https://doi.org/10.1590/1806-9282.20220190

Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis

John L Frater[1*], Cara Lunn Shirai[1]

Dear Editor,

Luo and colleagues have recently published a study entitled "Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis" in *Revista da Associação Médica Brasileira* examining the role of mean platelet volume (MPV) to distinguish adult-onset Still's disease (AOSD) from sepsis[1]. This is a potentially impactful article, since AOSD can be difficult to distinguish from sepsis and other reactive conditions. In particular, the use of complete blood cell count (CBC) data, which is nearly universally available, can provide a cost-effective means to arrive at the correct diagnosis. The goals of this letter are to (1) compare Luo et al's data to earlier work on this subject and (2) add additional comments regarding the clinical application of MPV.

We followed the guidelines for systematic reviews of diagnostic accuracy studies[2] and PRISMA guidelines[3]. Because this study used publicly available data, it did not require ethical board approval. We conducted an electronic search using Medline (PubMed interface), Scopus, and Web of Science using the keywords "MPV" or "mean platelet volume" AND "Still disease" OR "Still's disease," without restrictions. The date of the search was January 22, 2022. The titles and abstracts were screened, and the full-text articles were then obtained for all potentially relevant studies. After all relevant studies were identified, the reference lists from each paper were reviewed for potentially relevant studies and a search of the PubMed and Google Scholar databases for citations of each paper was conducted to identify additional eligible articles. The included studies were assessed using a standardized data extraction form. The mean and standard deviation (SD) of MPV values were included in a meta-analysis, with the calculation of weighted mean difference (WMD) and its 95% confidence interval (95%CI) in AOSD patients versus patient cohorts with diseases clinically resembling AOSD. For studies where the mean value and SD were not reported, we used the model of Hozo et al.[4] in order to determine the SD from the sample size, median value, and range. Statistical calculations were performed using Meta Mar (www.meta-mar.com, accessed date January 25, 2022). The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS)[5], with the articles independently assessed by each author. A final score for each paper was arrived at by consensus.

After a search of the databases, screening of results, and review of reference lists and citations, a total of five studies met selection criteria[1,6-9] (see Table 1). The studies were conducted in China (four studies)[1,6,7,9] and Turkey (one

Table 1. Characteristics of studies analyzing mean platelet volume in adult-onset Still's disease.

Study	Year	Country	AOSD sample size	Control group(s), size and clinical features	Age (years, mean and range)	MPV, AOSD vs. disease control (fL)	Analyzer	NOS
Ge et al.[6]	2021	China	110	84, sepsis	36 (16–74)	9.69±1.31 vs. 10.85±1.24	Sysmex XE 2100	8
Liu et al.[7]	2019	China	82	48, sepsis; 76 healthy	36 (18–74)	9.8 ± 1.2 vs. 11.1 ± 1.1	Sysmex XE 2100	8
Luo et al.[1]	2021	China	68	55, sepsis	33 (18–74)	10.08±1.11 vs. 11.14±1.09	Sysmex XE 2100	6
Ulutas et al.[8]	2021	Turkey	61	61, FMS	39 (19–73)	8.3±1.2 vs. 9.3±1.0	NS	8
Zhang et al.[9]	2020	China	91	89, FUO; 81 healthy	32 (16–74)	9.80±1.23 vs. 10.42±1.03	Sysmex XE 2100	6

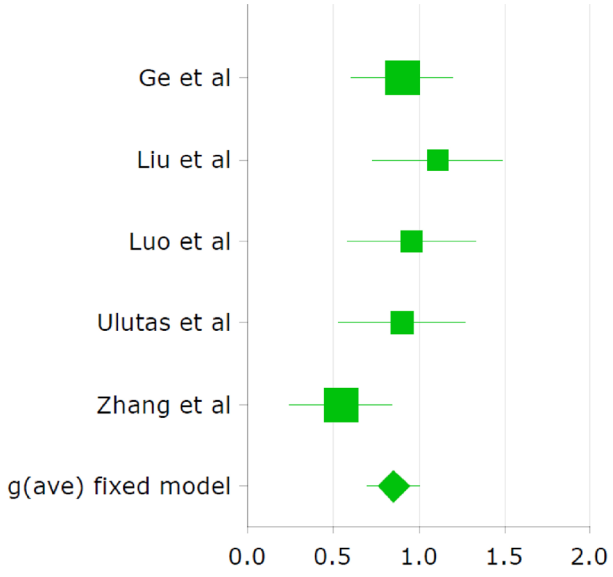
MPV: mean platelet volume; AOSD: adult-onset Still's disease; NOS: Newcastle-Ottawa Scale; FMS: fibromyalgia syndrome; NS: not stated; FUO: fever of unknown origin.

[1]Washington University, Department of Pathology and Immunology – St. Louis (MO), USA.
*Corresponding author: jfrater@wustl.edu

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 10, 2022. Accepted on February 27, 2022.

study)[8]. The studies included data on 412 AOSD patients, with sample sizes varying between 61 and 110 subjects. The control populations included 337 patients with clinical features resembling AOSD, including sepsis (3 studies)[1,6,7], fibromyalgia syndrome (1 study)[8], and fever of unknown origin (1 study)[9]. A total of 157 healthy control subjects were included in two studies[7,9]. Four studies used CBCs performed on the Sysmex SE analyzer (Kobe, Japan)[1,6,7,9]; for the remaining study, the blood analyzer was not identified[8]. The standardized mean difference (SMD) for five studies is shown in Figure 1. Since heterogeneity (I^2 statistic) was <50%, a fixed-effects model was used. MPV was found to be significantly higher in disease control patients compared to AOSD patients (SMD=0.85, 95%CI 0.7–1.0). The cumulative data thus support a potential role for MPV in the differential diagnosis of AOSD.

There are several points we would like to emphasize, in particular for clinicians and others interested in the use of MPV for clinical purposes and to assess the MPV as a potential biomarker in AOSD. First, although the quality of the studies was overall adequate or good, with NOS score ranging from 6 to 8, there was overall a lack of information about preanalytical phase variables that could potentially impact results. These variables include time between phlebotomy and analysis, choice of anticoagulant, and storage/transport conditions[10]. Researchers should control for these variables, and clinicians should be aware of these potential sources of bias. In addition, all studies that reported the hematology instruments used in obtaining the MPVs (n=4) used the same instrumentation platform (Sysmex XE, Sysmex). This potentially limits the generalizability of the data since there are continuing problems with cross-platform harmonization of the MPV[11]. Therefore, the reproducibility of these findings has not yet been established when other instrumentation platforms/methodologies are used. In addition, the difference in MPV between the Still's disease and control groups was on



Study	SMD	95%CI Lower	95%CI Upper	Weight (%)-fixed model
Ge et al.[6]	0.90255774	0.60575354	1.199361939	25.69052942
Liu et al.[7]	1.11001512	0.731066673	1.488963566	15.75987892
Luo et al.[1]	0.956677612	0.583757636	1.329597587	16.27353282
Ulutas et al.[8]	0.899687163	0.52938281	1.269991517	16.50423893
Zhang et al.[9]	0.543694439	0.247358704	0.840030173	25.77181991

Figure 1. Standardized mean difference (SMD) and 95% confidence interval (95%CI) of mean platelet volume values in patients with adult-onset Still's disease versus control populations with symptoms suggesting Still's disease.

average ~1 fL. Given the current limitations of the technology and potential problems with preanalytical and analytical variables, it would be difficult to meaningfully interpret individual patient results.

In summary, our analysis adds additional context to the paper by Luo et al that describe the potential role of MPV in AOSD patients. We again thank Luo et al for their addition to this evolving literature and hope that our comments are useful to the readership of *Revista da Associação Médica Brasileira*.

AUTHORS' CONTRIBUTIONS

JLF: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **CLS:** Data curation, Formal Analysis, Writing – review & editing.

REFERENCES

1 Luo L, Zhang L, Jiang J, Ding X. Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis. Rev Assoc Med Bras (1992). 2021;67:1443-7. https://doi.org/10.1590/1806-9282.20210649

2 Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM, Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. Ann Intern Med. 2008;149:889-97. https://doi.org/10.7326/0003-4819-149-12-200812160-00008

3 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. https://doi.org/10.1136/bmj.b2535

4 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. https://doi.org/10.1186/1471-2288-5-13

5 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): The OttawaHospital Research Institute; 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed January 22, 2022).

6 Ge S, Ma Y, Xie M, Qiao T, Zhou J. The role of platelet to mean platelet volume ratio in the identification of adult-onset still's disease from sepsis. Clinics (Sao Paulo). 2021;76:e2307. https://doi.org/10.6061/clinics/2021/e2307

7 Liu JP, Wang YM, Zhou J. Platelet parameters aid identification of adult-onset Still's disease from sepsis. Neth J Med. 2019;77(8):274-9. PMID: 31814574

8 Ulutas F, Senol H, Çobankara V, Karasu U, Kaymaz S. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in adult-onset still disease, their relationship with baseline disease activity and subsequent disease course: a retrospective cohort study. J Clin Diagn Res. 2021;15:18-21. Available from: https://www.jcdr.net/articles/PDF/14774/47913_CE[Ra1]_F[SK]_PF1(AKA_SL)_PFA(KM)_PN(KM).pdf

9 Zhang M, Wang Y, Li J, Zhou J. Adult-onset Still's disease presenting as fever of unknown origin: a single-center retrospective observational study from China. Ann Palliat Med. 2020;9(5):2786-92. https://doi.org/10.21037/apm-20-268

10 Frater JL. Comments on: "Is mean platelet volume related to disease activity in systemic lupus erythematosus?" Int J Clin Pract. 2021 Jul 29:e14676. Int J Clin Pract. 2021;75(12):e14954. https://doi.org/10.1111/ijcp.14954

11 Buttarello M, Mezzapelle G, Plebani M. Effect of preanalytical and analytical variables on the clinical utility of mean platelet volume. Clin Chem Lab Med. 2018;56:830-7. https://doi.org/10.1515/cclm-2017-0730