







MONOCYTE-LYMPHOCYTE, NEUTROPHIL-LYMPHOCYTE, AND
PLATELET-LYMPHOCYTE RATIOS AS INFLAMMATORY
BIOMARKERS OF CLINICAL DENGUE SEVERITY

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Abstract

The literature describes monocyte-lymphocyte (MLR), neutrophil-lymphocyte (NLR), and platelet-lymphocyte (PLR) ratios as prognostic biomarkers. However, in the case of dengue infection, patient clinical management and nonspecific laboratory tests determine the prognosis. Therefore, this study analyzed MLR, NLR, and PLR as prognostic biomarkers of dengue infection. Our study was based on a clinical cohort of dengue patients in Brazil between 2012 and 2013. From 193 patients, 164 (85.0%) were classified as dengue fever (DF), 19 (9.8%) as dengue hemorrhagic fever (DHF), and 10 (5.2%) as intermediate DF/DHF. DHF cases were significantly associated with MLR > 0.13 (OR: 5.72, 95% CI: 1.28-25.60, $p < 0.05$) and PLR \leq 80.68 (OR: 4.26; 95% CI 1.60-11.33; $p < 0.05$). Our results suggest that MLR increase, and PLR decrease indicate a higher likelihood of worsening the clinical status.

Keywords: Blood cell count. Dengue hemorrhagic fever. Dengue virus. Leukocyte count. Prognostic.

1. Introduction

Dengue is the most relevant arthropod-borne viral disease in humans worldwide. It is caused by the dengue virus (DENV), a Orthoflavivirus member of the *Flaviviridae* family, and transmitted by *Aedes spp* mosquitoes (WHO 2009). Dengue is endemic in several countries, with approximately 105 million cases per year, of which 51 million are clinically apparent with febrile episodes and four million are severe cases requiring hospitalization (WHO 2009; Cattarino et al. 2020).

The disease may develop as an asymptomatic syndrome or manifest with nonspecific clinical symptoms to a broad clinical spectrum (Brazil 2016). The clinical and laboratory characteristics of dengue indicate that patient clinical management aids disease prognosis by monitoring the signs of alertness and severity (Pang et al. 2016; Vasey et al. 2020). Dengue morbidity and mortality significantly increases hospitalizations, the workload of multidisciplinary teams, and economic costs in endemic regions, thus requiring a prognostic marker to predict dengue severity and potentially guide the screening and premature clinical management of patients (Barniol et al. 2011; Leo et al. 2013; Vasey et al. 2020).

New biomarkers from blood cell counts are gaining prominence due to their prognosis predictability, low cost, and easy attainment from blood cell counts. The monocyte-lymphocyte (MLR), neutrophil-lymphocyte (NLR), and platelet-lymphocyte (PLR) ratios represent prognostic biomarkers in viral

infections (Meng et al. 2016; Pujani et al. 2021), cancer (Tan et al. 2018; Mandaliya et al. 2019; Cong et al. 2020), and cardiovascular (Xiang et al. 2018) and metabolic (Demirdal and Sen 2018; Gao et al. 2019) diseases. Calculating ratios from the blood count is less expensive and considerably effortless than other inflammatory markers, representing two cellular immune system populations isolated and independently. However, there is little knowledge about these ratios in dengue infections and their association with the clinical severity of the disease. Kotepui et al. (2017) observed that NLR and MLR were significantly lower in dengue patients than those with malaria. However, this research did not evaluate the ratios combined with different clinical presentations of dengue. The present study analyzed MLR, NLR, and PLR as prognostic biomarkers of DENV infection in patients with the disease's diverse clinical presentations.

2. Material and Methods

Study design and population

This study was based on a clinical cohort of 452 patients diagnosed with dengue infection in Goiânia, Goiás (1.4 million inhabitants; IBGE, 2013; Latitude: -16.6799, Longitude: -49.255 16° 40 '48 "South, 49 15° 18 "West), central Brazil. In 2013, the dengue epidemic in the referred state highlighted the co-circulation of DENV-1, DENV-2, DENV-3, and DENV-4, with an incidence of 2,088/100,000 cases per inhabitant (Brazil 2014; Argolo et al. 2016; Rocha et al. 2017).

From January 2012 to July 2013, individuals with dengue infection suspicion were recruited from eight public healthcare units in Goiânia and followed up for 30 days since the onset of symptoms. These patients answered a questionnaire containing socio-demographic information, disease clinical history, and information concerning the day of sample collection and examinations. Laboratory tests were conducted in the public healthcare units and the Rômulo Rocha laboratory of the School of Pharmacy at the Federal University of Goiás.

Data collection and eligibility criteria

The present study extracted patients' clinical and laboratory data from a database with information about the time of sample collection and laboratory tests. The study included patients with laboratory-confirmed dengue status, applying the following exclusion criteria: a) patients younger than 13 years; b) having one or more of the following clinical conditions: pregnancy, diabetes mellitus, chronic kidney disease (CKD), asthma, lupus, cancer, AIDS, hepatitis B or C, and organ transplantation; c) using steroidal or non-steroidal anti-inflammatory drugs; d) presenting hemograms without differential blood counts.

Variables, definition of cases, and ratios

The socio-demographic and clinical-laboratory variables collected from study participants were age, sex, dengue serotype (DENV 1-4), infection type (primary and secondary), clinical presentation of the disease (dengue fever (DF), dengue hemorrhagic fever (DHF), or intermediate DF/DHF), anti-DENV antibodies (IgM and IgG), blood cell parameters (hematocrit, leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts), aspartate aminotransferase or glutamic-oxaloacetic transaminase (AST/GOT), alanine aminotransferase or glutamic pyruvic transaminase (ALT/GPT), albumin, and creatinine. NLR, MLR, and PLR were calculated from blood cell counts by dividing the absolute number of monocytes (mm^3), neutrophils (mm^3), and platelets (mm^3) by the absolute number of lymphocytes (mm^3).

The classification of confirmed dengue cases followed the World Health Organization 1997 guide and the Brazilian Health Ministry 2005, distributing them into three clinical presentations with different severity levels: a) DF: acute febrile illness with two or more nonspecific symptoms, such as headache, retro-orbital pain, myalgia, arthralgia, prostration, and rashes; b) DHF: besides classic disease symptoms, hemorrhagic manifestations occur, such as positive tourniquet test, petechiae, ecchymosis or purpura, mucous membrane bleeding, gastrointestinal bleeding, plasma leakage, pleural or pericardial effusion, ascites, or hypoalbuminemia; and c) Intermediate DF/DHF (used in Brazil): suspected dengue cases

progressing to severity or death without all DHF symptoms, or patients with at least one of the following clinical/laboratory abnormalities: neurological complications, cardiorespiratory dysfunction, hepatic failure, gastrointestinal bleeding, pleural, pericardial, and ascites effusion, thrombocytopenia, and leukocytosis (WHO 1997; Brazil 2005).

Data analysis

The SPSS statistical program, version 22, hosted the exploratory and descriptive analyses. The χ^2 test analyzed categorical variables, and the Mann-Whitney and Kruskal-Wallis tests investigated continuous variables. MedCalc version 19.03 calculated the ROC curve, MLR, NLR, and PLR cutoffs according to the Youden index. The GraphPad Prism 6.0 provided graphic representations. The p values were statistically significant when < 0.05 .

Ethical considerations

The ethics committee of the Federal University of Goiás approved this study under CAAE number 84535317.3.0000.5083, following the guidelines and standards of regulatory agencies for research involving human beings from resolutions 466/2012 and 510/16, and the Helsinki Declaration, as revised in 2013.

3. Results

This study included 193 samples from individuals with laboratory-confirmed dengue infection. Table 1 presents patients' clinical and laboratory characteristics according to disease classifications (DF, intermediate DF/DHF, and DHF). DF patients (85%, $n = 164$) were the majority of the study population, followed by 19 (9.8%) with DHF and 10 (5.2%) with intermediate DF/DHF. Median ages in the respective groups were 33 years (14-78 years), 41 years (16-56 years), and 49 years (16-81 years), with female predominance. Serotype identification was possible in 55 of 193 samples, showing 29 patients with DENV-4, 22 with DENV-1, and four with DENV-3. Patients also presented a higher prevalence of secondary infections: 78% ($n = 113$) in DF and 66.7% in intermediate DF/DHF ($n = 6$) and DHF ($n = 12$).

DHF patients demonstrated lower neutrophil ($1390/\text{mm}^3$ vs. $2032/\text{mm}^3$, $p < 0.05$) and platelet ($67300/\text{mm}^3$ vs. $136500/\text{mm}^3$, $p < 0.05$) counts, a decrease in albumin (3.3 g/dL vs. 3.8 g/dL, $p < 0.05$), and an increase in ALT/GPT (53 U/L vs. 38 U/L, $p < 0.05$) compared to DF patients. Hematocrit, leukocyte, lymphocyte, monocyte, AST/GPT, and creatinine levels did not differ between groups (Table 1). Ratio comparison between DF and DHF showed higher MLR in DHF patients (0.18 vs. 0.23, $p < 0.05$), while PLR was lower in this group (122.36 vs. 59.67, $p < 0.05$) (Table 2).

Figure 1-A demonstrates MLR, NLR, and PLR variations throughout the acute phase of dengue. DF cases showed NLR and PLR decreasing from day one to days three to four (2.16 vs. 1.57 and 146.45 vs. 118.0; $p < 0.05$), five (2.16 vs. 1.23 and 146.45 vs. 85.29; $p < 0.05$), and six to seven (2.16 vs. 1.23 and 146.45 vs. 72.36; $p < 0.05$). An additional analysis showed that platelets followed the trends, decreasing from day one to days three and five (148000 mm^3 vs. 120000 mm^3 ; $p < 0.05$). However, lymphocytes increased from day one to days three, five (953 mm^3 vs. 1573 mm^3 ; $p < 0.05$), and six to seven (953 mm^3 vs. 1948 mm^3 ; $p < 0.05$), and from day four to day six to seven (1190 mm^3 vs. 1948 ; $p < 0.05$). DHF patients showed platelets decreasing from day one to day three and six to seven (95680 mm^3 vs. 43600 ; $p < 0.05$). MLR, neutrophil, and monocyte analysis findings did not vary significantly.

Figure 1-B compares daily MLR, NLR, and PLR during the acute phase of dengue from the onset of symptoms to the end of the first week of illness, according to patients' clinical manifestations. MLR differed between DF and DHF ($p = 0.038$) in the sixth and seventh days of symptoms. In the same period, PLR also differed between DF and DHF ($p = 0.005$) on day four ($p = 0.005$). DHF patients presented higher MLR and lower PLR in the sixth and seventh days of disease than DF patients (0.27 vs. 0.108, $p < 0.05$, 26.34 vs. 72.36, $p < 0.05$, respectively). On the fourth day of illness, PLR increased in DHF compared to DF patients (160.19 vs. 118.0, $p < 0.05$). The same analysis did not present significant NLR variations.

Table 1. Clinical-laboratory, socio-demographic, and epidemiological findings of dengue patients stratified by clinical classification (n = 193).

	DF n = 164 (%)	Intermediate DF/DHF n = 10 (%)	DHF n = 19 (%)
Demographics			
Median age in years (min-max)	33 (14-78)	49 (16-81)	41 (16-56)
Female sex median (%)	85 (51.8)	5 (50)	14 (73.6)
Serotype median (%)			
DENV-1	15 (33.3)	3 (100)	4 (57.1)
DENV-3	4 (8.9)	0 (0)	0 (0)
DENV-4	26 (57.8)	0 (0)	3 (42.9)
Antibody response pattern median (%)			
Primary	32 (22)	3 (33.3)	6 (33.3)
Secondary	113 (78)	6 (66.7)	12 (66.7)
Laboratory test median (min-max)			
Hematocrit (%)	43.6 (30.9-52.6)	45.7 (35-52.2)	42 (32.6-53.4)
Leukocyte (10 ³ XμL)	3645 (1490-16400)	3095 (1780-6800)	3150 (1400-12700)
Neutrophils (10 ³ XμL)	2032.5 (678-14256)	1618.5 (1050-3876)	1390.0 (1292-1993)
Lymphocytes (10 ³ XμL)	1175.5 (195-8036)	998.0 (492-2380)	1029.0 (385-5080)
Monocytes (10 ³ XμL)	215.5 (7-1086)	250.0 (98-294)	231.0 (20-1651)
Platelet (10 ³ XμL)	136500 (25000-417000)	108500 (16900-250000)	67300 (30000-113000)
AST/GOT (U/L)	39 (11-716)	31.5 (21-66)	53 (10-162)
ALT/GPT (U/L)	38 (6-329)	44.5 (28-153)	53 (24-207)
Albumin (g/dL)	3.8 (2.2-6)	3.6 (2.7-4)	3.3 (2.7-3.9)
Creatinine (mg/dL)	0.8 (0.4-4.1)	1 (0.5-1.3)	0.8 (0.5-1.63)

Dengue-specific serotype related to clinical severity during the 2012/2013 epidemic in central Brazil. DF: dengue fever. DHF: dengue hemorrhagic fever.

The ROC curve analysis provided an MLR, NLR, and PLR cutoff to indicate dengue severity by associating these biomarkers with DF vs. DHF (Figure 2). An MLR > 0.13 (AUC= 0.642, 95% CI: 0.568-0.71, *p* < 0.05, sensitivity = 89.5%, and specificity = 40.2%) indicated a fivefold higher chance of patients evolving to DHF (OR: 5.72, 95% CI: 1.28-25.60, *p* < 0.05) and PLR ≤ 80.68 (AUC = 0.690, 95% CI: 0.618 - 0.756, *p* < 0.05, sensitivity = 63.2%, and specificity= 75%) indicated a fourfold higher chance of developing DHF (OR: 4.26; CI 95% 1.60-11.33, *p* < 0.05) (Figure 2). Ratio cutoff values in DF vs. intermediate DF/DHF were not statistically significant.

Table 2. Hematological biomarkers MLR, NLR, and PLR according to dengue severity and trend comparison between clinical groups.

	Classification			Association	
	DF	Intermediate DF/DHF	DHF	DF x Intermediate DF/DHF (<i>p</i> -value)	DF x DHF (<i>p</i> -value)
MLR median (min-max)	0.18 (0.00-1.14)	0.21 (0.13-0.38)	0.23 (0.02-0.82)	0.224	0.043
NLR median (min-max)	1.58 (0.25-31.47)	1.73 (1.25-3.60)	1.15 (0.38-8.00)	0.475	0.284
PLR median (min-max)	122.36 (8.95-846.15)	102.94 (19.32-221.54)	59.67 (7.08-238.41)	0.323	0.007

Mann-Whitney. *p*-value < 0.05; DF: dengue fever. DHF: dengue hemorrhagic fever. MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio.

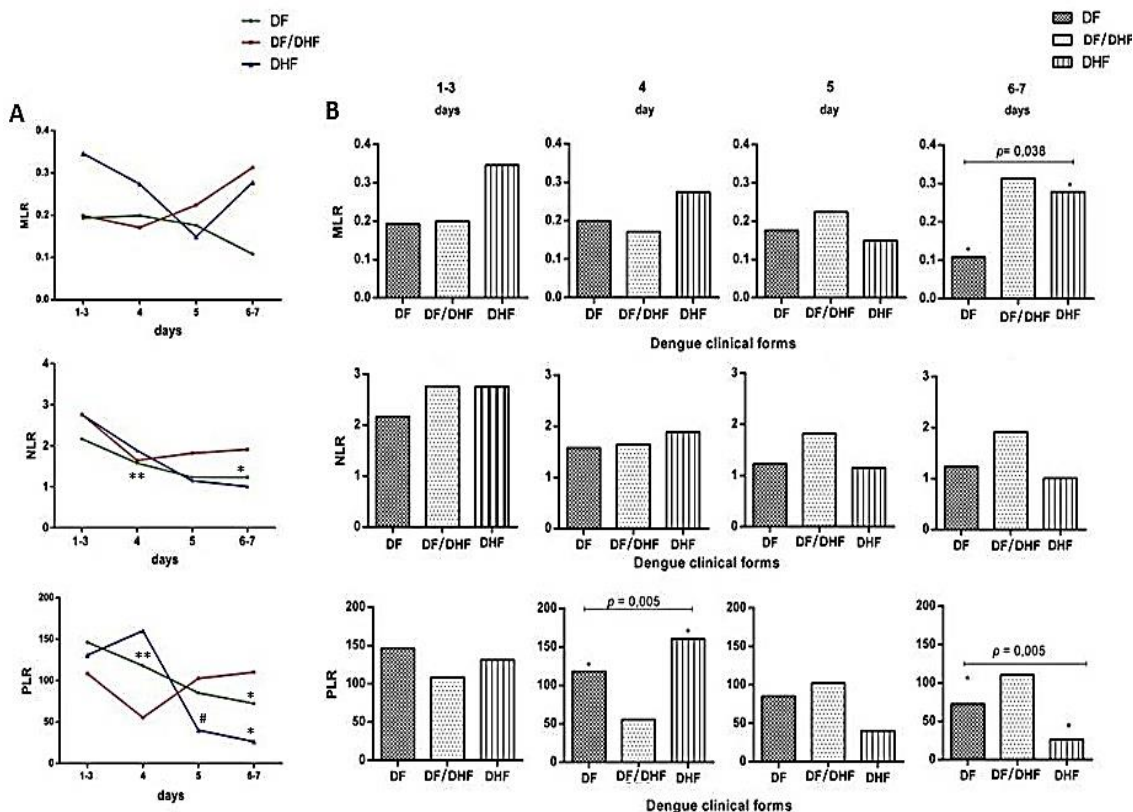
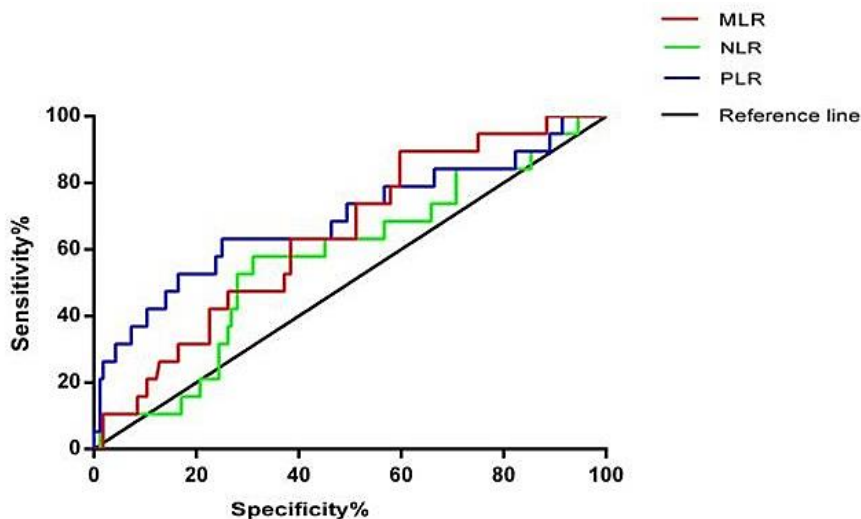


Figure 1. Association of ratios according to dengue types in the first seven days (A), and the comparison between each day of the disease (B). MLR: monocyte to lymphocyte ratio. NLR: neutrophil to lymphocyte ratio. PLR: platelet to lymphocyte ratio. DF: dengue fever. DF/DHF: intermediate dengue with complications. DHF: dengue hemorrhagic fever. A: * $p < 0.05$ compared to day four; ** $p < 0.05$ compared to day one to day three; # $p < 0.05$ compared to day one to day three and four.



		DF x DHF							
	cutoff	AUC (CI 95%)	p	Sensitivity	Specificity	PPV	NPV	OR CI 95%	p
MLR	>0.135	0.642 (0.568-0.711)	0.02*	89.5	40.2	14.8	97.0	5.72 (1.28-25.60)	0.02*
NLR	≤1.231	0.575 (0.500-0.648)	0.28	57.9	68.9	17.7	93.3	2.96 (1.12-7.79)	0.02*
PLR	≤80.68	0.690 (0.618-0.756)	0.01*	63.2	75.0	22.8	94.5	4.26 (1.60-11.33)	0.004*

Figure 2. ROC curve: monocyte-lymphocyte ratio (MLR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and the analysis of the probability in predicting dengue hemorrhagic fever prognosis. p : significance value (*statistically significant). AUC: area under the ROC curve. CI: confidence interval. PPV: positive predictive value. PPN: negative predictive value. OR: odds ratio.

4. Discussion

Dengue is a dynamic disease, and through the course of the infection, a set of signs, clinical symptoms, and hematological and biochemical parameters guide patient clinical management and enable monitoring and intervention when signs of severity appear. However, the search for markers to predict clinical severity remains under investigation.

Laboratory parameters are relevant prognosis indicators and should be tested when patients present suggestive dengue infection symptoms (Hottz et al. 2014). The decrease in neutrophils, platelets, and albumin and the increase in alanine aminotransferase (ALT) found in the present study have been reported in more severe dengue patients (Samanta and Sharma 2015; Chaloeuwong et al. 2018).

Similar to our findings in dengue groups, a study in Sri Lanka observed a reduction in albumin levels in dengue hemorrhagic fever (DHF) patients, potentially due to the plasma leakage typical of this infection²⁴. ALT, a transaminase found mainly in the liver, probably increased because of the inflammatory process of dengue virus (DENV) infection, in which the parenchymal lesion induces ALT release into the blood circulation (WHO 2009; Rodrigues et al. 2017).

Three well-characterized clinical phases occur during disease progression: initial febrile phase from the first to the third day of illness, critical phase from the fourth to the sixth or seventh day, and recovery or death (Argolo et al. 2016). Similar to another study, the neutrophil-lymphocyte ratio (NLR) was > 1 in the first five days, then reversed around day six onward. However, applying this parameter for prognostic analysis is questionable due to the lack of differences between clinical presentations (Chaloeuwong et al. 2018). Monocyte-lymphocyte (MLR) and platelet-lymphocyte (PLR) ratios differed between groups, showing mild clinical manifestations to the most severe. Therefore, characterizing the time this alteration occurred within the viremic period is relevant.

The higher MLR in DHF from day six to seven of the disease allowed our study to characterize it as a late severity biomarker, and the ratio increase seemed a consequence of monocyte increase. Chaloeuwong et al. 2018 indicated that differential leukocyte counts might represent markers to distinguish dengue fever (DF) and DHF, showing high neutrophil and monocyte counts in DHF patients (Khan et al. 2010; Chaloeuwong et al. 2018).

Monocytes elicit an innate immune response after DENV infection. However, these phagocytes reportedly participate in the immunopathology of severe dengue, contributing to viral replication, nitric oxide production, and high cytokine production (Castillo et al. 2019). Monocytes seem to favor DENV replication due to antibody receptors (FcR), inducing infection by suppressing innate responses and providing conditions for viral replication, especially in mononuclear cells of DHF patients (Halstead 1988; Costa et al. 2013).

The lower PLR in DHF observed in our findings was due to the drop in platelet counts in DHF, as this number is inversely proportional to disease severity. The primary mechanisms involved with thrombocytopenia in dengue may include impaired megakaryopoiesis; direct infection of precursor or spinal stromal cells; increased consumption by platelet activation, potentially caused by cytokines, infected endothelial cells, coagulation factors, among other mechanisms; and platelet destruction by antibodies from previous infections and the direct virus activity, causing structural changes and subsequent apoptosis (Lin et al. 2001; Basu et al. 2008; Hottz et al. 2014).

A limitation of this study concerns the sample size, which potentially interfered with ROC curve results and other analyzed parameters. However, the findings support the hypothesis that MLR and PLR are suitable biomarkers for prognostic analysis at the end of the viremic period of DHF, which is essential for clinical practice. Thus, this study is a pioneer in verifying MLR, NLR, and PLR as severity indicators in DENV infections, contributing to patient monitoring and management.

5. Conclusions

This study proposed $MLR > 0.13$ and $PLR \leq 80.68$ as cutoffs, demonstrating the ability to indicate a higher risk of severe DENV infection in individuals. However, NLR was not a robust biomarker to assess dengue severity because it did not show differences between DF, intermediate DF/DHF, and DHF. Thus,

correlating these ratios to other parameters assessing severity may represent a positive strategy to provide complementary prognostic information.

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Ethics Approval: This study was approved by the ethics committee of the Universidade Federal de Goiás under the CAAE number 84535317.3.0000.5083, following the guidelines and standards of regulatory agencies for research involving humans from the resolutions 466/2012 and 510/16, and in accordance with the Helsinki Declaration as revised in 2013.

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