

Changes in routine blood parameters of patients with generalized tonic clonic seizure: a retrospective study

Jiankang Huang, PHD, Jun Yang, BM, Jiali Miao, BM, Hongbo Wen, MD.

ABSTRACT

الأهداف: لتحليل التغيرات في بارامترات الدم الروتينية لدى هؤلاء المرضى. نوبة الصرع التوتيرية الرمعية المعممة هي نوع رئيسي من الصرع المعمم. اكتشف الأطباء مؤخرًا تغييرات في معايير الدم الروتينية لدى مرضى GTCS.

المنهجية: أجريت دراسة بأثر رجعي لعدد 45 مريضًا من GTCS و 200 عنصر تحكم سليم. أجرينا الفحوصات الروتينية للدم في قسم الطوارئ وفي اليوم الثاني من الدخول. كما أجرينا تحليل التغيرات في معايير الدم الروتينية يوم نوبة الصرع واليوم الثاني بعد النوبة بما في ذلك عدد خلايا الدم الحمراء (RBC)، وعدد خلايا الدم البيضاء (WBC)، وعدد الصفائح الدموية، وعدد الخلايا الليمفاوية، وعدد العدلات، ونسبة العدلات إلى الخلايا الليمفاوية (NLR) في يوم نوبة الصرع والثاني بعد يوم من تحليل النوبة.

النتائج: كان لدى مرضى GTCS زيادة في عدد الصفائح الدموية، وعدد كرات الدم الحمراء، وعدد كرات الدم البيضاء، وعدد العدلات، وعدد الخلايا الليمفاوية، و NLR، خاصة عند بداية حلقة GTCS، مقارنةً بالضوابط. انخفضت هذه المعلمات في اليوم الثاني بعد بداية النوبة. كان عدد العدلات وعدد كرات الدم البيضاء في حالات GTCS مع مدة النوبة أقل من 5 دقائق أقل بكثير من تلك التي كانت مدة النوبة أكثر من 5 دقائق. ومع ذلك، لم يتم ملاحظة هذه الظاهرة في المؤشرات الأخرى.

الخلاصة: قد تؤدي GTCS إلى زيادة في عدد كرات الدم الحمراء، وعدد كرات الدم البيضاء، وعدد الصفائح الدموية، والارتفاع الواضح في عدد العدلات. هناك علاقة معينة بين عدد كرات الدم البيضاء ومدة النوبات. قد توفر التغيرات في معلمات الدم الروتينية التي لوحظت في مرضى GTCS معلومات مفيدة سريريًا.

Objectives: To analyze the alterations in routine blood parameters in these patients. Generalized tonic clonic seizure (GTCS) is one main type of generalized epilepsy. Clinicians have recently found changes in routine blood parameters in GTCS patients.

Methods: A retrospective study of 45 GTCS patients and 200 healthy controls was conducted. Blood routine tests in emergency ward and on the second

day of admission were retrieved. Changes in routine blood parameters, including red blood cell (RBC) count, white blood cell (WBC) count, platelet count, lymphocyte count, neutrophil count, and neutrophil-to-lymphocyte ratio (NLR) on the seizure episode day and the second day after seizure were analyzed.

Results: The GTCS patients had increased platelet count, RBC count, WBC count, neutrophil count, lymphocyte count, and NLR, especially at onset of GTCS episode, compared to the controls. These parameters had decreased on the second day after seizure onset. The neutrophil count and WBC count in GTCS cases with seizure duration <5 min were significantly lower than those with seizure duration >5 min. However, this phenomenon was not observed in other indices.

Conclusion: The GTCS may induce a transient increase in RBC count, WBC count, and platelet count, and obvious elevation in neutrophil count. There is a certain correlation between WBC count and the duration of seizures. Changes in routine blood parameters observed in GTCS patients may provide useful information clinically.

*Neurosciences 2023; Vol. 28 (2): 123-129
doi: 10.17712/nsj.2023.2.20220135*

From the Department of Neurology, Nanjing Lishui People's Hospital, Zhongda Hospital Lishui Branch, Southeast University, Jiangsu Province, China.

Received 18th November 2022. Accepted 15th March 2023.

*Address correspondence and reprint request to: Dr. Hongbo Wen, Department of Neurology, Nanjing Lishui People's Hospital, Zhongda Hospital Lishui Branch, Southeast University, Jiangsu Province, China. Email: 230199183@seu.edu.cn
ORCID: <https://orcid.org/0000-0001-6527-2400>*

Epilepsy is a relatively common neurological disorder which is characterized by persistent susceptibility to seizures and the associated cognitive and psychosocial consequences.¹ Epilepsy is among the top 3 most contributing diseases to the global burden in terms of

neurological disorders.^{2,3} The estimated global incidence of epilepsy is 0.76%,⁴ And an estimated 45 million people are affected by epilepsy worldwide.⁵ Epilepsy can result from any pathophysiological process that deranges extracellular ion homeostasis or alters receptor function, energy metabolism, or transmitter uptake.⁶

Generalized tonic clonic seizure (GTCS) is one of the fundamental types of generalized epilepsy (also known as grand mal seizures) characterized by seizures with a tonic phase followed by clonic muscle contractions.^{7,8} The GTCS is the most regular type of motor seizure in epilepsy cases. The seizure emanates from a certain point in the epileptic network composed of subcortical structures and bilateral cerebral cortex and rapidly affects the whole network.^{9,10} The GTCS is more pervasive in elders, and can be caused by a plethora of reasons, including hypoxia, ischemia, low-grade glioma, cortical dysplasia, encephalitis, trauma, and cerebrovascular diseases.¹¹⁻¹³ It is a severe neurological emergency and is often accompanied by altered consciousness or complete loss of consciousness. Lack of timely control of the seizure may lead to life-threatening respiratory depression, joint muscle injury, and brain edema. Severe cases of epilepsy have a significantly worse prognosis. Thus, early risk stratification of epileptic patients is a key imperative to improve outcomes.¹⁴

Routine laboratory investigations are broadly implemented in clinical settings and are of great clinical importance in predicting the diagnosis and progression of many diseases, such as anemia,¹⁵⁻¹⁷ infectious diseases,^{18,19} tumors,^{20,21} and cardiovascular diseases.²²⁻²⁴ Routine blood investigations are inexpensive and easily conducted. Routine blood parameters such as platelet count, white blood cell (WBC) count, and neutrophil-to-lymphocyte ratio (NLR) have been widely studied in clinical practice²⁵ as markers of many pathological conditions, such as inflammation. For example, NLR is increased in various inflammatory disorders including thyroid conditions,²⁶ irritable bowel disease,²⁷ diabetes mellitus,²⁸ and SARS Cov2 infection.²⁹ Recent studies have found changes in routine blood parameters in epileptic patients, especially those with GTCS. Epileptic seizure was found to correlate with NLR and platelet-lymphocyte ratio (PLR).^{30,31} In our clinical practice, some patients with GTCS showed significantly increased WBC counts during emergency

routine blood investigations. However, subsequent observation showed no signs of secondary infection, and these parameters gradually returned to normal after stabilization of the patient's condition. Thus, additional explorations were essential to investigate the changes in routine blood parameters in patients with GTCS.

In this study, we retrospectively analyzed the changes in routine blood parameters, such as WBC count, red blood cell (RBC) count, lymphocyte count, neutrophil count, platelet count, and NLR in patients with GTCS, especially on the day of seizure episode and on the second day after seizure. This study may provide meaningful information for the clinical diagnosis and treatment of GTCS.

Methods. Data source. This was a retrospective study of data retrieved from the electronic medical record system (Neusoft Corporation) of the Zhongda Hospital Lishui branch, Southeast University, China. The database contains data of all patients admitted to the hospital since January 1, 2020. The data include detailed clinical information including vital signs, diagnoses, and treatment details.

All authors of this study were authorized to access the electronic medical record system after approval of the hospital administration. This research was permitted by the Ethics Committee of Zhongda Hospital Lishui Branch, Southeast University.

Participants. Patients with epilepsy were hospitalized in Neurology Department of Zhongda Hospital Lishui branch, Southeast University between January 1, 2020 and March 31, 2021, and eligible for inclusion. The inclusion criteria included: (1) patients diagnosed with GTCS; (2) availability of routine blood test results at the onset and after admission to hospital. The exclusion criteria were: (1) patients with respiratory or urinary tract infection; (2) patients with hematological disorders such as aplastic anemia, leukemia, and granulocytosis; (3) patients with serious heart, liver, and/or kidney disease; (4) patients admitted 24 h after the onset of GTCS. A total of 45 cases (25 males and 20 females; mean age: 63.7 ± 15.2 years) qualified the study-selection criteria and were considered in the research. A total of 200 healthy subjects (105 males and 95 females; mean age: 65.3 ± 9.2 years) were enrolled as the control group. The healthy subjects were enrolled from the general physical examination center (January 1, 2020 to March 1, 2021).

Biochemical tests. Demographic characteristics, comorbid diseases, blood routine tests in emergency ward and on the second day of admission, and liver and kidney function indices of all selected patients were retrieved. All biochemical tests were performed

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

in the Clinical Laboratory of the institution. All tests were conducted on venous blood samples. The YSMEX automatic blood cell analyzer was used for routine blood tests, and Beckman-Coulter 5800 automatic biochemical analyzer was used for the measurement of liver and kidney function indices. Comorbid diseases, liver and kidney function indices, WBC count, RBC count, lymphocyte count, neutrophil count, platelet count, and NLR were studied between the 2 groups. Within the GTCS group, we compared the WBC count, RBC count, lymphocyte count, neutrophil count, and platelet count on the day of seizure episode with those on the second day after onset.

Data analysis. The Statistical Package for the Social Sciences 26.0 (IBM Corp, Armonk, NY, USA) software

was adopted for statistical analysis. Continuous variables were presented as mean±standard deviation (SD) and between-group differences were assessed for statistical significance using independent t test. Paired t test was applied for comparing blood indices in the acute phase and 1 day after the GTCS episode. Categorical variables are presented as frequency (percentage), and between-group differences were assessed using Chi-square test. $p < 0.05$ was considered indicative of statistical significance.

Results. Demographic data. There was no significant difference between GTCS patients and healthy controls with respect to age and sex distribution, or the prevalence of comorbid diseases such as hypertension or diabetes. Moreover, there were no significant between-group differences regarding the liver and kidney function indices (Table 1).

Increased RBC and platelet counts in GTCS patients.

The mean RBC count and platelet count in the control group were $(4.28 \pm 0.55) \times 10^{12}/L$ and $(163 \pm 51) \times 10^9/L$, respectively. The mean RBC count and platelet count of patients with GTCS immediately after the epileptic attack were $(4.46 \pm 0.51) \times 10^{12}/L$ and $(181.36 \pm 64.24) \times 10^9/L$, respectively. The mean RBC and platelet count on the second day after GTCS episode were $(4.11 \pm 0.53) \times 10^{12}/L$ and $(159.33 \pm 56.59) \times 10^9/L$, respectively. The mean RBC count in GTCS group at emergency was higher than that in control ($p < 0.05$). And it was also

Table 1 - Demographical and clinical features of subjects.

Parameters	GTCS Group (n=45)	Control Group (n=200)	P-value
Male (%)	25 (55.6)	105 (55.6)	0.711
Age (year)	63.7±15.2	65.3±9.2	0.505
Hypertension (%)	14 (31)	68 (34)	0.844
Diabetes (%)	13 (28.9)	56 (28)	0.905
Cr (μmol/L)	6.29±1.51	7.99±4.85	0.358
Ur (mmol/L)	68.9±13.5	61.2±18.7	0.387
ALT (U/L)	22.4±7.2	31.2±18.1	0.220
AST (U/L)	23.1±5.7	24.8±6.8	0.592

ALT - alanine aminotransferase, AST - aspartate aminotransferase, Ur - urea, Cr - creatinine, GTCS - Generalized tonic clonic seizure

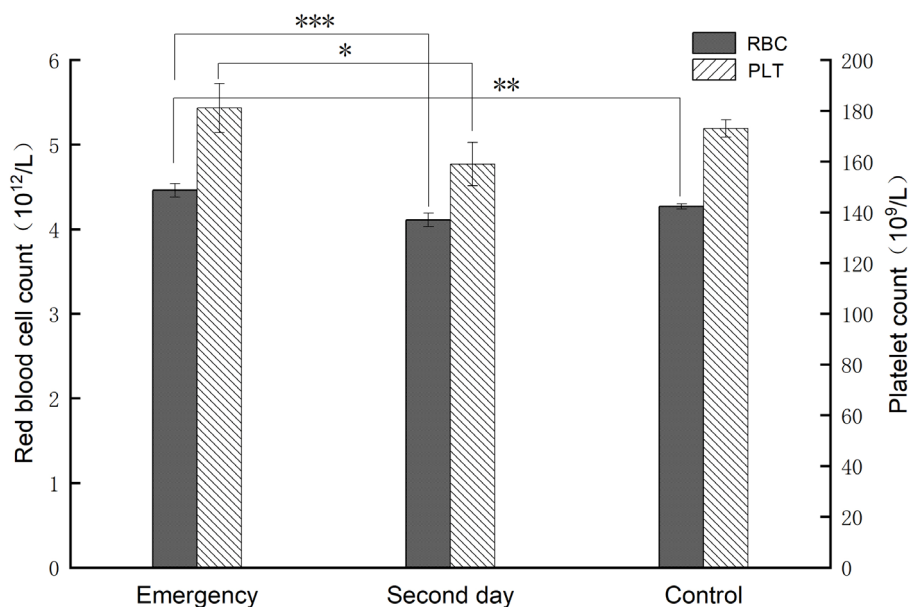


Figure 1 - Change in the RBC and PLT count in GTCS patient. RBC - red blood cell, PLT - platelet, GTCS - generalized tonic clonic seizure

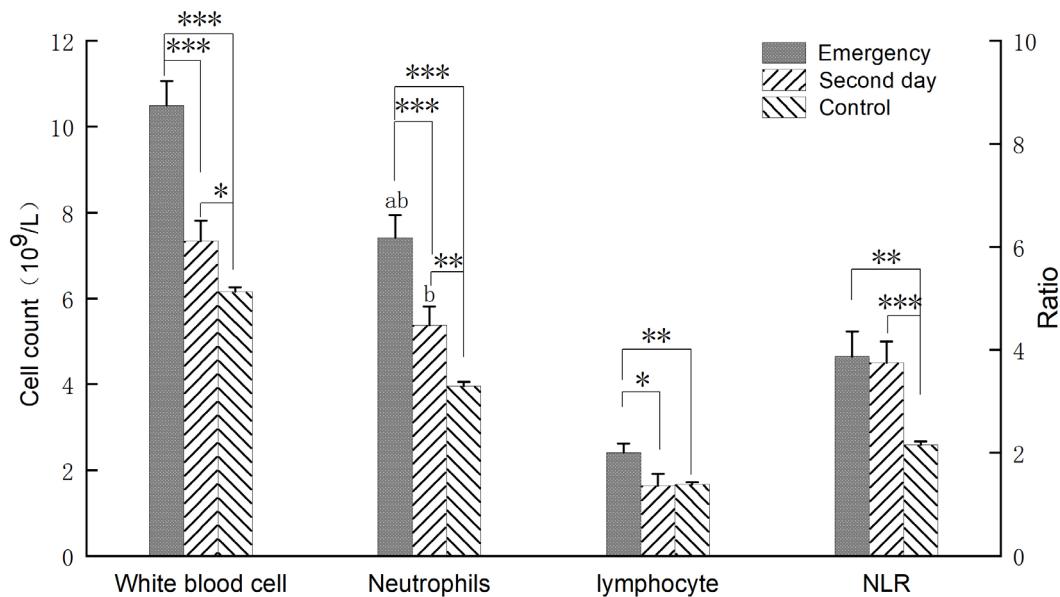


Figure 2 - Changes in the WBC count in GTCS patients

Table 2 - Routine blood parameters in GTCS patients with different seizure duration.

Parameters	GTCS duration		P-value
	≤5 min (n=20)	>5 min (n=25)	
Red blood cell count (10 ¹² /L)	4.61±0.89	4.66±1.07	0.891
Platelet count (10 ⁹ /L)	184±66	179±65	0.779
White blood cell count (10 ⁹ /L)	8.23±2.65	11.96±4.20	0.001
Neutrophil count (10 ⁹ /L)	5.70±1.61	8.65±4.09	0.002
Lymphocyte count (10 ⁹ /L)	2.15±1.39	2.74±1.94	0.254
NLR	4.09±3.51	6.02±6.74	0.224

NLR - neutrophil to lymphocyte ratio, GCTS - generalized tonic clonic seizure

significantly higher than that on the second day of attack. However, the RBC count of GTCS patients on the second day was similar to that in the control group ($p>0.05$). This indicated a transient increase in the RBC count in GTCS patients.

The platelet count in the GTCS group at emergency was slightly higher to that in control but not significantly ($p>0.05$). The platelet count in GTCS group at emergency was higher compared to that on the second day of attack ($p<0.05$). There was no significant different in the platelet count on the second day of GTCS group compared to the control ($p>0.05$). In GTCS patients, the trend of change in platelet count was similar to that of the RBC count, showing highest levels on the day of

seizure attack. The RBC and platelet counts showed a response to GTCS attack (Figure 1).

Increased WBC count in GTCS patients. Nineteen (42.2%) cases in the GTCS group had WBC count greater than the normal range at the onset of seizure attack at emergency. After seizure attack, the mean WBC count, neutrophil count, and lymphocyte count were $(10.49\pm3.83) \times 10^9/L$, $(7.41\pm3.53) \times 10^9/L$, $(2.40\pm1.47) \times 10^9/L$, respectively. The mean WBC count, neutrophil count, and lymphocyte count on the second day of attack were $(7.34\pm3.17) \times 10^9/L$, $(5.38\pm2.85) \times 10^9/L$ and $(1.64\pm1.84) \times 10^9/L$, respectively. The mean WBC count, neutrophil count, and lymphocyte count in the control were $(6.16\pm1.44) \times 10^9/L$, $(3.96\pm1.30) \times 10^9/L$ and $(1.67\pm0.54) \times 10^9/L$, respectively (Figure 2).

Compared to the control, WBC count, neutrophil count, and lymphocyte count were higher in GTCS group at emergency ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). In the GTCS group, all three indices were also remarkably greater at emergency compared to those on the second day of attack ($p<0.001$, $p<0.001$, and $p<0.05$, respectively). Moreover, all 3 indices in GTCS group on the second day after admission were higher than those in the control ($p<0.05$ and $p<0.05$, respectively). However, there was no significant between-group difference with respect to lymphocyte count ($p>0.05$). These results showed that WBCs,

including neutrophils and lymphocytes, increased in response to the GTCS episode.

The NLR in peripheral blood reflects the balance between systemic immunity and inflammation and can be used as a prognostic biomarker in various diseases.²⁵ NLR of GTCS patients in emergency at initial attack, on the second day after attack, and in the controls were 4.64 ± 3.96 , 4.50 ± 3.28 , 2.59 ± 1.20 , respectively. The NLR in the GTCS group, either in emergency or at the second day after attack, was larger than that in control ($p < 0.001$ and $p < 0.001$, respectively). In GTCS group, the NLR at emergency was similar to that on the second day ($p > 0.05$). These results indicated a potential role of inflammation in GTCS attack (Figure 2).

Correlation of blood-routine parameters and GTCS duration. The GTCS cases were categorized into two groups in accordance with the duration of the seizure attack. In 20 GTCS patients, the seizure duration was ≤ 5 min, while in 25 GTCS patients, the seizure duration was > 5 min. There were no significant differences between these two groups regarding age, sex, or prevalence of basic comorbid conditions (data not shown). The RBC count, lymphocyte count, platelet count, and NLR were also comparable between GTCS patients with seizure duration ≤ 5 min and those with seizure duration > 5 min. However, the WBC count and neutrophil count in GTCS cases with seizure duration ≤ 5 min were significantly lesser than those in GTCS cases with seizure duration > 5 min, respectively ($p = 0.001$ and $p = 0.002$). These results suggest a potential correlation of WBC count and neutrophil count with the duration of GTCS attack (Table 2).

Discussion. Generalized tonic clonic seizure (GTCS) is caused by a disturbance in the functioning of both sides of the brain.³² It usually occurs suddenly and the patients are typically admitted to hospital from the emergency center. In clinical settings, disease history and EEG are used for the diagnosis and surveillance of GTCS. Development of more methods to facilitate the diagnosis and monitoring of this disease is a key imperative. Characterization of other biological changes, such as RBC and WBC counts, associated with GTCS may help in designing management strategies and improving patient prognosis. Changes in routine blood parameters were recently shown to correlate with GTCS. Herein, we retrospectively scrutinized the changes in routine blood parameters in GTCS patients, especially on the day of seizure episode and 1 day after the onset. The results showed changes in the WBC count, RBC count, lymphocyte count, neutrophil count, platelet

count, and NLR in GTCS patients. In particular, these indices increased on the day of seizure episode, followed by a decrease on the subsequent day. GTCS patients with seizure duration ≤ 5 min showed significantly lower WBC and neutrophil counts compared with GTCS patients with seizure duration > 5 min.

Only a few studies have investigated the changes in routine blood parameters in GTCS patients. Guneş and Buyukgol³⁰ determined PLR, NLR, and mean platelet volume (MPV) during GTCS, and investigated their relationship with seizures. They found a relationship of seizure with PLR and inflammation mediated by neutrophils; the increase in NLR by 1 unit was shown to correspond to 1.95-fold increase in the risk of seizure. In our study, GTCS was found to have induced a transient increase in the RBC count, platelet count, and WBC count. Among these, the extent of increase in WBC count was most significant (nearly 40%). The RBC count, platelet count, and lymphocyte count returned to normal on the second day after attack; however, the total leucocyte count and the neutrophil count were still higher compared to those in the control. The transient increase in RBC count and platelet count may be due to the decrease in plasma volume induced by blood concentration, and the consequent relative increase in erythrocyte volume. The GTCS patients may experience excessive sweating and vomiting during a seizure episode. This may cause dehydration, which can lead to blood concentration, manifesting as increase in RBC count and platelet count. Further studies should investigate the relation of clinical symptoms with RBC count and platelet count.

This study found that GTCS may induce a transient increase in RBC count, WBC count, and platelet count. Among these, the most obvious elevation was found in neutrophil count. There is a certain correlation between the increase in WBC count and the duration of seizures. Generally, routine blood investigations on the second day can show a significant decline. Clinicians should carefully assess the clinical manifestations and the results of repeat investigations on the subsequent day in order to avoid unnecessary antibiotic treatment on the presumption of infection based on increased WBC counts. In specific cases, if the description about the seizure is not clear or when the seizure episode occurred in the absence of any bystander, the possibility of grand mal seizure and the severity of the attack can be speculated through the elevation of RBC count and WBC count. The increase in WBC count may be used to monitor the status of GTCS patients after the

seizure. Our results may provide useful information for management of patients hospitalized due to GTCS.

Some limitations of this study should be acknowledged. This was a retrospective single-center study with a relatively small sample size. Data about the duration of seizure episodes was based on the description provided in the medical history, which may not be entirely accurate. Our results indicate a need to investigate the correlation between seizure duration and routine blood parameters. More rigorous and in-depth research about the seizure should be conducted to clarify this issue. Besides, the blood indices in this study were evaluated only at 2 time-points: on the day of seizure episode and on the second day after admission. More detailed investigation of dynamic changes was not performed. Prospective investigations in a larger population are required to further clarify the changes in routine blood indices in GTCS. Besides, the detailed mechanisms should also be taken in consideration to clarify the correlation between change in blood-routine parameters and GTCS.

Conclusion. In conclusion, this retrospective study analyzed the changes in the levels of routine blood parameters in GTCS patients, at GTCS onset and 1 day after the seizure episode. We found a transient increase in RBC count, platelet count, and lymphocyte count and more significant increase in WBC and neutrophil counts during the GTCS process. The WBC count and neutrophil count in GTCS cases with seizure duration ≤ 5 min were significantly lower than those in GTCS cases with seizure duration > 5 min. Further studies are required for in-depth characterization of changes in blood parameters in GTCS, which may provide insights into the pathophysiology and outcomes of the disease episode for better patient management.

Acknowledgment. We would like to thank Medjaden Inc. for English language editing.

References

- Jetté N, Kirkpatrick M, Lin K, Fernando SMS, French JA, Jehi L, et al. What is a clinical practice guideline? A roadmap to their development. Special report from the Guidelines Task Force of the International League Against Epilepsy. *Epilepsia* 2022; 63: 1920-1929.
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1789-1858.
- Mela A, Staniszevska A, Wrona W, Poniatowski ŁA, Jaroszyński J, Niewada M. The direct and indirect costs of epilepsy in Poland estimates for 2014-2016 years. *Expert Rev Pharmacoecon Outcomes Res* 2019; 19: 353-362.
- Alva-Díaz C, Navarro-Flores A, Rivera-Torres O, Huerta-Rosario A, Molina RA, Velásquez-Rimachi V, et al. Prevalence and incidence of epilepsy in Latin America and the Caribbean: A systematic review and meta-analysis of population-based studies. *Epilepsia* 2021; 62: 984-996.
- Nishida T, Lee SK, Wu T, Tiamkao S, Dash A. Efficacy and safety of perampanel in generalized and focal to bilateral tonic-clonic seizures: a comparative study of Asian and non-Asian populations. *Epilepsia* 2019; 60: 47-59.
- Balestrini S, Arzimanoglou A, Blümcke I, Scheffer IE, Wiebe S, et al. The aetiologies of epilepsy. *Epileptic Disord* 2021; 23:1-16.
- Kodankandath TV, Theodore D, Samanta D. Generalized tonic-clonic seizure. Treasure Island (FL): StatPearls Publishing; 2022.
- Zhang Y, Huang G, Liu M, Li M, Wang Z, Wang R, et al. Functional and structural connective disturbance of the primary and default network in patients with generalized tonic-clonic seizures. *Epilepsy Res* 2021; 174:106595.
- Gao H, Sander JW, Xiao Y, Zhang Y, Zhou D. A comparison between the 1981 and 2017 International League Against Epilepsy classification of seizure types based on an outpatient setting. *Epileptic Disord* 2018; 20: 257-264.
- El Atrache R, Tamilia E, Amengual-Gual M, Mohammadpour Touserani F, Yang Y, Wang X, et al. Association between semiologic, autonomic, and electrographic seizure characteristics in children with generalized tonic-clonic seizures. *Epilepsy Behav* 2021; 122: 108228.
- Gursahani R, Gupta N. The adolescent or adult with generalized tonic-clonic seizures. *Ann Indian Acad Neurol* 2012; 15: 81-88.
- Driscoll J, Almas M, Gregorian G, Kyrychenko A, Makedonska I, Liu J, et al. Pregabalin as adjunctive therapy in adult and pediatric patients with generalized tonic-clonic seizures: A randomized, placebo-controlled trial. *Epilepsia open* 2021; 6: 381-393.
- Kaur S, Garg R, Aggarwal S, Chawla SPS, Pal R. Adult onset seizures: Clinical, etiological, and radiological profile. *J Family Med Prim Care* 2018; 7: 191-197.
- Pack AM. Epilepsy Overview and Revised Classification of Seizures and Epilepsies. *Continuum (Minneapolis)* 2019; 25: 306-321.
- Kamenetz Y, Beloosesky Y, Zeltzer C, Gotlieb D, Magazanik A, Fishman P, et al. Relationship between routine hematological parameters, serum IL-3, IL-6 and erythropoietin and mild anemia and degree of function in the elderly. *Aging (Milano)* 1998; 10: 32-38.
- Joosten E. Iron deficiency anemia in older adults: A review. *Geriatr Gerontol Int* 2018; 18: 373-379.
- Zhou D, Xu P, Peng M, Shao X, Wang M, Ouyang J, et al. Pre-treatment red blood cell distribution width provides prognostic information in multiple myeloma. *Clin Chim Acta* 2018; 481: 34-41.
- Salci H, Catik S, Salci ESO, Ozakin C. Peritoneal fluid analysis of the newborn calves with intestinal atresia - a clinical approach. *Acta Scientiae Veterinariae* 2019;47: 1-9.

19. Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. *PloS one* 2020; 15: e0238160.
20. Amabile MI, De Luca A, Tripodi D, D'Alberti E, Melcarne R, Imbimbo G, et al. Effects of inositol hexaphosphate and myo-inositol administration in breast cancer patients during adjuvant chemotherapy. *J Pers Med* 2021; 11: 756.
21. Schavgoulidze A, Cazaubiel T, Perrot A, Avet-Loiseau H, Corre J. Multiple myeloma: Heterogeneous in every way. *Cancers (Basel)* 2021; 13: 1285.
22. Lao X, Ma L, Ma Q, Ma Q, Yang Z, Guo L, et al. Hematological factors associated with immunity, inflammation, and metabolism in patients with systemic lupus erythematosus: Data from a Zhuang cohort in Southwest China. *J Clin Lab Anal* 2020; 34: e23211.
23. Gheissari A, Dehghan B, Ghaed Sharafi B, Abedini A, Merrikhi A, Madihi Y, et al. Importance of mean platelet volume in predicting cardiac mechanics parameters and carotid-intima media thickness in children with end-stage renal disease and comparison with healthy children. *Ther Apher Dial* 2019; 23: 451-459.
24. Gijssberts CM, den Ruijter HM, de Kleijn DPV, Huisman A, Ten Berg M, de Groot M, et al. Hematological parameters outperform plasma markers in predicting long-term mortality after coronary angiography. *Angiology* 2018; 69: 600-608.
25. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Scientific reports* 2021; 11: 464.
26. Afsin H, Aktas G. Platelet to Lymphocyte and Neutrophil to Lymphocyte Ratios are useful in differentiation of thyroid conditions with normal and increased uptake. *Ethiop J Health Dev* 2021; 35: 149-153.
27. Aktas G, Duman TT, Atak BM, Kurtkulagi O, Bilgin S, Basaran E, et al. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. *Fam Med Prim Care Rev* 2020; 22: 107-110.
28. Bilgin S, Aktas G, Kocak MZ, Atak BM, Kurtkulagi O, Duman TT, et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. *Aging Male* 2020; 23: 923-927.
29. Khalid A, Jaffar MA, Khan T, Lail RA, Ali S, Aktas G, et al. Hematological and biochemical parameters as diagnostic and prognostic markers in SARS-COV-2 infected patients of Pakistan: a retrospective comparative analysis. *Hematology* 2021; 26: 529-542.
30. Güneş M, Büyükgöl H. Relationship between generalized epileptic seizure and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and neutrophil mediated inflammation. *Int J Neurosci* 2020; 130: 1095-100.
31. Tazeen S, Prasad K, Harish K, Sagar P, Kapali AS, Chandramouli S. Assessment of Pretreatment Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Prognosis of Oral Squamous Cell Carcinoma. *J Oral Maxillofac Surg* 2020; 78: 949-960.
32. Li Y, Qin B, Chen Q, Chen J. Altered dynamic functional network connectivity within default mode network of epileptic children with generalized tonic-clonic seizures. *Epilepsy Res* 2022; 184: 106969.