DIAGNOSTIC ROLE OF HEMATOLOGICAL MARKERS IN POST-DURAL PUNCTURE HEADACHE IN CESAREAN PARTURIENT AT A TERTIARY CARE HOSPITAL, PESHAWAR

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Abstract

Background: *Spinal anesthesia is commonly utilized for cesarean deliveries; however, post-dural puncture headache (PDPH) remains a significant complication. Cerebrospinal fluid (CSF) loss due to dural puncture is a primary cause of PDPH. The current study aims to investigate the diagnostic utility of hematological inflammatory markers in identifying PDPH.*

Material & Methods: *This prospective case-control study evaluated a total of one hundred and thirty-two (n=132) parturient; case group (n=56) and controls(n=76), after elective cesarean section under spinal anesthesia. Demographics information, clinical features, and associated symptoms were collected followed by a complete blood count (CBC). Hematological markers included red cell and platelet indices, white blood cell differential counts, and various ratios between parameters such MLR, RDWMPV were recorded. Statistical tests such as chi-square, independent t, Receiver Operating Characteristic (ROC) curve, and Mann-Whitney U were run on data.*

Results: *Majority, (91%) of the cases experienced PDPH within 48 hours post-operatively. A significant difference (p=0.04) in Mean platelets volume (MPV) was observed between case and control groups. The RDW/MPV (p=0.02; AUC: 0.612), and MLR (p=0.02; AUC: 0.613) were statistically significant with sensitivity 67.9% and 63.2% and specificity 53.9% and 47.4% respectively. The highest likelihood ratio (LR+) for RDW/MPV and MLR were 1.24 and 1.28 with a cut-off of 1.82, and 0.22 respectively.*

Conclusion: *This study identifies a higher MPV in parturient with PDPH and introduces new markers, RDW-MPV and MLR, as a potential diagnostic tools. RDW-MPV and MLR are novel parameters in the context of PDPH, a large multi-center studies will require before incorporation in clinical practices.*

Keywords: *Cesarean section, Inflammatory markers, Mean platelet volume; PDPH, Peripheral platelets count*

INTRODUCTION

Spinal anesthesia (SA) is commonly used for cesarean section (CS) due to its simplicity, safety and cost-effectiveness (1). However, spinal anesthesia has certain complication for parturient such as Post-dural puncture headache (PDPH), with both short and long-term consequences (2).The reported incidence rates of PDPH among parturient varies from 0.5-25% (3). As per the International Headache Society (IHS), PDPH is characterized by dull bilateral pain that intensifies within 15 mints of sitting/standing position, and improves within 15 mints of resting. Other associated signs and symptoms are photophobia, neck stiffness, tinnitus, nausea, vomiting, diplopia, and dizziness (4).

During pregnancy certain hematological changes observed such as expanded plasma volume, dilutional anemia, mild neutrophilia and prothrombotic state (5). Hematological profile; a simple, cost effective, fast and reliable indicator for general health. Currently, certain hematological ratios of complete blood count (CBC), have been considered a potential biomarker for subclinical inflammation, various infectious, non-infectious stimuli and post-operative complications. These parameters are monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red cell

distribution width-to-platelet count ratio (RDW/PC), mean platelet volume-to-platelet count (MPV/PC) ratio, and red cell distribution width-to- mean platelet volume ratio (RDWMPV) (6, 7) . Recent study has shown that the above parameters are cost-effective, novel biomarkers having predictive and prognostic value in baseline inflammatory process (8).

As per International Headache Society (IHS) guidelines, the PDPH could be differentiated from other headaches based on clinical sign and symptoms (9). A study reported higher PC and lower MPV values in patient with PDPH compared to without PDPH (10). In addition, the diagnostic value of blood parameters ratios has been explored in various pathological conditions(11). Keeping in view the above facts, this study was designed to evaluate the clinical correlation of these hematological parameters among PDPH parturient.

MATERIALS AND METHODS

This case control study was carried out at Tertiary Care Hospital (LRH), Peshawar, Khyber Pakhtunkhwa, Pakistan from April to August 2024. Consecutive sampling techniques were utilized for sampling. The sample size was calculated by G-Power software (version 3.1.9.4; University of Kiel, Kiel, Germany) as mention elsewhere (10). The calculated sample size was 132 (case group n=56 vs. control group n= 76). All those parturient having gestational age of 38 weeks, presented for elective cesarean section without any co-existing morbidities were included, whereas emergency C-section and having history of blood and neurological disorders were excluded in the current study.

The demographic information and history of parturient were recorded on a semi-structure questionnaire and informed consent was obtained. The spinal block was carried out in setting position by consultant Anesthetist using 25gauge pencil point spinal needle. The parturient were classified into case and control groups as per International Classification of Headache Disorders (ICHD), 3rd edition (9). In total, fifty-six (n=56) experienced headache with in 72hrs post-operatively. The intensity of headache was classified on Likert scale (0-10) as follows; 7-10: severe, 4-6: moderate, 1-3: mild, and ,0: no headache. A 3ml blood was collected in EDTA tube (BD Vacutainer®, USA), from both case and control post-operatively. Hematological parameters such as red cell indices, platelets indices and white cell differential counts were determined from complete blood count test. Various ratios such MLR, NLR, PLR, RDW/PC, MPV/PC, and RDWMPV were calculated from CBC parameters.

SPSS version 22 (Chicago, IL, USA) was used for data analysis. The descriptive data was presented in percentages. The odd ratio (OR) was determined to stratify the risk between cases and controls. The association between nominal variables was obtained by chi -square test and $p<0.05$ was considered as significant. Normally distributed variables were analyzed using t-independent test. The median differences between groups were calculated by Mann-Whitney U test. Furthermore, the sensitivity and specificity were assessed by plotting Receiver Operating Characteristics (ROC) curve and cut-off value was determined by likelihood ratio (LR+).

ETHICAL APPROVAL

The approval for the current study was obtained from the Board of Advance Studies and Research, Nur International University, Lahore and from the Institutional Review Board (IRB) of Lady Reading Hospital wide a letter no.109/LRH/MTI, dated April 5th, 2024.

RESULTS
DEMOGRAPHIC INFORMATION

A total of one hundred and thirty-two (n=132) parturient participated in this study, with n=56 individuals allocated with case group and n=76 control group. Overall, the mean age of n=132 parturient was 28±5 years. The mean gravida and parity were 4.15±2.19 and 2.84±1.82 respectively. In the current study 56 %(n=35/56) of parturient who develop PDPH had normal BMI (18-25; $X^2(4) =21.78$, p=0.002) and majority, 64% (n=36/56) were from urban areas with odds ratio of 1.44 (95%) [CI: 0.703 to 2.95].

CLINICAL FEATURE

In case group 91% (n=51/56) of participants experienced severe headache 71% (n=40/56) and moderate headache 29% (n=16/56) with in 48hrs post-operatively. The nature of pain among the cases were as follows; throbbing pain 54 %(n=30/56), dull pain 27 %(n=15/56), itchy pain 12% (n=7/56) and pressure-type headache 7% (n=4/56). Based on anatomical sites the distribution of pain was; occipital: 11 %(n=6/56), frontal: 25 %(n=14/56) and both types: 64% (n=36/56). Overall, 64% of the parturient were physically confined whereas 5% were severely confined. The observed symptoms developed among the parturient with PDPH were as follows; nausea 57% (n=32/56), vomiting 5% (n=3/56), shoulder pain 91 %(n=51/56), photophobia 48% (n=27/56), reduced visual acuity32% (n=18/56), double vision18% (n=10/56) and tinnitus 55% (n=31/56).

HEMATOLOGICAL PARAMETERS

Red cell indices, including red blood cell count (RBC), hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (HCT), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW), and WBC indices is shown in Table I.

Table I. Hematological markers of post-dural puncture headache vs. control parturient presented for elective cesarean section at tertiary care hospital, Peshawar from April to August 2024

Parameters	PDPH+	PDPH-	p value
Red Blood Cells	Mean ±S.D	Mean ±S.D	
RBC(10e6/μl)	3.76±.52	3.83±.49	0.44
HGB (g/dL)	10.65±1.48	10.73±1.52	0.77
HCT (%)	32.56±5.06	32.60±5.02	0.96
MCV (fL)	86.00±6.37	85.34±8.63	0.61
MCH (pg)	28.46±2.32	28.10±2.76	0.42
MCHC(g/dL)	33.14±1.65	33.02±1.68	0.65
RDW (%)	15.48±2.47	15.11±2.76	0.17
Platelets			
Platelet count(10⁹/L)	218.28±77.49	223.70±66.23	0.67
MPV(fl)	8.99±1.97	8.40±1.34	0.04
White Blood Cells			
Neutrophils(10e3/μL)	9.46±3.44	9.62±3.69	0.79
Lymphocyte(10e3/μL)	1.76±.72	1.54±.64	0.09
Monocytes(10e3/μL)	0.62±.34	0.66±.30	0.52
Eosinophils(10e3/μL)	0.173±.37	0.08±.12	0.10
Basophils(10e3/μL)	0.007±.01	0.02±.08	0.28

Note: RBC: Red blood cells, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution, MPV: Mean platelets volume, 10e6/μl: one million per micro liter, g/dL: gram per deciliter, fL: femtoliter, pg: pictogram, 10e3/μL:1000/ micro liter, PDPH+: post-dural puncture headache present, PDPH-: post-dural puncture headache absent, S.D: standard deviation

DIAGNOSTIC MARKERS

The platelet count (PC) was comparatively lower in the case group (218.28±77.49×10⁹/L) compared to the control group (223.70±66.23×10⁹/L). A significant MPV was observed for case group; (8.99±1.97 fl) vs. control group; (8.40±1.34 fl), with a notable mean difference (*p*=0.04). On ROC analysis both PC and MPV were statistically insignificant (*p*=0.39 vs. *p*=0.15), (Table I, Fig. 1).

The NLR showed no significant difference between the case (Mdn=5.482) and control groups (Mdn=5.981), p=0.191. The blood parameters ratios for peripheral inflammatory markers such as PLR, NMR, MLR, MPLR, PC/MPV, MPV/PC, MPV/LR, RDW/PC, RDW/MPV is shown in Table II and Fig. 2. Furthermore, the AUC values were significant for RDWMPV and MLR (p=0.02 vs. p=0.02). The AUC for RDWMPV was 0.612; specificity and sensitivity were 53.9% and 67.9% respectively.

The cut-off value was 1.82 at LR+ of 1.24. Similarly, the AUC for MLR was 0.613; specificity and sensitivity were 47.4% and 63.2% respectively. The likelihood ratio for MLR was 1.28 at cut-off values of 0.22 as shown in Table III.
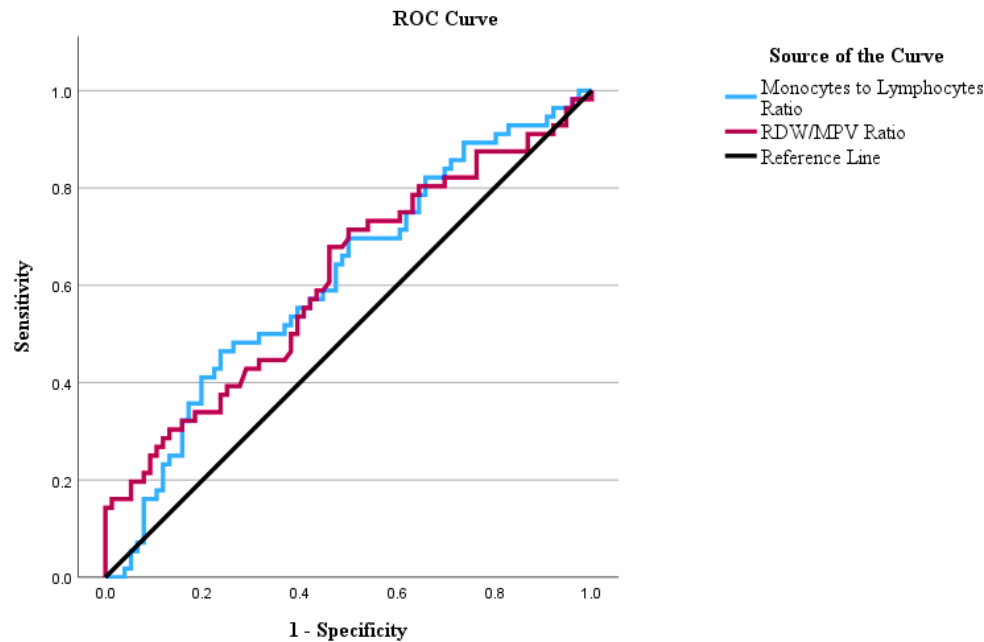
Fig. 1. ROC curves for red cell distribution-to-mean platelets volume and monocytes-to-lymphocytes ratios. auc_{rdwmpv}=0.612, auc_{mlr}=0.613, in parturient presented for elective cesarean section at tertiary care hospital, Peshawar from April to August 2024

Table II. Comparison of various diagnostic ratios of post-dural puncture headache vs. control parturient presented for elective cesarean section at tertiary care hospital, Peshawar from April to August 2024

Diagnostic ratios	PDPH+		PDPH-		p value	r
	Mdn	IQR	Mdn	IQR		
RDWMPV	1.69	1.44-2.03	1.87	1.58-2.24	0.02	0.19
RDWPC	.07	0.05-0.09	0.07	0.05-0.09	0.79	-
MPVPC	0.04	0.02-0.06	0.03	0.02-0.04	0.28	-
PCMPV	23.18	16.42-35.24	25.32	20.26-34.48	0.18	-
MPVLR	5.12	4.06-6.81	5.65	3.91-7.64	0.53	-
NLR	5.48	4.24-7.16	5.98	4.30-8.84	0.19	-
PLR	119.80	91.40-186.47	143.92	103.23-193.32	0.09	-
NMR	15.00	11.34-22.46	14.14	10.06-20.09	0.21	-
MLR	0.33	0.22-0.50	0.43	0.29-0.63	0.02	0.19

Note: RDWMPV: red distribution width/mean platelets volume, RDWPC: red distribution width/platelets count, MPVPC: mean platelets volume/ platelets count, PCMPV: platelets count/ mean platelets volume, MPVLR: mean platelets volume-Lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelets-to-lymphocytes ratio, NMR: Neutrophil-to-monocytes ratio, MLR: Monocytes- to-lymphocytes ratio, Mdn: Median value, IQR: Inter quartiles range, r: effect size<.3 (small effect)

Table III. Diagnostic utility of blood ratios in identifying PDPH in parturient presented for elective cesarean section under spinal anesthesia at tertiary care hospital, Peshawar from April to August 2024

Diagnostic ratios	AUC	% Sensitivity	% Specificity	Cut-off value	CI	p value
RDWMPV	0.612	67.9	53.9	1.82	0.51-0.71	0.02*
RDWPC	0.510	39.1	24.2	0.83	0.47-0.61	0.84
MPVPC	0.432	26.8	76.3	0.02	0.33-0.53	0.18
PCMPV	0.567	42.3	11.8	19.83	0.46-0.66	0.19
MPVLR	0.479	92.9	17.1	3.58	0.37-0.57	0.67
NLR	0.567	51.8	39.5	0.19	0.46-0.66	0.18
PLR	0.416	7.1	94.7	327.06	0.31-0.51	0.10
NMR	0.564	76.8	38.2	11.23	0.46-0.66	0.20
MLR	0.613	63.2	47.4	0.22	0.51-0.71	0.02*

Note: AUC: area under the curve, %: percent, CI: Confidence interval, p*: indicates statistical significance
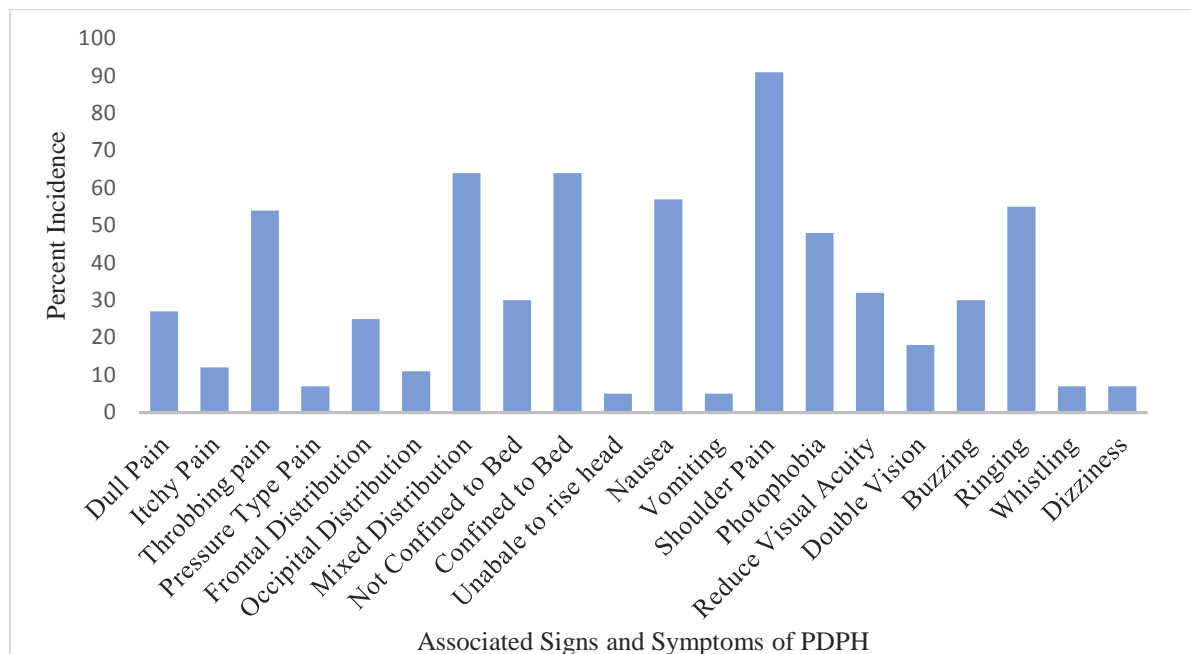
Fig. 2. Post-dural puncture headache and associated signs and symptoms in parturient presented for elective cesarean section at tertiary care hospital, Peshawar from April to August 2024

DISCUSSION

Previous studies identified that demographics attributes contribute to the risk of PDPH. Different studies indicate that younger age and female gender are associated with increased susceptibility to PDPH (12). In the current study, body mass index (BMI) was significantly linked with the incidence of PDPH (p = 0.002). However, literature showed conflicting findings regarding BMI; lower BMI increases the risk of PDPH (p = 0.013), while others studies reported no significant association, rendering the relationship inconclusive (13, 14).

In the current study parturient from urban area with odd ration 1.4 to develop PDPH in comparison to rural areas. Studies show that regular physical activity and practices; yoga enhance the level of β-endorphin, which improved mood, sense of euphoria, and stress regulation. Rural women engage more frequently in physical activities, boosts endorphin levels, that alleviate pain, and improve well-being (15, 16). In contrast, sedentary lifestyle among urban parturient might be a risk factor for the incidence PDPH.

The current study is the first to examine the RDW/MPV ratio in relation to PDPH, a biomarker previously studied in chronic obstructive pulmonary disease, pulmonary heart disease, and panic disorder (17, 18). Our findings align with these studies in terms of effect, size and significance level, however, sensitivity and specificity data for RDW/MPV remains limited.

Analysis revealed that PC count and MPV were lower and significantly higher (p=0.047) respectively in case group. In contrast, a higher PC and lower MPV were observed in control group. MPV serves as an indicator of PC size and activity, and inversely related to each other (19). The arachnoid and dural layers differ in elasticity, and damage to these layers as a result of dural puncture may lead to PDPH (20). Platelets are involved in hemostasis and tissue repair, stimulated by chemical substances and cytokines resulted into its aggregation on the injury site (21). Epidural blood patch and platelet-rich plasma contain platelets might contribute to healing process in individual suffered from PDPH (22, 23).

In our study we observed a high level of significance between RDWMPV and MLR (p=0.02 vs. p=0.02), which is in accordance with the previous report. Interestingly, as per accessible literature, this is the first study to observe the association of these parameters with PDPH (24). In addition, RBC support the hemostasis via platelets migration and release of platelets activating factor; adenosine 5'-diphosphate (ADP), whereas a higher MPV indicates aggregation of platelets. Thus, it contributes to tissue healing and repair (25). Furthermore, a previous study showed that MPV and RDW are useful biomarkers to reflect inflammatory responses, oxidative stress and for predicting endometrial cancer (26).

Monocyte to lymphocyte ratio is considered a potential predictor for diagnosis and prognosis. In the current study the MLR was significantly lower in parturient experienced PDPH (p=0.02). Previously, the same findings have been observed in migraine headache, prostate cancer and breast cancer (27, 28). Though, the correlation and prognostic role of MLR was determined in various pathologies, but as per our knowledge this is the first study to report its importance in PDPH (29).

Our study has certain limitation such single center study, small sample size, single population (only parturient) were include in the study. Hence a large multi-center studies with diverse population are required to validate and utilized these markers for early intervention or risk stratification.

CONCLUSION

In this study, we reported a significant association of RDW/MPV and MLR with PDPH parturient, which could possibly be used as early diagnostic marker for PDPH. However, before generalization of the findings and its utilization in clinical practice need a through large scale investigation.

Conflict of interest:

The authors declare that we have no competing interests.

Funding:

Authors' contributions:

MU & IA Study design and manuscript writing; MA & SN; Review of literature data entry and analysis; HA & BD; Conception of study, development of research methodology design; SAJ & NL Study design and manuscript writing. All authors reviewed the manuscript and approved the final version.

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