J Surg Med. 2019;3(9):685-688.
DOI: 10.28982/josam.567491

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of the platelet volume index as a prognostic factor after aneurysmal subarachnoid hemorrhage

Anevrizmatik subaraknoid kanama sonrası prognostik faktör olarak platelet volüm indeksinin değerlendirilmesi

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Abstract

Aim: Subarachnoid Hemorrhage (SAH) originating from an intracranial aneurysm is a severe and life-threatening disease, witnessed by physicians in Emergency Departments (ED). Despite the improvements in diagnostic and therapeutic techniques, morbidity and mortality rates of SAH remain high. Several parameters based on biochemical analysis and imaging techniques are used to evaluate the prognosis. However, efforts for identifying an ideal marker have not been successful. For many years, Fisher Grading System, which is based on computerized tomography (CT), has been used as a reliable predictive scale to identify SAH. Besides, the immune response plays an active role in determining neuro-damage after SAH. Recently, Mean platelet volume (MPV) to platelet count (PLT) ratio has become a trend indicator to anticipate the outcome of a patient suffering from SAH. This study aims to determine whether the comparison of the immune response marker [Platelet Volume Index (PVI)] with the Fisher Grading System could be used as a prognostic factor in subarachnoid hemorrhages with ruptured intracranial aneurysms.

Methods: In this retrospective cohort study, 52 patients diagnosed with spontaneous SAH in the ED were included. The patients' ages, genders, Fisher grades, locations of the ruptured aneurysm, PVI and Glasgow Coma Scale (GCS) scores were recorded. MPV:PLT ratio was defined as MPV value(fL) x100 /PLT (per 1000). Each patient's GCS at the time of their admission to the ED was noted. An experienced radiologist graded their initial CT scans immediately according to the Fisher Grading System. Patients' GCS scores were noted by the investigators and PVI was calculated. A retrospective review was carried out regarding medical records of age, sex, and other conditions. The Pearson Correlation Coefficient was used in the analysis of the interrelationship.

Results: The correlation among the PVI with GCS and Fisher Grade test was found to be positive statistically correlation. Relevant literature establishes the same result. Additionally, analyses established a significant positive correlation between the Fisher Grading Scale and the PVI among the data of ruptured aneurysms.

Conclusion: The PVI can be used as a prognostic, predictive factor for SAH. Nevertheless, further studies concerning the prognosis of SAH are needed to confirm this hypothesis.

Keywords: Platelet volume index, Mean platelet volume, Inflammatory markers, Subarachnoid hemorrhage

Öz

Amaç: Anevrizmatik subaraknoid kanama (SAK), acil servislerde görülen şiddetli ve ölümcül bir hastalıktır. Tanı ve tedavi tekniklerinde ki tüm gelişmelere rağmen halen yüksek morbidite ve mortalite oranına sahiptir. Biyokimyasal ve görüntüleme analizlerini içeren bir çok prognostik yöntemler olmasına rağmen, halen ideal bir belirteç mevcut değildir. Anevrizmatik subaraknoid kanamalarda Fisher skalası, beyin bilgisayarlı tomografisi (BT) görüntülerinden elde edilen ve uzun yıllardır güvenle kullanılan bir prognoz göstergesidir. Diğer yandan immün yanıt ise nöronal hasarın dolayısı ile prognozun ana belirleyicisidir. Ortalama platelet hacminin platalet sayımına oranı olan platelet hacim indeksini (PHİ), immün yanıt göstergesi olarak kullanan çalışma sayısı gittikçe artmaktadır. Biz de çalışmamızda immün yanıtın göstergesi olan platalet hacim indeksini, güvenilir bir yöntem olan Fisher skalası ile karşılaştırarak prognoz belirteci olma olasılığını araştırdık.

Yöntemler: Bu retrospektif kohort çalışmaya, acil servise başvuran 52 hasta çalışmaya dahil edildi. Hasta yaşı, cinsiyet, Fisher değeri, rüptüre anevrizmanın lokalizasyonu, PHİ, Glasgow koma değeri (GKS) ile çalışma kartı oluşturuldu. PHİ'i ortalama platalet volümü (fL) x100 / platalet sayısı (per 1000) olarak belirlendi. Tecrübeli nöroradyolojist tarafından, başvuru anındaki BT'e göre Fisher değeri hesaplandı, beyin cerrahisi ve acil tıp doktorları tarafından GKS değeri kayıt edildi. Pearson korelasyon testi, veri analizi amacıyla kullanıldı.

Bulgular: PHİ'i ile GKS ve Fisher değerleri arasında istatiksel olarak anlamlı ilişki bulundu. Bu sonuç literatür ile uyumluydu. Dahası, PHİ ile Fisher skala değeri arasında istatiksel olarak anlamlı, pozitif yönde bir korelasyon olduğu görüldü.

Sonuç: PHİ'i SAK'larda prognostik bir belirteç olabilir. Fakat daha fazla hasta sayısı ile yapılan çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Platalet hacim indeksi, Ortalama platalet hacmi, İnflamatuar belirteç, Subaraknoid kanama

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Ethics Committee Approval: The study was approved by the Ethics Committee of Bezmialem Vakıf University (2018.876).
Etik Kurul Onayı: Ankara Bu çalışma Bezmialem Vakıf Üniversitesi Etik Kurulu (2018.876) tarafından onaylandı.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/21/2019
Yayın Tarihi: 21.09.2019

How to cite / Atıf için: Dündar TT, Kitiş S, Abdallah A, Yurtsever İ, Gülen B. Evaluation of the platelet volume index as a prognostic factor after aneurysmal subarachnoid hemorrhage. J Surg Med. 2019;3(9):685-688.

Introduction

Subarachnoid hemorrhage (SAH) following a ruptured intracranial aneurysm is a severe and life-threatening disease [1,2]. The term "ruptured intracranial aneurysm" includes consequent bleeding in the subarachnoid, intraventricular or subdural spaces. Despite improvements in diagnostic and therapeutic techniques, SAH has a high morbidity and mortality rate. Moreover, only 25% of patients are able to live without assistance [1,3,4].

When present in the subarachnoid space, blood components act as potent activators for neuroinflammation. Following SAH, the immune system recognizes the blood components and irritated brain tissue as well as the antigens to which they are exposed. This triggers a robust neuroinflammatory response. The mechanism of the immune response is still not well understood. Many factors contribute to the activation of neuroinflammation after SAH, one of the components being platelet functions [5,6]. The role of activated platelets in thrombosis and neuroinflammation after SAH have been well studied [7]. Platelets play an active role in the regeneration of injured vessel wall and regulation of immune response. Mean Platelet volume (MPV) is one of the parameters analyzed in a CBC. Platelet count (PLT) and mean platelet volume (MPV) are readily available in the first complete blood count (CBC) in the ED [2]. Platelets' activation and functions are positively related to the MPV. Larger mean platelet volume is an indicator of rapid reaction to thrombosis, with inflammation and activation. Therefore, an increase in the MPV values indicates activated inflammation [8]. In summary, the stage of inflammation affects the size of platelets and consequently, MPV. An increase in platelet volume is associated with several conditions such as severe preeclampsia, active or chronic infection, ischemic stroke [7,8].

Recent studies are increasingly examining the ratio of MPV to platelet count detected in the CBC as a more specific index to predict platelet-related immune response [7]. On the other hand, computerized cranial tomography (CCT) is frequently made use of as the initial imaging modality while diagnosing SAH [9]. CCT clearly demonstrates density differences between hyperdense acute hemorrhage and the surrounding parenchyma. Many studies have demonstrated the close relationship between initial CCT and clinical outcome. The primary CCT evaluation has a strong relationship with the development of neurological deficits. To this end, several criteria are used to evaluate neurological prognosis after SAH. One of these is the Fisher scale (FS). FS is the initial and best-known classifying system for subarachnoid hemorrhage on CT scans. This scale is useful in predicting the mortality, morbidity and/or vasospasm. FS as well as some other image related variant scales have been widely used as reliable predictive scales for many years. The Fisher scale evaluates the amount of blood seen on computed tomography (CT) and predicts the prognosis of the clinical outcome. The significance of the Fisher Scale is evident in identifying patients at higher risk of increased morbidity or mortality. Therefore, it indicates the need for a closer and more aggressive observation [10].

Several bio-markers have frequently used certain parameters based on biochemical analysis, but perfect markers have not yet been identified. This study aims to determine whether the comparison of immune response marker [Platelet volume index (PVI)] with Fisher grading system could be used as a prognostic factor in subarachnoid hemorrhages with ruptured intracranial aneurysms.

Materials and methods

Patient population and data collection

The institutional ethical board approved the study (2018.876). We obtained the data of all patients admitted to the Emergency Department with SAH between November 1, 2016 and February 31, 2019. The study involved a retrospective chart review with no risk to the patients.

All patients admitted to the Department of Emergency Medicine with SAH underwent a CBC and CCT upon initial admission. CBC included the MPV and PLT values. Neuro-imaging and other records are available for all patients. The assessment of all initial CCT scans were carried out by the same examiner who has ten years of experience in neuroradiology. The images were graded according to the FS (Table 1). Neurological examinations were performed using the Glasgow coma scale (GCS) by the same specialists.

All patients had undergone treatment (clipping or endovascular alternatives) within 3-24 hours after the onset of SAH at the Department of Neurosurgery. Patients who suffered from coagulation abnormalities, malignancies, renal or liver dysfunction, severe myocardial dysfunction, any active or chronic infection findings, and any other immune deficiency syndrome (AIDS, leukemia) were excluded from this study, as well as patients admitted later than 48 hours from the onset of symptoms, since MPV and/or PLT may show progressive change following acute inflammatory disorders [19,20]. Patients who were included in the study were those experiencing SAH confirmed by a CCT without trauma, accompanied by a cerebral angiogram confirming an intracranial aneurysm.

Calculation of PVI

PVI was described as $\frac{MPV\ value(fL)}{PLT\ per\ 1000}$ x100. Investigators who calculated the platelet volume index were blinded to patient's clinical condition and outcome. PVI value of each patient was noted.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) software 24.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The normality of distribution was assessed with Kolmogorov Smirnov test. Pearson correlation test was used for correlation analyses. *P*-values <0.05 were considered statistically significant. According to the power analysis based on platelet count, a sample size of 40 patients was required for 80% power and %5 conventional two-sided type 1 error.

Table 1: Fisher scale

Grade	CT finding
I	No subarachnoid (SAH) or intraventricular hemorrhage (IVH) detected
II	Diffuse thin (<1 mm) SAH, no clots
III	Localized clots and/or layers of blood >1 mm in thickness, no IVH
IV	Diffuse or no SAH, CH or IVH present

Results

We studied 52 patients diagnosed with SAH who had ruptured aneurysms. 30 (57.7%) of them were female, while the other 22 (42.3%) were male. Mean age of the cohort was 52.73 (13.23) (min=24, max=89).

Patients' ages, genders, the Fisher grades, the locations of the ruptured aneurysms, PLT index and GCS scores were noted (Table 2). A moderately to highly significant negative correlation was found between FS and GCS (r=-0.476, *P*=0.001) (Table 3, Figure 1 and 2). Between FS and PVI, there was a positive, strong and highly significant (r=0.731, *P*=0.001) (Table 3, Figure 3).

Table 2: Baseline demographic and clinical characteristics of patients

Characteristics	n (%)
Gender	
Female	30 (57.7)
Male	22 (42.3)
	mean (SD) (min, max)
Age	52.73 (13.23) (24, 89)
GCS	13.54 (2.42) (6, 15)
Fisher Grade	2.96 (1.23) (1, 4)
PVI	3.91 (1.55) (1, 8.39)
Location of aneurysm	n (%)
Anterior circulation	48 (92.3)
Posterior circulation	4 (7.7)
Clinical Presentation	n (%)
Headache	21 (40.4)
Lethargy	5 (9.6)
Seizure	2 (3.8)
Hemiplegia	7 (13.7)
Headache, Stupor	12 (23)
Headache, Ptosis	1 (1.9)
Headache, Vomiting	4 (7.6)

SD: Standard deviation, PVI: Platelet volume index

Table 3: The Pearson correlation coefficients were used to determine the relationship between either PVI or FS and GCS

		FS	PVI	GCS
FS	Pearson Correlation	1	0.731	-0.476
	P-value		<0.001	<0.001
	n	52	52	52
PVI	Pearson Correlation	0.731	1	-0.237
	P-value	<0.001		0.090
	n	52	52	52
GCS	Pearson Correlation	-0.476	-0.237	1
	P-value	<0.001	0.090	
	n	52	52	52

PVI: Platelet volume index, FS: Fisher scale, GCS: Glasgow coma scale

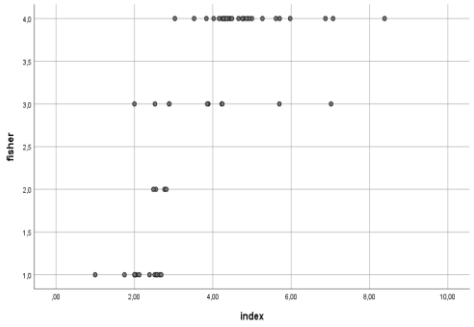

Figure 1: The correlation between the platelet volume index and Fisher scale (r -0.731, *P*-value <0.001)

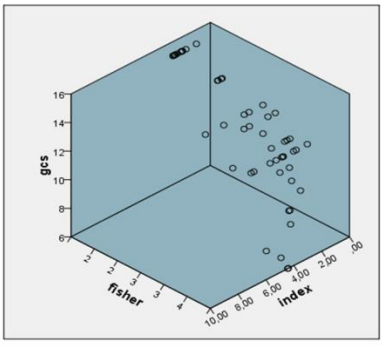

Figure 2: The correlation between platelet volume index, Glasgow coma scale and Fisher scale with the box pyramid table

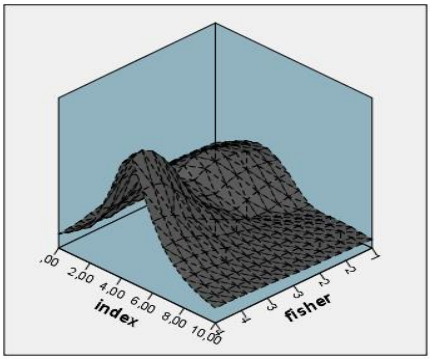

Figure 3: The correlation between platelet volume index and Fisher scale with distribution diagram

Discussion

SAH resulting from ruptured aneurysm is associated with significant morbidity and mortality rates. The mortality rate ranges from 32% to 67%. Approximately 10% to 16% of patients die before hospital admission, and around 25% patients remain dependent on assistance [8]. Clinical symptoms of SAH include varying degrees of neurological disorders, from headache and aphasia to hemiplegia or coma [3,4]. The most common clinical symptom in our study was headaches (Table 2). Although extensive studies have been performed about neuro-degeneration after SAH, factors causing poor clinical outcome have not yet been clearly established [11,12]. Rebleeding, hydrocephalus, seizures, delayed cerebral ischemia, elevated intracranial pressure and several systemic complications contribute to serious neurodegeneration following intracranial aneurysm rupture [8]. The intensity of bleeding observed in the subarachnoid space on CT has a strong relationship with the prognosis [10]. The Fisher grading scale, the initial and most established classifying system in subarachnoid hemorrhages, relies on brain CT scans [12]. Several other scales that have been proposed include various parameters, and have been helpful in predicting mortality, morbidity and/or vasospasm. The Fisher scale is still more widely preferred [14,15]. Fishers scale is described by four grades based on the amount of blood in the intracranial area. This grading scale is rather practical and useful for prognosis and prediction of patient outcomes in SAH. Score increases in this grading have been associated with poor prognosis in numerous studies, with the exception of the risk of clinical vasospasm, which is higher Fisher grade 3 than grade 4. In accordance with the existing literature, our study found a negative correlation between FS and GCS that is significant at a moderate-to-high level. Higher grades in this scale indicate the need for more aggressive and serious observation of the patient. Its importance for higher risk of developing cerebral damage, especially vasospasm, is evident [15,16].

Uncontrolled inflammation that is observed has been attributed to primary neuro-damage. According to this hypothesis, uncontrolled inflammation is a driving factor for poor outcomes following SAH [17]. Extravasated blood cell breakdown components in the subarachnoid space trigger the inflammatory cascade [18]. Platelet activation is also associated with worsening neuro-injury. Recently, studies have demonstrated that several cytokines, growth factors and platelet-derived molecules are elevated after SAH. Platelet activation causes provocation in such a way as to complement the spread of

inflammation and feeds the cycle of injury expansion (18). The mean platelet volume, one of parameters of complete blood count (CBC), is associated with platelet function and activation. When the size of platelets is increased, cytokines, chemokines or coagulation factors become activated. Increased MPV values indicate activated platelet functions and are associated with neuro-inflammation [8,11]. Platelet size changes during megakaryocytopoiesis. This activation is regulated by thrombopoietin, several growth factors and cytokines. This organization is the response of the bone marrow to inflammation [20]. After all, neuro-inflammation and prothrombotic agents, which alter the microenvironment of platelets, cause increases in platelet volume, changing the discoid platelet shape to spherical. The purpose of platelet activation is to restrict the damage of brain tissue [8,21,22]. In several studies, platelet size has been reported as a prognostic factor in acute ischemic stroke, but more studies are needed regarding SAH. The aim of this study was to compare the PLT index with the Fisher grading scale which is a well-established prognostic factor for SAH. Intracranial vasospasm is the most serious complication resulting from SAH. Treating or preventing the progression of vasospasm after SAH is highly challenging. The main cause of intracranial vasospasm (and therefore, of poor prognosis) is the immune response to blood fragments in either the subarachnoid space or the intraparenchymal area [7,16]. In our study, we investigated a possible correlation between the thrombocyte index as an immune response marker and the Fisher grading system, and concluded that there is a positive, strong correlation between FS and PVI that is moderately-to-highly significant.

Limitations

We believe the wide spectrum of PVI distribution (ranging between 1 and 8.39) is most likely due to the differences in the timing of patients' hospital admissions. It seems that the shortcoming of the study was the lack of standardization in terms of admission time due to the low number of patients included in the study.

Conclusion

This study has demonstrated a statistically significant correlation between the Fisher grading scale and PLT index among the study group. Therefore, we suggest that PLT index can be used as a prognostic, predictive factor for SAH. Nevertheless, further research studying the prognosis of SAH is needed to support this hypothesis.

Acknowledgements

Special thanks to Prof. Dr. Sedat Ziyade, who managed the statistical analysis, and thanks to Ali Conor Alakus for English grammar redaction.

References

1. Galea J, Cruickshank G, Teeling JL, Boche D, Garland P, Perry VH. The intrathecal CD163-haptoglobin-hemoglobin scavenging system in subarachnoid hemorrhage. Journal of Neurochemistry. 2012;121:785–92.
2. Balik MS, Erkut A, Guvercin Y, KeskinD. Mean Platelet Volume as a Predictive Marker for Inflammatory Reactivation after Total Hip Arthroplasty. Bakırkoy Tıp Dergisi. 2018;14:57-62.
3. Wang Y, Liu Y, Li Y, Liu B, Wu P, Xu S, et al. Protective effects of astaxanthin on subarachnoid hemorrhage-induced early brain injury: Reduction of cerebral vasospasm and improvement of neuron survival and mitochondrial function. Acta Histochem. 2019;121:56-63.
4. Nakano F, Kawakita F,Liu L, Nakatsuka Y, Nishikawa H, Okada T, et.al. Anti-vasospastic Effects of Epidermal Growth Factor Receptor Inhibitors After Subarachnoid Hemorrhage in Mice. Mol Neurobiol. 2018;1-11.
5. Hirashima Y, Hamada H, Kurimoto M, Origasa H, Endo S. Decrease in platelet count as an independent risk factor for symptomatic vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2005;102:882-7.
6. Zhou Y, Jiang Y, Peng Y, Zhang M. The Quantitative and Functional Changes of Postoperative Peripheral Blood Immune Cell Subsets Relate to Prognosis of Patients with Subarachnoid Hemorrhage: A Preliminary Study. World Neurosurgery.2017;206–215.
7. Ray B, Tinsley L, Ford L, Thompson DM, Sidorov EV, Bohnstedt BN .Trends of Platelet Volume İndex Predicts Delayed Cerebral Ischemia after Subarachnoid Hemorrhage. World Neurosurg. 2018;624-31.
8. Young GB. Encephalopathy of infection and systemic inflammation. J Clin Neurophysiol. 2013;30(5):454-61.
9. Chung TS, Joo JY, Lee SK, Chien D, Laub G. Evaluation of cerebral aneurysms with high-resolution MR angiography using a section-interpolation technique: correlation with digital subtraction angiography. AJNR Am J Neuroradiol. 1999;20(2):229-35.
10. Oliveira AM, Paiva WS, Figueiredo EG, Oliveira HA, Teixeira MJ. Fisher revised scale for assessment of prognosis in patients with subarachnoid hemorrhage. Arq Neuropsiquiatr. 2011;69(6):910-3.
11. Savarraj JP, McGuire MF, Parsha K, Hergenroeder G, Bajgur S, Ahn S, et al. Disruption of thrombo-inflammatory responses and activation of a distinct cytokine cluster after subarachnoid hemorrhage. Cytokine. 2018;334-41.
12. Şimşek BK, Özer G. Evaluation of stroke mortality and related risk factors: A single-center cohort study from Gaziantep, Turkey. 2019;(3)3:231-4.
13. Lindvall P, Runnerstam M, Birgander R, Koskinen LO. The Fisher grading correlated to outcome in patients with subarachnoid haemorrhage. Br J Neurosurg. 2009;23(2):188-92.
14. Foreman PM, Chua MH2, Harrigan MR, Fisher WS, Tubbs RS, Shoja MM, et al. External validation of the Practical Risk Chart for the prediction of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2017;126(5):1530-6.
15. Oliveira AM, Paiva WS, Figueiredo EG, Oliveira HA, Teixeira MJ. Fisher revised scale for assessment of prognosis in patients with subarachnoid hemorrhage Arq Neuropsiquiatr 2011;69(6):910-3.
16. Mata-Mbemba D, Mugikura S, Nakagawa A, Murata T, Ishii K, Kushimoto S et al. Traumatic midline subarachnoid hemorrhage on initial computed tomography as a marker of severe diffuse axonal injury. J Neurosurg. 2018;5:1-8.
17. Bester J, Pretorius E. Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity, Sci. Rep. 2016;1-10.
18. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis, Pharmacol Rev. 2004;549–80.
19. Oh GH, Chung SP, Park YS, Hong JH, Lee HS, Chung HS, et al. Mean platelet volume to platelet count ratio as a promising predictor of early mortality in severe sepsis. Shock. 2017;47:323-30.
20. Kapsoritakis AN, Koukourakis MI, Sfiridaki A, et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. Am J Gastroenterol. 2001;96:776-81.
21. Frontera JA, Aledort L, Gordon E, Egorova N, Moyle H, Patel A, et al. Early platelet activation, inflammation and acute brain injury after a subarachnoid hemorrhage: a pilot study. J Thromb Haemost. 2012;10:711-3.
22. Teo M, Guilfoyle MR, Turner C, Kirkpatrick PJ, et al. What factors determine treatment outcome in aneurysmal subarachnoid haemorrhage in the modern era? – a post-hoc STASH analysis. World Neurosurgery. 2017;270-81.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine