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Influence of inflammation on cognitive status and depression in ''60+'' patients Inflammation and geriatrics

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ABSTRACT

Background: It has been well documented that inflammation is closely related to major depression, even though it remains uncertain whether inflammation is a cause or a result of the mental illness. Meanwhile inflammatory processes may contribute to risk for age-related brain degeneration. A new, easily calculated from white blood cell essay, and inexpensive option, suitable for routine use to show inflammation, is the measurement of the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR)[1,2]. Hence this study was designed to explore the role of systemic inflammation in the pathogenesis of cognitive decline and major depression by using NLR, MLR and PLR as inflammatory markers.

Methods: 166 patients aged ≥ 60 years without a history of cognitive disorder were recruited. Their cognitive function and depression assessments were performed. Neutrophils, lymphocytes, monocytes and platelets counts of the participants were measured and NLR, MLR and PLR were calculated.

Results: The overall prevalence of cognitive impairment among patients aged ≥ 60 years was 27.5%. The mean age of the patients was 72.02 years. In this population mild cognitive impairment had 17.6%, moderate cognitive impairment had 6.6% and severe cognitive impairment had 3.3% of the target group. Weak negative correlations were observed between NLR, PLR and cognitive function scores (r=-0.337; r=-0.326). No correlation was found between MLR and MMSE scores (r=-0.1.59). Weak negative correlation was found between MMSE scores and Geriatric Depressive Scale scores (r=-0.342). Between NLR, PLR, MLR and Geriatric Depression Scale scores were found no correlations (r=-0.008; r=0.103; r=0.126).

Conclusions: This study revealed negative correlation between NLR, PLR and MMSE scores. However, no significant correlation was found between MLR and MMSE scores and NLR, MLR, PLR and Geriatric Scales scores.

Keywords: Cognition, depression, inflammation,geriatrics

Background

The nervous and immune systems have evolved in parallel from the early bilaterians, in which innate immunity and a central nervous system (CNS) coexisted for the first time, to jawed vertebrates and the appearance of adaptive immunity. The CNS feeds from and integrates efferent signals in response to somatic and autonomic sensory information. The CNS receives input also from the periphery about inflammation and infection[3].

Cognition is "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses[4]. Thus, an understanding of the determinants of cognitive decline is important for improving the quality of life for the growing number of older adults. Is systemic inflammation one such determinant of cognitive decline at older ages.

It has been well documented that inflammation is closely related to Major Depression, even though it remains uncertain whether inflammation is a cause or a result of the mental illness. Major depression is frequently comorbid with systemic inflammatory diseases in which pro-inflammatory cytokines are overexpressed[5]. Normal aging is associated with heightened and prolonged inflammation throughout the body and – importantly for cognition – the brain. In turn, persistent increased levels of inflammation are associated with neurodegeneration, impaired neurogenesis, atherosclerotic processes, and chronic diseaseS[6]. The limited evidence on the inflammation-cognitive decline link has been mixed. Cross-sectional studies of non-demented populations identified associations between worse cognitive function and higher levels of two biomarkers of inflammation, interleukin-6 levels and C-reactive protein, among older adults in the Netherlands[7] and among white and black elderly Americans[8]. A new, easily calculated from white blood cell essay, and inexpensive option, suitable for routine use to show inflammation, is the measurement of the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) [9,10] . NLR was developed to provide a suitable parameter reflecting the intensity of stress and systemic inflammation in critically ill patients following the shock, multiple trauma, major surgery or sepsis. By now, there is not a shared and approved cut-off value for NLR that discriminate normal from abnormal values. Some studies categorized their

patients according to NLR intervals (e.g., tertiles, quartiles, quintiles) while other studies used specific NLR cutoff pointS[11]. Neutrophils are the first line of immune defense: they exhibit phagocytic and apoptotic action through the secretion of various inflammatory factors, in particular, cytokines[12]. Inflammation triggered by cytokines can induce further inflammation due to cell dysfunction and to oxidative stress. On the other side, lymphocytes are specific inflammatory mediators, with a regulatory or protective function; low lymphocyte counts reflect poor general health and physiologic stress[13]. NLR may be useful to detect the inflammatory response, reflecting the intensity of stress and systemic inflammation, and the following cytokine cascade. Studies have shown significant correlations of NLR with established markers of inflammation like CRP and other pro-inflammatory cytokines, suggesting NLR as a useful marker to detect the inflammatory response, reflecting the intensity of stress and systemic inflammation, and the following cytokines cascade[14, 15].

MLR is another low-cost effective and readily available new index. Microglia play an essential role regarding pathologic synaptic pruning and impaired neuroplasticity[16,17]. Last, PLR considers together platelets and lymphocytes, and it may predict the inflammatory response[18]. Platelets are a nonspecific first line inflammatory marker; they modulate endothelial permeability and recruitment of neutrophils and macrophages. Platelets involve a considerable amount of serotonin and glutamate in their dense granules. Several studies have evidenced that these inflammatory ratios can be used as biomarkers of poor prognosis or major inflammation among patients with chronic medical conditions such cardiovascular diseases[19,20], malignancies [21,22], acute pancreatitis[23,24], autoimmune diseases[25,26], chronic obstructive pulmonary disease[27,28], metabolic syndrome-related conditions[29,30]. The growing interest in inflammation dysfunction in patients with cognitive decline and major depressive disorder (MDD) and the availability of these easy obtainable inflammatory ratios have resulted in studies investigating NLR, PLR, and MLR in neuropsychiatric disorders. On the other hand patients with MDD have been found carrying elevated NLR values in comparison with healthy controls[31-34]. Patients without antidepressant therapy showed increased NLR values in comparison with healthy controls. Interestingly, Demircan et al. also showed that the difference dissolved after 3 months of SSRI treatment. Moreover, PLR has been found elevated in patients with MDD compared with healthy controls. In addition, NLR value has been positively correlated with the severity of depression in patients with MDD[35,36] and seems to be a trait marker for suicidal vulnerability in patients with MDD even if Meydaneri et al., found no significant difference between NLR and PLR in patients who may attempt suicide[37]. NLR also seems to be positively correlated with age at onset in patients with MDD[38] .Comparing elderly MDD patients with healthy controls it was found lower NLR in elderly depressed patients; however, stratifying the patients higher NLR was observed in patients with the first-episode. Older adults with Alzheimer's disease have higher NLR than healthy control [39], even if this result seems to be more properly related to the age.de depression compared with recurrent depression. However, the precise role of inflammation in each of these conditions is not well understood.

Methods

This is a cross sectional study: 166 patients aged ≥ 60 years without a history of cognitive disorder were recruited. Their cognitive function was assessed by using Mini Mental State Examination (MMSE test). The total score for the MMSE ranges from 0 to 30, scores 24-30 indicate basically no cognitive impairment, 19-23 point out mild cognitive impairment, 10-18 moderate cognitive impairment and scores ≤9 show severe cognitive impairment. Inclusion criteria were patients of age ≥ 60 years of both genders with level of education at least 8 years at school. Exclusion criteria included patients with co-morbid conditions that affect cognitive function such as neurological disorders, psychiatric disorders, history of acute / other chronic illness, patients on medications (Steroids, Chemotherapy, Antibiotics, Immunomodulators, Neuropsychotropic drugs).The study was approved by Institutional Ethical Committee. The purpose, risks and benefits of the study were explained to all the participants and Informed consent was obtained from each of them. A brief history of their education, duration of disease, current treatment and co-morbid conditions were obtained. Depression assessments were performed by using Geriatric Depression Scale (long Form). Cutoff: normal-*0-9*; mild depressives-10-19; severe depressives-20-30. Neutrophils, lymphocytes, monocytes and platelets counts of the participants were measured and NLR, MLR and PLR were calculated. Values from the complete blood count with differential were obtained within 2 days of patient's examination. If we have data on the NLR, PLR, MLR and MMSE, Geriatric depressive Scale scores of various individuals and we wish to see if there is a relationship between NLR, MLR, PLR and depression, cognition, failing to control for age and gender when computing a correlation coefficient between these variables would give a misleading result; a measured correlation between the factors mentioned above might actually be contaminated by these other correlations. The use of a partial correlation avoids this problem.

Data were analysed using IBM SPSS, version 24. Pearson's correlation was used to find out the correlation between the variables. P value < 0.05 was considered significant. We calculated partial correlations between MMSE scores, Geriatric Depression Scale Scores and NLR, MLR and PLR controlling for patient's age and gender. We divided target population into groups:

- Normal cognitive status in females
- Normal cognitive status in males
- MCI in females
- MCI in males
- Moderate cognitive impairment in females
- Moderate cognitive impairment in males
- Severe cognitive impairment in females
- Severe cognitive impairment in males
- No depression
- Mild depression
- Severe depression

Results

The overall prevalence of cognitive impairment among patients aged ≥ 60 years was 27.5%. The mean age of the patients was 72.02 years. In this population no cognitive impairment had 72.5%, mild cognitive impairment had 17.6%, moderate cognitive impairment had 6.6% and severe cognitive impairment had 3.3% of the target group . The prevalence of depressive disorders in this population was 25.3%. Here, 74.7% had no depression, 16.9%- mild, 8.4 % had severe depressive declines .Table 1 provides some characteristics of different groups.

Table 1: *Basic characterisitics of different groups.*

Groups	Mean± SD(NLR)	Mean± SD (MLR)	Mean ±SD(PLR)	Gender (%)	Age
Normal Cog.	1.75±0.7	0.24±0.06	120.19±38.03	62.3	69.76±7.74
Normal Cog. (Males)	1.89±0.84	0.26±0.07	108.78±50.27	37.7	71.72±7.43
MCI (females)	1.57±0.6	0.25±0.08	124±39	86.7	76.08±9.61
MCI(males)	2.02±0.83	0.2±0.05	111±43.8	13.3	72.50±16.2
Mod. Cog. Impairment(females)	2.71±1.55	0.31±0.09	160.75±47.59	80	76±11.35
Mod. Cog. Impairment (males)	2.38±0.83	0.27±0.05	110±43.8	20	80±6.2
Severe Cog. Impairment (females)	5.12±1.55	0.31±0.02	365±23.59	26	86±6.35
Severe Cog. Impairment (males)	2.83±0.43	0.33±0.25	124±42.8	74	86±3.2
No Depression	1.88±0.90	0.24±0.07	120±52.87	67.7(f), 32.3(m)	72.32±8.73
Mild Depression	1.84±0.82	0.25±0.09	127±42	71.4(f), 28.6(m)	71.64±8.67
Severe Depression	1.48±0.39	0.47±0.03	133±48.49	71.4(f), 28.6(m)	71.32±9.74

Normal cognitive status

In the group without cognitive decline, 37.7% were males and 62.3% females.

1. Normal cognitive status in women

In females with normal cognitive status, mean ± SD (NLR) =1.75±0.7, mean ± SD (MLR) =0.24±0.06, mean ± SD (PLR) =120.19±38.03, mean ± SD (age) =69.76±7.74. Among female patients with normal cognitive status 78.9% had no depression, 10.5%-mild, 10.6 % severe depressive declines.

2. Normal cognitive status in men{\displaystyle \sigma }

In this group, mean ± SD (NLR) =1.89±0.84, mean ± SD (MLR) =0.26±0.07, mean ± SD (PLR) =108.78±50.27, mean ± SD (age) =71.72±7.43. Among males with normal cognitive status 78.3% had no depression, 17.4% had mild, 4.3% severe depressive declines.

Mild Cognitive Impairment (MCI)

3. MCI in women

In females with MCI, mean ± SD (NLR) =1.57±0.6, mean ± SD (MLR) =0.25±0.08, mean ± SD (PLR) =124±39, mean ± SD (age) =76.08±9.61. Among female patients with MCI, 69.2% had no depression, 30.8%-mild depressive decline.

4. MCI in men

In males with MCI, mean ± SD(NLR)=2.02±0.83, mean ± SD(MLR)=0.2±0.05, mean ± SD(PLR)=111±43.8,,mean ± SD(age)=72.50±16.2. Among male patients with MCI, 50% had no depression, 50%- mild depressive declines.

Moderate cognitive impairment

5. Moderate cognitive impairment in women

In this group, mean ± SD (NLR) =2.71±1.55, mean ± SD (MLR) =0.31±0.09, mean ± SD (PLR) =160.75±47.59, mean ± SD (age) =76±11.35. Among female patients with moderate cognitive impairment, 50% had no depression, 25%-mild, 25% severe depressive declines.

6. Moderate cognitive impairment in men

In males with moderate cognitive impairment, mean ± SD (NLR) =2.38±0.83, mean ± SD (MLR) =0.27±0.05, mean ± SD (PLR) =110±43.8, mean ± SD (age) =80±6.2. Here, 56% had no depression, 19%- mild, 25% severe depressive declines.

Severe cognitive impairment

7. Severe cognitive impairment in women

In this group, mean ± SD (NLR) =5.12±1.55, mean ± SD (MLR) =0.31±0.02, mean ± SD (PLR) =365±23.59, mean ± SD (age) =86±6.35. Among female patients with moderate cognitive impairment, 55% had no depression, 20%-mild, 25% severe depressive declines.

8. Severe cognitive impairment in men

In males with severe cognitive impairment, mean ± SD(NLR)=2.83±0.43, mean ± SD(MLR)=0.33±0.25, mean ± SD(PLR)=124±42.8,mean ± SD(age)=86±3.2. Here, 61% had no depression, 9%- mild, 30% severe depressive declines.

9. No depressive disorder

In the group, 67.7% were females and 32.3% males. Here mean ± SD (NLR)=1.88±0.9, mean ± SD (MLR)= 0.24±0.07, mean

± SD (PLR) = 120±52.87, In the group without any depressive disorders , 79.1% were without cognitive impairment,14.5% with mild, 4.8% with moderate and 1.6% with severe cognitive impairments. In this group mean ± SD (MMSE) = 25.45±4.55, mean ± SD (age) 72.32 ± 8.73.

10. Mild depressive disorder

In the group with mild depressive disorder, 28.6% were males and 71.4% females. In this group mean ± SD (NLR) =1.84±0.82, mean ± SD (MLR) =0.25± 0.09, mean 35.7± SD (PLR) =127± 42. 35.7% of patients with mild depressive disorder had mild cognitive impairment, 7.1% had moderate and 57.2% had no cognitive impairment. Here, mean ± SD (MMSE) =24.29± 4.48, mean±.SD (age) =71.64±8.67.

11. Severe depressive disorder

In the group, 71.4% were females and 28.6% males. Here mean ± SD (NLR) =1.48±0.39, mean ± SD (MLR) = 0.47±0.03, mean ± SD (PLR) = 133±48.49. In the group with severe depression, 65% were without cognitive impairment, 29 with mild, 2% with moderate and 4% with severe cognitive impairments. In this group mean ± SD (MMSE) = 26.45±4.55, mean ± SD (age) 71.32 ± 9.74.

Partial Correlation

Partial correlations between MMSE scores, Geriatric Depression Scale scores and NLR, MLR and PLR controlled for patient's age and gender were represented as below (Table 2). Weak negative correlations were observed between NLR, PLR and cognitive function scores (r=-0.337; r=-0.326). No correlation was found between MLR and MMSE scores (r=-0.1.59). Weak negative correlation was found between MMSE scores and Geriatric Depressive Scale scores(r=-0.342). Between NLR, PLR, MLR and Geriatric Depressive Scale scores were found no correlations (r=-0.008; r=0.103; r=0.126).

Table 2: *Partial correlations between MMSE , Geriatric Depression Scale Scores and NLR, MLR, PLR controlled for patient's age and gender.*

Comparators	NLR	MLR	PLR
MMSE	r=-0.337	r= -0.159	r=- 0.326
Geriatric Depressive Scale(GDS)	r= -0.008	r=0.103	r=0.126

Discussion

This study has several limitations. A larger sample size, longer time frame, and more frequent measurement would add power and precision. Inflammation may influence only specific aspects of cognitive ability, e.g., working memory or executive function, nuance that might be lost with the general cognitive measure used here. It is necessary to consider the confounding factors (i.e. age, body mass index, smoking, and so on) that affect systemic inflammation. Additionally, we did not collect data of other inflammatory markers (ie. ESR and C-reactive protein, inflammatory cytokines such as IL-6 and TNF-⍰,). Finally, using NLR, MLR, PLR in a single blood sample does not allow for assessing the stability of these variables over time.

The relationship between NLR, PLR in people with subjective, mild cognitive impairment and with early Alzheimer's disease has been demonstrated in a study by M.E. Kuyumcu[40] they found that patients with Alzheimer's disease had elevated NLR compared with a control population.

The relationship between NLR and MDD has been demonstrated in a study by T. Kalelioglu et al[41]. The findings of the study reveal that NLR tends to be higher in patients with MDD, and a high NLR value supports the view that inflammation is a critical factor in the etiology of MDD.

This study has several benefits over previous studies of inflammation, MDD and cognition. Rather than just one measure of inflammation, this study used three biomarkers (NLR, MLR, PLR). These advantages add strength to the conclusions of this study. While a link between inflammation and subsequent incident dementia, and MDD has been demonstrated in some previous work, the results of this study indicate that this relationship may not be universal.

This study revealed negative correlation between NLR, PLR and MMSE scores. However, no significant correlation was found between MLR and MMSE scores and NLR, MLR, PLR and Geriatric Scales scores.

Further larger prospective trials are necessary to validate these findings and determine if NLR, MLR, PLR can be used as a simple predictors of cognitive dysfunction and MDD. It is necessary to consider the confounding factors (i.e. age, body mass index, smoking, and so on) that affect systemic inflammation. The authors should describe more in detail on the relationship between these three parameters and more popular inflammation parameters such as hsCRP and inflammatory cytokines such as IL-6 and TNF-⍰, citing relevant literatures.

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