothelial integrity restricts the homing of peripheral immune cells to the brain parenchyma. However, this trafficking is enhanced under acute and chronic pathological conditions such as infection, ischemia, trauma, and neurodegeneration (Daneman and Prat, 2015; Pillay et al., 2010; Profaci et al., 2020). Multiomic spatial analysis of innate immune cells at human blood brain barrier has revealed diverse myeloid subsets including CNS-associated macrophages, dendritic cells, monocytes and CD4+/CD8+ T-lymphocytes are involved in trafficking of neuroinflammatory products across the blood brain barrier (BBB) (Sankowski et al., 2024). Transitory monocytes predominate the choroid plexus and dura mater of the normal adult brain despite a paradoxical absence in accumulation of neutrophils within the perivascular space. As alluded, both human and animal models of myeloid activation reveal a temporal hierarchy of neutrophil proliferation followed by subsequent expansion of both classical and nonclassical/intermediate monocyte pool (Mócsai et al., 2015; Swirski and Robbins, 2013; Zimmermann et al., 2012). Several factors that are outside the scope of this review skew the gradient between the absolute pool of peripheral neutrophils and lymphocytes (Liew and Kubes, 2019; Rosales, 2020). Neutrophils also give rise to byproducts such as matrix metalloproteinase-9 (MMP-9), which directly induces BBB disruption (Duan et al., 2018). Thus neutrophils are the primary periphery-derived immune cells responsible for resulting in age- and disease-related fluxes in cytokines, proteases, reactive oxygen species, and other cytotoxic products that result in secondary damage to neural, glial, and endothelial tissue (Ceulemans et al., 2010; Pluvinage and Wyss-Coray, 2020; Van Avondt et al., 2023). Non-invasive markers of neuroinflammation have advanced in recent years, however positron emission tomography (PET) radioligands have not been consistently compared with PBMC ratios across in neuropsychiatric diseases models (Ory et al., 2014). Nonetheless, there is promise for the incorporation of PET imaging in Alzheimer's Disease where emergent evidence supports

Table 1
Characteristics of the studies reviewed.

Disease model	Study authors	Sample	Cellular marker	Imaging marker	Outcome	NLR/MLR values
Alzheimer's Disease	Hou et al. (2022)	1107 adults 73.2 ± 7.3 yrs.	NLR	T1-W GMV PET Aβ	↑ NLR = ↓ HPV ↓β amyloid	CN NLR = 2.1 AD NLR = 2.7
Alzheimer's Disease	Qiang et al. (2023)	313,448 60.4 ± 5.4 yrs.	NC LC	FA MD	↑NC,↓LC = ↓ FA ↑ MD ↑NC = ACD, VD	ACD NC = 62.5 CN NC = 60.9 ACD LC = 27.3 CN LC = 28.7
Alzheimer's Disease	Mehta et al. (2023)	1544 adults MCI 73.0 ± 7.6 CN 75 ± 5.7 yrs.	NLR, LMR	PET Aβ PET tau	↑NLR = ↑ Aβ ↓cognition	AD NLR = 2.7 CN NLR = 2.3 AD LMR = 4.6 NC LMR = 5.1
Alzheimer's Disease	Li et al. (2023)	1551 adults 60.0 ± 11.4 yrs.	NLR	PET Aβ	↑ NLR = ↓cognition ↑ anxiety ↑DSS ↓ GMV ↑ Aβ	
Cerebrovascular Disease	Lan et al. (2021)	165 adults CN 60.9 ± 10.3 BPPV 61.9 ± 12.2 ACL 62.1 ± 11.4	NLR	T1-W GMV WMV		
Dementia	Fang et al. (2022)	6003 adults aged ≥60 yrs.	NLR	WMV	↑NLR = ↓cognition ↑ WMV + ↑ MVD	
Depression	Aruldass et al., 2021	129 adults (83 depressed) aged 25–50 yrs.	NC MC LC CRP	Network FC	↑NC ↑CRP	
Depression/PTSD	Benedetti et al. (2021)	42 COVID-19 survivors, 54.9 ± 7.9 yrs.	SII	Network FC	↑SII = ↑DSS ↑PTSD = ↓FC	
Depression	McIntosh et al. (2022)	66 adults, aged ≥65 yrs.	NLR	Seed to whole brain	↑NLR = ↑DSS	
Depression	Zhao et al. (2022)	66 adults (33 depressed), 55.2 ± 7.3 yrs.	NLR	FC IFG-caudate	↑NLR = ↓FC	
Depression	Duan et al. (2024)	1065 adults (685 minimally depressed), 72.3 ± 7.3 yrs.	NC	Limbic GMV DWI	↑NC = ↓GMV ↓DWI	
Frailty	Dillon et al. (2023)	589 adults, YA 50.5 yrs. OA 64.4 yrs.	NLR	Sensory network FC	↑NLR = ↓grip strength ↓ FC	

Acute cerebral infarction (ACI) group, All cause dementia (ACD), Benign paroxysmal positional vertigo (BPPV) group, Cognitively normal (CN), Cortico-striato-thalamo-Cortical loop (CSTL), Degenerative cervical myelopathy (DCM), Depression symptom severity (DSS), Diffusion Weighted Imaging (DWI), Functional connectivity (FC), Fractional Anisotropy (FA), Gray Matter Volume (GMV), Hippocampal (Hipp), Hippocampal Volume (HCV), Interior Frontal Gyrus (IFG), Lymphocyte Count (LC), Mean diffusivity (MD), Microvascular disease (MVD), Mild cognitive impairment (MCI), Monocyte (MO), Monocyte to lymphocyte ratio (MLR), Neutrophil count (NC), Neutrophil-lymphocyte ratio (NLR), Older adults (OA), Systemic Immune Inflammation Index (SII), Vascular dementia (VD), White matter volume (WMV), Younger adults (YA).

an positive association between NLR and cerebrospinal fluid amyloid beta (Aβ) levels deposition in the hippocampus (Li et al., 2023).

Overall, in the acute or chronic disease state trafficking of neutrophils and monocytes and their signaling proteins interfere with the synthesis, release, reuptake, and breakdown of neurotransmitter systems within subcortical and cortical networks. It is important to note that peripheral leukocyte trafficking is but one of several mechanisms for the altered neuroglial function observed in geriatric syndromes. The complementary role of a glymphatic system that prevents the accumulation of the protein and waste products that trigger neuroinflammatory responses should also be taken into account (Cai et al., 2024; Natale et al., 2021; Szlufik et al., 2024). Although outside the scope of the current review, it should be noted that neuroimaging also holds promise for in vivo assessment of perivascular fluid movement in the glymphatic system through diffusion tensor imaging of free water motion properties (Kaur et al., 2020; Lee et al., 2022; Naganawa et al., 2024).

2. The NLR and MLR in infectious disease

The diagnostic value of the NLR emerged in emergency care settings where the measure was shown to outperform conventional markers of systemmic inflimation such as C-reactive protein (CRP), white blood cell (WBC) count, and lymphocyte count in the diagnosis of sepsis (de Jager et al., 2010). Indeed, the NLR is particularly sensitive to bacterial infections and may demonstrate greater proliferation in response to viral infections (Gurol et al., 2015; Holub et al., 2012; Huang et al., 2020; Naess et al., 2017). Nonetheless, both the NLR and MLR demonstrate good predictive value for the prognosis and neuropsychiatric sequelae of a host of viral infections ranging from tuberculosis (TB) and Hepatitis C to the more recent SARS-CoV-2 (Alkhatip et al., 2021; Li et al., 2020b; Meng et al., 2016). For example, in a study of patients hospitalized for SARS-CoV-2 presenting with primary neurological delirium found evidence of greater middle cerebral artery ischemia in patients with higher neutophil counts and lower lymphocyte counts reinforcing the role of neutrophil expansion in intracranial atherosclerotic processes (Dehnavi et al., 2022). Additionally, an increased systemic inflammatory index, indicated by lymphocyte, neutrophil, and platelet counts, predicted aberrant resting state functional connectivity (rsFC) of major brain networks implicated in neuropsychiatric dysfunction including the default mode, language, frontoparietal, salience and dorsal attentional networks (Benedetti et al., 2021; Koch et al., 2016; Yan et al., 2019). Neutrophil- and monocyte-to-lymphocyte ratios are also adept at the prognosis of immunosuppression, neuropsychiatric impairment, and brain atrophy in persons co-infected with HIV and TB (Choudhary et al., 2019; Gatechompol et al., 2021; Miyahara et al., 2019). Although nadir CD4 count and ratioto CD8 t-lymphocytes has been the gold standard in prognosis of HIV disease the field has yet to establish a reliable peripheral biomarker of HIV-associated neurocognitive disorder (Hassanzadeh-Behbahani et al., 2020; Nichols et al., 2019; Samboju et al., 2018). However, soluble $CD14^{+}$ and $CD16^{+}$ monocyte counts were recently found to out-perform CD4:CD8 ratio in predicting cerebral hypoperfusion and gray matter atrophy, and dementia (Burdo et al., 2023)(Joseph et al., 2023). Given that monocyte activation and translocation across the BBB is a known mechanism for HIV-associated neuropathogenesis, a breadth of markers of monocyte activation such as monocyte chemoattractant protein-1 and CCR5 are implicated in neuropsychiatric manifestations of HIV disease (Burdo et al., 2013; McIntosh et al., 2015; Williams et al., 2014; Weiss et al., 1999). For example, in a sample of women living with and without HIV, $sCD14^{+}$ was the only soluble myeloid marker predicting smaller frontal and temporal cortical volumes across the entire cohort. However, sCD163 was linked to smaller volume of the middle frontal gyrus in the HIV-seropositive group only (Kamkwalala et al., 2020). In another combined sample of women living with and without HIV both stimulated and unstimulated monocyte expression of TNF-α predicted lower rsFC between the medial profrontal cortex and nucleus acumbens, regions involved in emotion regulation (McIntosh et al., 2024). Biomarkers of neutrophil activation such as neutrophil gelatinase-associated lipocalin (NGAL) were also linked with reduced volume of the medial prefrontal cortex in a cohort of persons living with HIV in South Africa (Williams et al., 2020). Notably, the association between NGAL and impaired motor performance was statistically mediated by reductions in cortical volume. While evidence of monocyte activation in the manifestation of HIV-associated neurocognitive

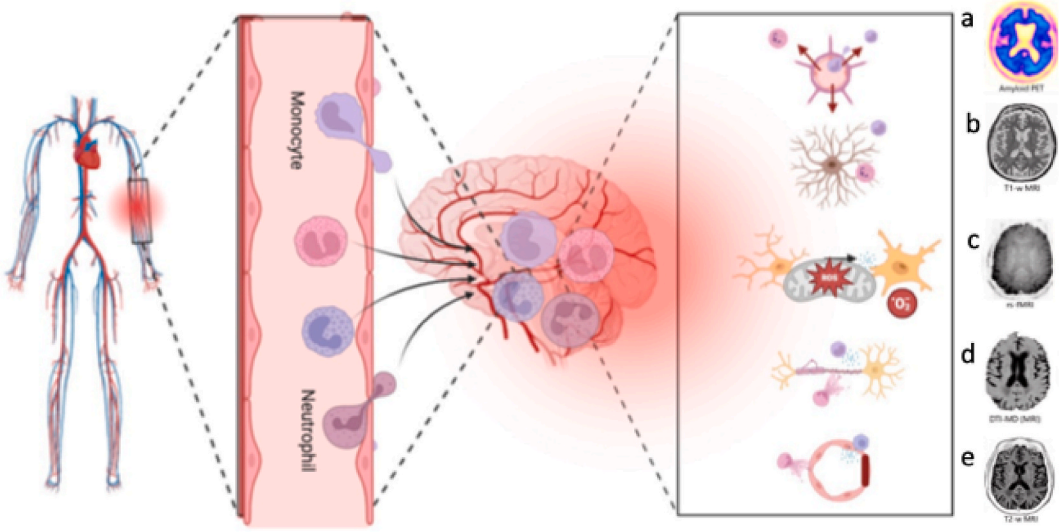

Fig. 1. Mechanisms implicated in neuroimaging correlates of skewed NLR and MLR.
Increase in NLR and MLR in conjunction with other resident and non-resident cells facilitates trafficking of peripheral blood mononuclear cells (PBMC) to the brain parenchyma. This influx contributes to the increased expression of neuronal nitric oxide synthase in circulating neutrophils can contribute to elevated levels of reactive oxidative species directly relates to in vivo AB deposition which can be detected via PET imaging (a). Release of neutrophil extracellular traps as well as pro-inflammatory cytokines and chemokines is linked to neuronal injury and altered release of neurotransmitters, the sum of which can manifest in aberrant brain structure (b) and functional connectivity (c). Neutrophils and monocytes may also contribute to the atherosclerotic processes that manifest in diffusion weighted imaging of white matter tracts in the brain (d). The extensive interaction of immune and endothelial cells may also manifest in small vessel disease which can be revealed through T2-FLAIR MRI (e).

impairment has emerged from several labs in recent years more work is needed to explore the structural and functional brain changes associated with monocyte and neutrophil expansion in HIV and other infectious disease models (Imp et al., 2017; Rempel et al., 2013; Singh et al., 2023; W Williams et al., 2014).

3. Effects of NLR and MLR on cerebrovascular disease

It is widely accepted that inflammatory-immune processes contribute to the development of atherosclerotic plaques in cerebrovascular disease. The release of pro-inflammatory cytokines, as well as the expression of reactive oxidative species and other degradative enzymes spawned by neutrophils have an adverse effect on the cerebrovascular endothelium (Mayer et al., 2013). Conversely, lymphocytopenia coincides with deficits in anti-inflammatory cytokines such as IL-10 and IL-4 and mitigation of restorative processes in the cerebrovascular endothelium (Iulita et al., 2019; Pelidou et al., 1999). Greater NLR is linked with cerebral large artery atherosclerosis independent from cerebral small vessel disease (CSVD) (Arola et al., 2023; Chung et al., 2020). Moreover, these neutrophils may also support monocyte adhesion to the vascular endothelium, a process known to directly contribute to the formation of atherosclerotic plaque (Soehnlein et al., 2009). In addition to the atherosclerotic mechanisms involved in stenosis of intracranial vessels peripheral markers of myeloid expansion are associated with white matter hyperintensities and microstructural abnormalities evidenced by diffusion-weighted imaging (Li et al., 2020a; Nam et al., 2017). While the etiology of the axonal degradation resulting from myeloid expansion and lymphocyte exhaustion is unclear there is proclivity for interactions between peripheral immune cells and genes controlling altered extracellular matrix remodeling, remyelination, and inflammation within the brain parenchyma (Jickling et al., 2022).

Neuropsychiatric research over the last 10 years has converged to lend support for the role of cerebrovascular disease and neuroinflammation in motor, cognitive, and emotional impairmentytu hy6 gty64er (Aronica et al., 2022; Clancy et al., 2021, 2022; Enache et al., 2019; Jokinen et al., 2022; Steffens, 2023). Emergent empirical evidence for altered patterns of low frequency fluctuations in the resting brain state specifically implicates neutrophil byproducts such as myeloperoxidase (MPO) DNA and NETs in the prediction of cognitive impairment in CSVD patients versus healthy controls (Shi et al., 2023). Elevated MPO is not only a molecular indicator of neutrophil turnover MPO oxidation but also reduces HDL-mediated inhibition of apoptosis and inflammatory processes which lead to cerebral small vessel disease (Karel et al., 2022). Moreover, neutrophils and MPO levels correspond to enlarged perivascular spaces within the basal ganglia in community-dwelling older adults (Jiang et al., 2022).

Pre-clinical evidence of a causative effect for neutrophils expansion on neuroinflammatory insult to neuronal tissue remains elusive. Work in Parkinson's disease (PD) suggest dopaminergic neuronal loss in the substantia nigra with the accumulation of nitric oxide and nitric oxide synthase in rodent models of PD, a finding which corresponds with the elevated expression of neuronal nitric oxide synthase in circulating neutrophils of patients with progressive PD (Bogdan, 2001; Gatto et al., 2000; Muñoz-Delgado et al., 2021). Evidence from animal models of Alzheimer's disease also show that an increase in reactive oxidative species from neutrophil hyperactivation and neutrophil extracellular trap formation is directly related to in vivo Aβ deposition in patients with AD (Uhl et al., 2016; Van Avondt et al., 2023). Although putative mechanisms involved in the aforementioned falls outside the scope of the current paper animal models of peripheral sources of inflammatory insult on cerebrovascular tissue has been instrumental shaping our understanding the causal role of neutrophil infiltration on behavioral brain changes. For example, in chronic stress–induced mouse models of depression, the BBB shows increased permeability to IL-6 in limbic regions such as the nucleus accumbens (NAc) (Dantzer et al., 2018; Menard et al., 2017), a finding that was replicated in post-mortem NAc of depressed patients. Despite the wealth of studies that trace neutrophil infiltration into the brain parenchyma neutrophils differ between rodents and humans in terms of their representation in peripheral blood, repertoire of receptors and secreted molecules, signaling pathways, granule proteins, as well as magnitude of reactive oxidative species production (Nauseef, 2023). Despite these and other noted inter-species differences, recent transcriptional work suggests that there is conservation in the drivers of the pro-inflammatory neutophil milieu by factors such as NF-κB family and AP-1 complex (Hackert et al., 2023).

Although there is no direct experimental evidence suggesting a causal effect for NLR or MLR on the functional connectivity of neural networks in humans indirect evidence does link aspects of the neutrophil-associated inflammatory milieu to disrupted connectivity within and between those networks. For example, it is well-established that the acute administration of endotoxin or vaccine products result in a time-dependent change in motivation and psychomotor slowing in healthy adultsvia reductions in ventral striatal blood oxygen level dependent activity (BOLD), dopamine (DA) bioavailability and metabolites in cerebrospinal fluid, and release of striatal DA (Felger and Treadway, 2017). These sum of these inflammation-related deficits in striatal neurotransmitter function can manifest in changes in mesolimbic functional connectivity and overall limbic function (Dipasquale et al., 2016; Harrison et al., 2009a). While these studies implicate transient increases in peripheral inflammation associated with endotoxin exposure to the observed neuropsychiatric deficits and not a specific immune cell subtype, it is important to note that expansion in the neutrophil and monocyte pool relative to lymphocytes may result from interferon-alpha treatment. Moreover, the pattern of abberant PET and fMRI-derived brain activations associated with exposure to typhoid vaccine include interoceptive brain regions germane to manifestation of sickness behaviors such as the insula, amygdala and dorsal anterior cingulate (Hannestad et al., 2012; Harrison et al., 2009b; Labrenz et al., 2016).

Several studies provide support for an increase in MLR and NLR with neuroimaging parameters that are indicative of white matter damage. White matter hyperintensities are a common manifestation of neuroinflammatory insult (Nam et al., 2022; Solé-Guardia et al., 2023). In a sample of 2875 adults confounder-adjusted analyses revealed that the NLR was not only correlated with higher volume of white matter hyperintensity but also a greater number of brain infarcts and extracranial atherosclerosis (Nam et al., 2017). Similarly, an index of platelet count × neutrophil count/lymphocyte count (SII) was associated with greater odd ratio for CSVD burden and risk of cognitive impairment indexed by the mini mental state exam in a cohort of adults over the age of 50 (Xiao et al., 2023). Similarly, longitudinal research in an Ecuadorian cohort of older adults revealed greater SII was associated with elevated white matter hyperintensity progression over 7 years suggesting innate immune cell proliferation may predict the trajectory of neuroinflammatory insult to connective tissue in the brain (Del Brutto et al., 2023).

4. Neuroimaging support implicating NLR and MLR in neuropsychiatric disorders

4.1. Mood disturbance and depression

Evidence is increasingly being leveraged for a phenotype of elevated neutrophil and monocyte ratios in a host of neuropsychiatric disorders principally characterized by the disruption of neural networks involved in the cognitive regulation of emotion. Those studies support a mechanistic hypothesis for granulocyte-and monocyte-derived induction of pro-inflammatory mediators such as microglial activation in the altered structure and function of brain regions underpinning mood disturbance (Hughes and Ashwood, 2020). Mechanistic evidence of the effects of peripheral neutrophil expansion on acute changes within the brain parenchyma is currently limited to pre-clinical models. For example, a

recent study using PET imaging to track neutrophil infiltration in AD transgenic mice found increase uptake of CAP37, a human neutrophil-derived chemotactic factor that is involved in monocyte recruitment, and microglia activation with advancing stages of behavioral impairment (Kong et al., 2020). In the case of major depressive disorder several neuroimmune mechanisms have been implicated. Peripheral inflammation can be linked to glucocorticoid resistance and HPA axis dysfunction, both common features of the depressive episode (Miller et al., 1999; Zunszain et al., 2011). Additionally, inflammation-induced reductions in serotonin synthesis and increased serotonin reuptake are a widely cited mechanism in preclinical and clinical studies of depression (Dantzer et al., 2011; Jeon and Kim, 2017; Müller et al., 2011). Concomitantly, elevated levels of circulating monocytes are reported in major depressive disorder (MDD) as well as other mood disturbances such as bipolar disorder and schizophrenia (Goldsmith et al., 2016). Inflammatory mediators are also shown to inhibit neurogenesis and disrupt functional connectivity in subcortical brain regions involved in mood disturbance such as the hippocampus, amygdala, and striatum (Colasanti et al., 2016; Marsland et al., 2017; Monje et al., 2003). It should be noted that increased, decreased, and unchanged peripheral blood mononuclear cell count and percentage have been observed in depressed patients relative to controls (Lanquillon et al., 2000; McAdams and Leonard, 1993; Schlatter et al., 2004; Seidel et al., 1996; Usta et al., 2019). Such variability in effects reported across studies may suggest peripheral NLR and MLR changes are not reliably associated with depression, but rather serve as non-specific indicators of neuropathology of severe mental illness. Typically, this variability across studies is attributed to individual differences in methodology used to phenotype and quantify mononuclear cell subsets which further underscores the utility of applying the simple ratio of these mononuclear cells to leukocytes providing reproducible results. Despite this, there is mounting evidence suggesting elevated NLR in patients with severe neuropsychiatric disorders compared to undiagnosed controls (Bhikram and Sandor, 2022; Mazza et al., 2018; Su et al., 2022). In fact, one study reported unmedicated patients with MDD express a higher NLR compared to healthy individuals, while MDD patients taking selective serotonin reuptake inhibitors had normalized physiological NLRs, highlighting the potential mitigating effects of antidepressant medications on lymphocyte function (Demircan et al., 2016). Although compelling, other cell ratios may be more sensitive in certain circumstances as the NLR did not outperform the platelet-to-lymphocyte ratio in predicting depressive symptom severity in a sample of MDD with elevated psychotic features (Kayhan et al., 2017). Nevertheless, meta-analytic studies of individuals mainly from European or Asian background show greater effect sizes for the NLR on all forms of depression compared to other white blood cell markers suggesting better discriminatory power (Cheng et al., 2022; Mazza et al., 2018; Su et al., 2022).

Both structural and functional MRI lend support for the inverse association of neutrophil and monocyte expansion on the volume and function of brain regions implicated in mood disturbance. For example, genes indicative of non-classical monocyte subset expansion were negatively associated with cortical thinning and cognitive impairment in aging healthy controls (Chen et al., 2022). A recent study of non-demented older adults from the Alzheimer's disease neuroimaging initiative (ADNI) revealed gene markers of neutrophil activation not only predicted cognitive progression but volumetric reductions in gray and white matter limbic regions amongst those with minimal depressive symptoms (Duan et al., 2024). A study examining a predominately African American cohort of young adults revealed an inverse association between classical monocyte count and lower rsFC within resting state networks associated with emotion regulation and executive functioning (Nusslock et al., 2019). Although the aberrant emotion regulation network connectivity was not corroborated by self-report or diagnostic indicators of depression in the study, absence of an association between monocyte counts and connectivity within anterior salience or default mode networks was noted. Not all studies comparing neuroimaging markers of monocyte expansion suggest an effect. Resting state connectivity analysis of the four networks characterized by Nusslock and colleagues was adopted for a study of older adults at risk for developing post-operative delirium only to find no association with the absolute count of monocytes or lymphocytes, although MLR was not characterized (Lichtner et al., 2021). Our group recently examined in a cohort of community dwelling older adults to assess converging evidence of structural and functional brain abnormalities concomitant with higher NLR an geriatric depression synptom severity. Not only were smaller hypothalamic volumes and lower subgenual cingulate connectivity with the vmPFC observed as a function of higher NLR, but these parameters predicted geriatric depressive symptom severity in the cohort (McIntosh et al., 2022). Notably, the subgenual cingulate was selected a priori due to the robust response observed as a function of acute inflammatory insult (Harrison et al., 2009a). The altered connectivity of the sgACC with a central hub of the default mode network suggests communication between these brain regions may be underlie the sickness behaviors including mood disturbance in persons with high inflammatory burden (Marsland et al., 2017). The DMN is not the only functional brain network implicated in mood disturbance and it is important to note that the alterations in functional brain connectivity found in the depressive state may extend to regions other than those underpinning emotion regulation and other forms of self-referential thought. For example, network-based statistical analysis of whole-brain connectivity differences between depressed adults and non-depressed controls revealed neutrophil, but not monocyte counts, negatively correlated with regions implicated in interoceptive processing, i.e., insular, inferior frontal, and posterior cingulate cortex (Aruldass et al., 2021). Compared to patients who did not develop depressive symptomology secondary to degenerative cervical myelopathy those with depression showed lower functional connectivity between the interior frontal gyrus and the caudate as a function of greater NLR (Zhao et al., 2022). Altogether, evidence has been levied in support of elevated neutrophil activation, count and ratio with aberrant structure and function of the brain regions involved in emotional, self-referential, and interoceptive processing germane to maintenance of a depressive mood state.

Although the current review highlights the geriatric manifestations of sickness behavior as a function of increased fluxes of neutrophils and monocytes in relation to lymphocytes, it is important to note that these neuroimmune alterations are also evident in childhood and adolescence. For example, data recently published from the Adolescent Brain Cognitive Development Study characterized decreased lymphocyte to monocyte ratio amongst individuals with increased functional connectivity within the DMN and less connectivity between the salience network and the left hippocampus (Cotter et al., 2024). Based upon normal developmental trajectories, this data suggests monocyte expansion relative to lymphocyte contraction is associated with increased segregation between-networks and increased connectivity within the DMN, both considered predictors of depression and mood disturbance (Afzali et al., 2022; Cotter et al., 2023; Herting et al., 2023).

4.2. *Cognitive impairment and dementia*

Neutrophils have long been deemed important contributors to Alzheimer's disease (AD) pathology through a mechanism involving their adhesion, capillary stalling, and the interruption of cerebral blood flow (Kuyumcu et al., 2012; Sayed et al., 2020). A growing number of studies from large American, Chinese, and UK cohorts provide stark evidence for elevated neutrophil- and monocyte-to-lymphocyte ratios in the persons at greater risk for dementia. These studies broadly implicate the NLR and GLR in the development of dementia over 6–8 years evidenced by odds ratios ranging from 1.12 to 1.50 (Chou et al., 2023; Ramos-Cejudo et al., 2021; Zhang et al., 2022). These ratios might provide some insight into the oxidative, phagocytic, and inflammatory byproducts and processes involved in neutrophil expansion ; Sayed et al., 2020;

Wu et al., 2020).

A recent cross-sectional study of older adults from the Framingham cohort comparing peripheral blood phenotypes of NLR, red cell distribution width, and mean platelet volume to neurocognitive measures and MRI found an association between NLR and volume of white matter hyperintensities, poorer visual memory and visuospatial performance (Fang et al., 2022). A longitudinal study from the same cohort revealed that the risk for developing dementia within 5.9 years was 34% higher in persons with above average NLR compared to those with below average NLR (Ramos-Cejudo et al., 2021). Perhaps the strongest evidence of skewed neutrophil and monocyte ratios with markers of cognitive impairment and neurodegeneration can be found in the Alzheimer's disease literature. A study featuring over 1000 individuals from ADNI found elevated NLR was associated with lower poorer global cognition, memory performance, executive function. Moreover, higher NLR was associated with β-amyloid, total CSF tau, as well as smaller hippocampal volume, and lower entorhinal cortex thickness (Hou et al., 2022). In a most recent study on over 1500 neurotypical, MCI, and AD diagnosed persons from ADNI the NLR and LMR were negatively and positively correlated with general cognitive function indexed by the Assessment Scale-Cognitive Subscale, respectively (Mehta et al., 2023). Although neither of the ratios were associated with tau deposition, the NLR did correlate with Aβ deposition on PET and longitudinal cognitive decline. While support for neutrophil ratios in Alzheimer's Disease is expansive, comparatively less work has been done to examine monocyte ratios in relation to the onset of dementia symptoms. However, a recent study reported inverse cross-sectional associations between lymphocyte-to-monocyte ratio and all-cause dementia in an Italian cohort of free-living nonagenarians (Lombardi et al., 2021). Furthermore, allied markers of monocyte proliferation such as soluble CD14 were linked to increased risk for dementia in a combine cohort of older adults from the Framingham and Cardiovascular Health Studies such that for every unit increase in sCD14 standard deviation was associated with a 12% increase in the risk of developing dementia within 10 years (Pase et al., 2020). Leveraging advanced imaging techniques to study trajectories of neutrophil and monocyte expansion on cognitive outcomes in longitudinal cohort studies may provide unique opportunities to better characterize the etiology of these age-related neuropsychiatric syndromes.

4.3. *Weakness and physical frailty*

Neutrophilia and lymphocytopenia are common features of the grouping of geriatric syndromes commonly described as the frailty phenotype. Frailty is defined as involuntary weight loss in the last year, muscle weakness, slow gait, self-reported fatigue, and low physical activity and is heightened in persons living with multimorbid chronic disease conditions (Abizanda et al., 2014; Fried et al., 2001; Fulop et al., 2010). Hence, NLR is shown to predict frailty both in the presence and absence of multiple disease comorbidities (Asik and Özen, 2022; Fernández-Garrido et al., 2014; Giri et al., 2022; Guan et al., 2022; Núñez et al., 2020). In a landmark study, the presence of chronic elevated myeloid cells over more than 15 years outperformed lymphoid derived T-, B-, or NK-cell numbers in predicting an index of frailty based upon 36 health parameters (Samson et al., 2019). The causal relationship between frailty status and myeloid ratios are unclear given multimorbidity of chronic disease may contribute to the proliferation and expansion of the myeloid cell pool and the multisystem mechanisms of pathology which may contribute to the phenotype.

Our group has also examined the prognostic capacity of NLR in relation to the functional connectivity of brain regions underpinning the generation of dynamic grip force. Specifically, the degree of centrality of the primary sensorimotor cortex not only predicted grip strength across in a lifespan sample, but age-related decrements in grip strength and centrality of subcortical and cortical motor control regions were observed as a function of increased NLR (Dillon et al., 2023). The NLR and MLR were assessed in a large longitudinal cohort of well-characterized patients diagnosed with Multiple Sclerosis. Whereas the NLR predicted depressive symptom severity, fatigue, and disability status, the MLR predicted whole brain atrophy after controlling for all clinical and demographic covariates (Hemond et al., 2019).

In addition to muscle weakness, exhaustion or fatigue is another central component of the frailty phenotype which corresponds with corresponds with the neutrophil and monocyte ratios (Doğrul et al., 2019; Fernández-Garrido et al., 2014; Fried et al., 2001). Not only is this phenotype expressed in primary frailty, but a host of other chronic illnesses ranging from chronic fatigue to multiple sclerosis (MS). As a clinical biomarker the NLR has particular significance in diagnosis, progression, and relapse of MS (Elgenidy et al., 2023; Haschka et al., 2020; Hasselbalch et al., 2018). Myeloid trafficking is of particular relevance to MS as the disease often manifests in a central form of fatigue involving disruption of the cortico-striato-thalamo-cortical loop as evidenced by a host of imaging modalities (Barbi et al., 2022; Capone et al., 2020; Jameen et al., 2019; Palotai and Guttmann, 2020). A recent study not only demonstrated higher NLR, in relation to fatigue, and MLR with increased whole-brain atrophy, but also showed these serum biomarkers successfully discriminated progressive from relapsing status (Hemond et al., 2019). Hence, a spectrum of frailty phenotypes appears to emerge, in conjunction with imaging biomarkers, with the elevation of neutrophil and monocyte ratios in older age.

5. Methodological advancements and future directions

Advancements in the tools used to track myeloid cell proliferation and the concomitant impact on CNS structure and function can be used to better understand the etiology of certain neuropsychiatric disorders. Advancements in the labeling, imaging, and manipulation of neutrophils using in vivo applications is a particularly exciting direction. Design and synthesis of hybrid polymer nanoparticles and magnetic quantum dots for neutrophil labeling can yield improved insight into neuropsychiatric sequelae when incorporated with magnetic resonance imaging techniques (Çamlıbel, 2023; Meng et al., 2022; Qiu et al., 2013; Shapiro, 2015). New insights are also being formed into the role of the NLR in predicting cerebral vasculopathies via deep-learning algorithms that more accurately segment gray and white matter tissues in the brain (Lan et al., 2021). Extant research is further expanding on the range of biomarkers used to index neutrophilia, lymphocytopenia and monocyte proliferation by incorporating genetic markers of innate and adaptive immune cell activation and function. For example, a recent study comparing platelet, eosinophil, neutrophil, basophils, monocyte, and lymphocyte counts, as well as their ratios to genetic markers of hippocampal atrophy revealed only deficits in the CD4 t-lymphocyte counts were able to survive statistical correction (Fani et al., 2021). Future work will benefit from the implementation of other imaging modalities that can non-invasively assess microstructural and functional organization of the brain as a way to characterize the range of neuropsychiatric syndromes that are concomitant with age- and disease-related effects on expansion of the neutrophil and monocyte pool relative to that of lymphocytes.

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No conflict of interest exists.

Data availability

No data was used for the research described in the article.

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