 doi:10.20944/preprints202210.0486.v1

Migraine and Inflammation: The Clinical Utility of Serial Systemic Immune Inflammatory Indices (SSIIi) during an inpatient setting

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Abstract

Background: Migraine is the commonest complex neurological disorder affecting over a billion people worldwide. Neuroinflammation has long been considered to play an important role in the pathophysiology of migraine. The main aim of this single-centre, proof of concept, retrospective study was to determine the possible clinical utility of systemic immune-inflammatory response in migraine with and without aura in a hospitalized cohort. We measured the role of universally available serial white blood cell counts to calculate the serial systemic immune-inflammatory indices (SSIIi) and the potential association between aura and SSIIi changes in a cohort of migraine patients admitted to tertiary care center in Melbourne Australia.

Main body: We retrospectively assessed patients' medical records presenting to Western Health with migraine over an 18 month period. Patients were classified as either having migraine with aura (MA) or without aura (MO) based on ICHD-3 criteria. Baseline demographics and brain imaging findings in each group were evaluated. Patients with two sets of white blood cell counts during the admission were included in the analysis. SSIIi were calculated as, neutrophil counts x platelet counts / lymphocyte counts. Correlation between SSIIi and MA and MO were assessed using SPSS27.

Conclusion: SSIIi were elevated in MA and MO followed by a downward trend in both groups, with MA being statistically significant. This proof-of-concept study suggests the potential role of systemic inflammation in pathobiology of of migraine. SSIIi appear to show clinical utility. Further comprehensive ,controlled , multicenter studies are required to clarify the exact role of systemic inflammatory response and the clinical utility of SSIIi in a subset of migraine in the Emergency department setting.

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Keywords: Migraine, inflammation, serial systemic immune-inflammatory indices (SSIIi), cortical spreading depression, aura

1. Introduction

Migraine is a debilitating neurological disorder that affects over a billion people worldwide [1, 2]. Migraine remains second among the world's causes of disability, first among people younger than fifty years of age, and first among women [3]. Approximately 15% of the population experience migraine and about one-third experience aura with some or all attacks [4, 5]. Pathobiology of migraine results from complex interactions of neurons, vasculature, glial cells and neurogenic inflammation. Diagnosis of migraine remains clinical. There are no objective biomarkers or tests to diagnose migraine. Migraine continue to be one of the most underdiagnosed medical conditions in the world. The absence of a biomarker and the overlap of phenotypic features with other primary and secondary headaches disorders may account for its underdiagnosis

While some have even recently argued that the role of inflammation in migraine is confined to animal models with limited human evidence, the link has been suggested for some time[10]. Cortical spreading depression, the proposed biological substrate of the migraine aura, induces a parenchymal inflammatory cascade that involves the activation and translocation of nuclear factor-kappa B and the expression of inflammatory gene products including arachidonic acid, cyclooxygenase, and nitric oxide synthase[11]. These inflammatory mediators are thought to activate peripheral nociceptors that innervate the meninges and meningeal blood vessels[11]. In addition, dural mast cell degranulation may also play a factor in the pathogenesis of migraine

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headache[12]. The role of systemic inflammation in headache in general and migraine in particular has been underscored by the striking association between Covid-19 and headache[13]. Systemic immune-inflammation index (SIIi) was developed as a unitary measure of chronic inflammation in colonic cancer in 2014 (Hu et al 2014) and later explored for its prognostic value in hepatocellular carcinoma (HCC) [12]. SIIi is based on easily and universally available peripheral blood counts of relative numbers of lymphocytes, neutrophils and platelets. The SIIi is defined as platelet count (P) multiplied by the neutrophil count (N) and divided by the lymphocyte (L) count (SIIi= Px N/L) (12). Hu et al reported that a single value of SIIi over 330 was]significantly associated with large tumors, early recurrence, and vascular invasion in the context of HCC [12].Wijeratne & Wijeratne described the clinical utility of serial measures of systemic immune inflammation indices (SSIIi) as a useful investigatio in the context of Post Covid-19 Neurological Syndrome [13]

We sought to explore the potential usefulness of SSIIi in predicting neuroinflammation in a cohort of migraine patients admitted to a tertiary care center .

To the best of our knowledge there is no currently published report using serial SIIi to predict patient outcomes in Migraine .

Hu et al in their original work noted that an optimal cutoff point for the SII of 330×10^9 stratified the patients with HCC into high (≥ 330) and low SII (< 330) groups in the training cohort. Univariate and multivariate analyses revealed the SII was an independent predictor for overall survival and relapse-free survival, and prognostic for patients with negative α-fetoprotein and Barcelona Clinic Liver Cancer stage 0+A. The AUCs of the SII for survival and recurrence were

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higher than other conventional clinical indices. An SII ≥ 330 was significantly associated with vascular invasion, large tumors, and early recurrence.

We recently defined and proposed the clinical utility of serial systemic immune-inflammatory indices (SSIIi) as a potential universal biomarker for Long-COVID (Post Covid-19 Neurological Syndrome) [15, 16]. We explored the possible clinical utility of serial systemic immune inflammatory indices as a potential indicator of neuroinflammation in a cohort of migraine as a proof-of-concept study .

2. Methods and Participants

We retrospectively collected data from patient electronic health records for patients admitted to Western Health, Melbourne Australia, with a diagnosis of migraine over 18 months. The cohort of patients were admitted to the hospital with an acute attack of migraine . Hospital admissions with no direct relevance acute exacerbation of migraine were excluded from the study. Our health service is the major tertiary care center that serves 1.2 million people with a significant culturally and linguistically diverse (CALD) population representing 166 languages.

Demographic data (age, gender, country of origin), cardiovascular risk factors, and atrial fibrillation were collected for patients with MA and MO as per International Classification of Headache Disorders-3 (ICHD-3) criteria.

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Patients with MA and MO and a minimum of two sets of white blood cell counts (neutrophil counts, platelet counts and lymphocyte counts) during the hospital admission were included in this study as this was needed to calculate the SSIIi as we described previously [15].

Serial Systemic immune inflammation indices were calculated based on individual neutrophil, platelet and lymphocyte counts as follows:

$$\frac{\textit{Neutrophil count x platelet count (indication of innate immune activity)}}{\textit{Lymphocyte count (indicative of adaptive immune activity)}}$$

Serial measurements indicate maladapted immune-inflammatory response as we described recently in the context of Long-Covid [15].

2.1 Sample Size

The number of patients included in the cohort were 262 (n = 164 MO vs n = 98 MA). Due to missing data for SSIIi, only 200 (n = 121 MO vs n = 79 MA) were included in the Repeated measures of ANOVA. Power calculation using GPower (v 3.1.9.7) showed high power (0.99) of n = 200 samples in the final analysis of ANOVA.

2.2 Statistical analysis

Data were analyzed using SPSS (v27). Repeated measures of ANOVA were used to compare within subjects of SSIIi changes over time 1 (baseline measures) vs. time 2 (12-24 hours' time interval). Comparison between subject effects were also conducted to assess any group differences between MO vs MA.

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3. Results

Demographic characteristics of patients are presented at Table 1. As shown 85.5 percent of the patients were female with an average age of 39.80 ± 12.94 years old. The majority of the participants birth origin was Australia followed by South Africa, Europe, Africa, Middle East, Central and South America and North America (Table 1). SSIIi measures were high for both groups at time 1, whereas, at time 2, there was a trend of lower SSIIi for MA but this was not statistically significant (Table 2). The within subject changes of SSIIi was significant over time ($f(1, 198)=4.138$, $p<0.05$) and significant drop in the level of SSIIi was observed at time 2 (12-24 hours after the baseline measures) for all participants. Moreover, a steep drop in SSIIi among the cohort of MA vs MO in between subject effects was observed (Figure 1). However, the between subject effects were not statistically significant ($p>0.05$) . Migraine cohort in this study revealed twice as higher number of SII with clear differences in the serial behaviour of SSIIi.

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Table 1. Demographic characteristics of patients (n=262*)

		Frequency	Percent
Sex	Female	224	85.5
	Male	37	14.1
Birth Region	1 Australia	187	71.9
	2 South East Asia	25	9.6
	3 Europe	29	11.2
	4 Africa	8	3.1
	5 North America	1	0.4
	6 Middle East	6	2.3
	7 Central and South America	4	1.5
Migraine Type	Without aura (MO)	164	62.6
	With aura (MA)	98	37.4
Age	Mean ± standard deviation (SD)	39.80 ± 12.94	

*n varies due to some missing data

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Table 2. Descriptive statistics of serial systemic immune-inflammatory indices (SSIIi)

Groups	Time	Mean	Std. Error	n	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Without aura (MO)	1	774.452	63.972	121	648.298	900.605
	2	718.470	45.810	79	628.133	808.808
With aura (MA)	1	824.707	79.171	121	668.581	980.834
	2	662.330	56.694	79	550.529	774.131

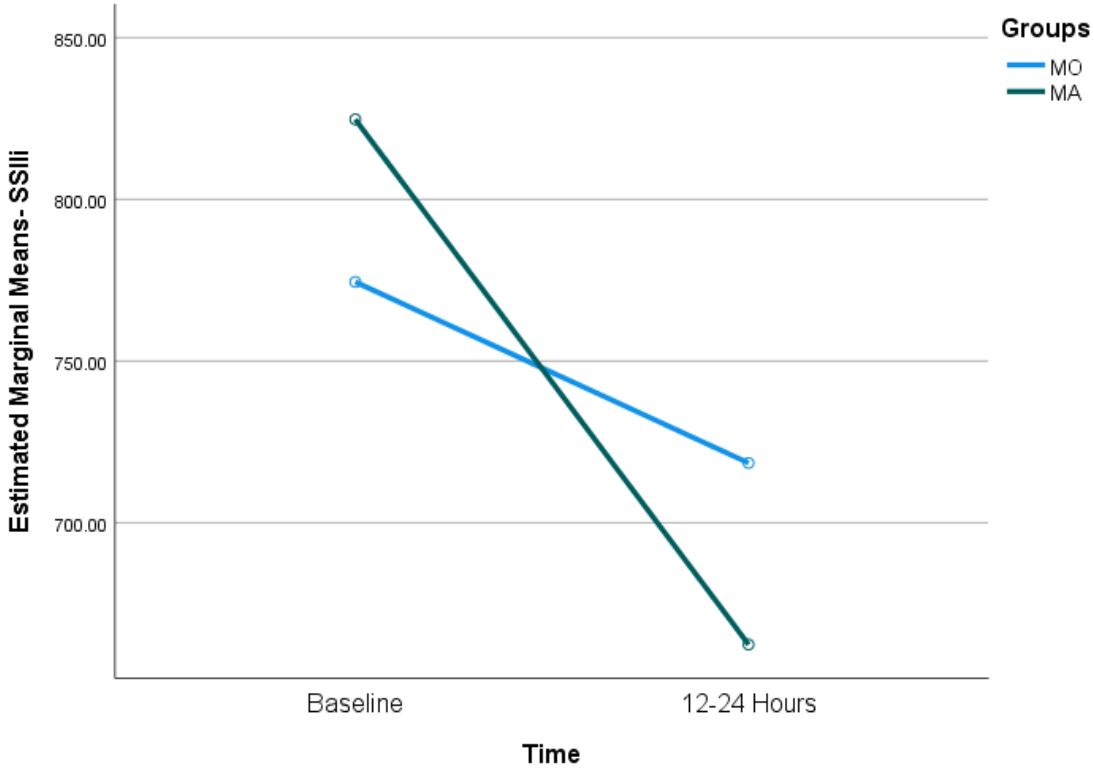

Figure 1: Serial systemic immune-inflammatory indices (SSIIi) at time 1 (baseline) compared to time 2 (after 12-24 hours) for both groups

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4. Discussion

We have shown that the first set of SSIIi values were significantly higher in patients with MA and MO, compared to historical levels found in patients with hepatocellular carcinoma [14, 15]. These findings suggest a systemic inflammatory response in the setting of acute migraine attacks are of potential importance in the field migraine. This is both in the context of pathophysiology as well as treatment.

Neuroinflammation describes release of inflammatory mediators and neuropeptides from peripheral nerves[10]. This is in the setting of injury or insult in some cases. Molecular markers of glial cell activation are commonly known as evidence of neuroinflammation.

Calcitonin gene related peptide (CGRP) plays a key role in migraine. CGRP is regarded as a molecule related to inflammation. Efficacy of Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in a group of migraine patients is well known.

SSIIi is universally available at a very low cost, worldwide. This simple biomarker is able to offer us a snapshot of both innate and adaptive immune system activity at a glance.

It is worth exploring the potential role of SSIIi in a well-planned prospective, multi-center study to see the clinical utility of this ratio in migraine populations.

Previous published papers have demonstrated increased platelet leucocyte interactions and platelet activation in patients with migraine [20, 21]. Platelets and leucocyte interaction may well be a part of a vascular-inflammatory pathobiological process in migraine [20, 21]. The platelet hypothesis of migraine date back to 1978 [22, 23].

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Previous work explored the levels of hematological parameters, neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR) as potential markers of inflammation in patients diagnosed with migraine [13, 24-28]. A retrospective study of 250 migraine patients and 215 healthy volunteers were followed up in a neurology clinic with the diagnosis of migraine [24]. C-Reactive protein (CRP), NLR, NMR, LMR and PLR ratios were compared between the two groups. Patients with migraine were further grouped according to functional impairment, presence of aura and severity of pain levels. 20.8 % of patients with a mean age of 36.37 ± 8.683 had MA[24]. It was noted that neutrophil-monocyte ratio (NMR) values in patients with MA were significantly higher to control subjects (n = 215 healthy volunteers) [24]. Moreover, the CRP, NMR and PLR values in MO were significantly higher than the sample healthy volunteers. Platelet values and mean platelet volumes (MPV) were higher in MA and MO compared to the control group [24]. Our observation of persistent immune inflammation in MA and MO is compatible with this body work.

In a Turkish study in an emergency department setting n = 235 patients with migraine diagnosis (as per ICHD-3 classification) and n = 166 healthy controls were evaluated. Patients with migraine were assessed during the attack by emergency medicine specialists in the emergency department and in attack-free periods in neurology clinics by neurologists [29]. Of the 235 patients, 77.02% were female and 22.98% were male. The neutrophil, NLR, PLR, and MLR levels were higher among migraine patients in comparison to the control group ($p < 0.05$). The serum CRP, neutrophil, NLR, MLR, and CAR levels were higher in the migraine cohort whilst albumin and lymphocyte levels were lower during migraine attack periods ($p < 0.05$). Patients

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with MA were noted to have higher serum NLR levels compared to MO patients ($p < 0.05$). Interestingly, patients with migraine who had a positive family history were shown to have higher NLR levels compared to patients without a family history ($p < 0.05$) raising the possibility of genetic predisposition in the context of systemic inflammation in the setting of migraine [29]. This work is compatible with what we have observed in our retrospective cohort.

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Serial measurement of immune indices are proven to be a better marker in comparison to a single point index [15]. Our study revealed the undeniable evidence of systemic immune inflammatory response in MA as well as MO. We observed a steep drop in SSIIi among the cohort of MA. We propose the initial immune inflammatory response likely to be higher in the phenotype of MA.

Our observation of elevated systemic immune inflammatory response in MA and MO with twice as higher values compared to hepatocellular carcinoma demonstrates the relationship between cerebral neurophysiological pathways and immune system. This relationship confers neurocognitive process the mechanism to regulate the immunologic processes and immune system and vice versa [30]. Life stress, inflammation and mental health maintain close associations [30]. The study of how neural, psychological, and immunologic processes interact and affect human health and behavior is known as Psychoneuroimmunology (PNI) [30].

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We believe the persistent, maladapted immune inflammatory processes play a key role in pathobiology of migraine with and without an aura in a subset of patients that can be explained by concepts of PNI.

Retrospective nature of the study as a single center implies limitations to the current study. The cohort in this study were either assessed by neurologists or emergency physicians and the diagnosis of migraine was based on individual interpretation of symptoms by these physicians. Lack of a matched control sample is another limitation of the current study.

Conclusion

In conclusion, we show SSIIi values in both MA and MO are significantly higher than what had been described in the field of oncology. SSIIi appears to demonstrate a rapid drop in value in MA compared to MO. Reduction in SSIIi with time suggests that systemic immune inflammatory response is likely to be an adaptive and potentially protective response best explained by the concepts of PNI. However, it must be noted that both groups (MO and MA) were treated with acute analgesics including non-steroidal anti-inflammatory medications (NSAIDs) which could reduce SSIIi. However, we suggest that this proof-of-concept work supports the hypothesis of persistent systemic inflammatory process in migraine. Systemic inflammation may play a role in pathophysiology of acute migraine requiring an ER visit. The SSIIi may have therapeutic implications. We propose that more comprehensive, controlled, multicenter studies are required to evaluate the immune inflammatory factors further and their involvement in the pathobiology of migraine.

Acknowledgements

The authors would like to thank the Health information Unit, Western Health Australia for providing access to electronic data for the retrospective analysis and all the patients.

Ethical approval

Ethical approval was received from Western Health IRB, Australia with approval number QA2014/20.

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