International Journal of Research in Medical Sciences
Gupta AK et al. Int J Res Med Sci. 2025 Mar;13(3):1190-1195
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250686

Original Research Article

Neutrophil-to-lymphocyte ratio as predictor of nausea and vomiting after elective laparoscopic cholecystectomy

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Received: 19 January 2025
Accepted: 13 February 2025

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ABSTRACT

Background: The neutrophil-lymphocyte ratio (NLR) or platelet-lymphocyte ratio (PLR) has been proposed as a parameter for the diagnosis of inflammatory diseases in different studies; however, the literature does not discuss this relationship for elective laparoscopic cholecystectomy. The purpose of this study was to determine whether preoperative NLR or PLR is associated with postoperative nausea and vomiting (PONV), one of the most common postoperative complications and whether it may act as a biomarker for the illness.
Methods: The clinical data of 146 patients with symptomatic cholelithiasis who underwent elective laparoscopic cholecystectomy (ELC) at our institution were collected and analyzed.
Results: We divided patients into PONV and No-PONV groups. and logistic regression analysis was used to identify predictors for PONV. In logistic regression analysis, the preoperative neutrophil-to-lymphocyte ratio (NLR) [odds ratio (OR): 1.61, 95% confidence interval (CI), p=0.01] was identified as an independent risk factor for the presence of PONV. On ROC analysis, the success of NLR in discriminating PONV was found to be statistically significant [area under curve (AUC)=0.631, p=0.01].
Conclusions: PONV can be predicted in patients undergoing ELC with NLR. As a result, blood parameters should be examined to enhance these patients' post-operative recovery period.

Keywords: Laparoscopic elective cholecystectomy, Neutrophil to lymphocyte ratio, Post operative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) is defined as gagging or nausea-vomiting within 24 hours after surgery. The prevalence of PONV varies depending on the type of surgery and mode of anaesthesia which is used. The incidence is reported to be between 30 to 80%.[1-3] Due to the complex aetiology of PONV and the lack of sole trigger for onset, it is challenging to determine its exact incidence. Without the administration of antiemetics, the incidence of PONV has been estimated to be between 25% and 30% for all surgical procedures and patient demographics.[4] However, compared to other types of surgery, laparoscopic cholecystectomy (LC) has a greater incidence rate of PONV. Patients who did not receive antiemetic therapy following LC were observed to have a rate ranging from 46% to 75%.[5-7] Although this is a minor complication but it decreases overall patient satisfaction and acts as a limiting factor in ambulatory daycare surgery. Despite the development of many new medications, PONV still remains an important problem after ELC. Several risk factors play an important role in the development of PONV. The study's goal is to look into the factors that might influence PONV in individuals who have undergone ELC. For patients undergoing ELC, general anaesthesia is the primary anaesthetic technique. However, 20% to 30% of surgical patients experience postoperative nausea and vomiting (PONV) as a result of general anaesthesia.[8] Numerous investigations discovered a strong relationship between the length of postoperative

stay and the degree of inflammation in cholecystitis, as well as between the preoperative NLR and PLR. The clinical importance of these biomarkers and their cut-off value that may be used to therapeutic management, however, remain the subject of conflicting data. For the diagnosis and monitoring of inflammatory disorders, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are utilized.[9] There hasn't been much research done on the mechanism underlying nausea. The vomiting center, which is located in the dorsolateral medulla oblongata, appears to be the source of the vomiting reflex. It is well recognized that inflammation raises the risk of PONV.[10] However, it has not been determined whether these indicators may anticipate PONV in patients following ELC. The present study evaluated the potential of preoperative NLR and PLR to anticipate PONV following ELC by retrospectively analysing the clinical data of such patients. The NLR or PLR has been proposed as a criterion to be employed in the diagnosis and follow-up of inflammatory illnesses in a number of studies.[11,12]

However, despite the fact that this association has only been mentioned in a small number of studies, the literature does not mention it in regard to laparoscopic cholecystectomy. The purpose of this study was to determine if preoperative NLR or PLR was a marker of PONV.

METHODS

Study design and setting

This retrospective study included 146 patients who underwent ELC at the tertiary care institute at a rural set-up from March 2022 to March 2023 after ethical approval from institute ethics committee. Laparoscopic cholecystectomy was performed under general anesthesia and administered following a standard technique.

Sample size was calculated using the formula-

$$n = \frac{Z_{\alpha}^{2} p(1-p)}{e^{2}}$$

where p is proportion, e is precision. Here, α=5% hence zα=1.96 p (prevalence of PONV) =10% e=5%. Using these values in above formula, n was coming as 140.[13]

Study population

All the patients who underwent elective laparoscopic cholecystectomy under general anesthesia at hospital during the study period were selected for the study.

Inclusion and exclusion criteria

Patients with symptomatic chronic cholelithiasis who underwent ELC under general anaesthesia met the inclusion criteria. Patients having a history of mental illness, history of antiemetic and anticholinergic medication usage, and age under 18 were excluded. All patients stopped consuming solid foods and liquids 6 hours prior to surgery. The same team of surgeons carried out each procedure. Acute cholecystitis cases (in patients who had one of the systemic signs of inflammation, such as fever, elevated white blood cell count, or elevated c-reactive protein level, or one of the local signs of inflammation, such as Murphy's sign, or a mass, pain, or tenderness in the right upper quadrant) were excluded from the study.

Premedication

Prior to the induction of anesthesia, premedication is administered. Premedications commonly administered were clonazepam (for anxious patients) and ranitidine.

Induction of anesthesia

For the induction of anesthesia, propofol was commonly used.

Muscle relaxants

Short-acting muscle relaxant succinylcholine is commonly used for endotracheal intubation. Other relaxants atracurium and vecuronium were used for the maintenance of muscles in a relaxed state for a longer duration.

Maintenance of anesthesia

Inhalation anesthetic agents were used for the maintenance of anesthesia. The inhalation anesthetic agents used were either oxygen with nitrous oxide, or oxygen with air. Other inhalational agents often used were isoflurane, sevoflurane, and halothane.

Adjuvant analgesics used per-operative

Injection paracetamol (intravenous) was administered through infusion during the per-operative period.

Surgical technique

Every patient underwent a standard laparoscopic procedure. A Veress needle was introduced into the peritoneum after an incision was created above the umbilicus. The insufflating gas utilised was CO_2. Two litres of CO_2 were inhaled at a low flow rate (2 l/minute) in order to prevent a vasovagal reaction and right shoulder pain; the flow rate was subsequently raised to 4 l/minute. For every patient, a 14-mmHg pneumoperitoneum was supplied. Lateral, midclavicular, and subxiphoid trocars were implanted. The fundus of the gallbladder was retracted anteriorly and laterally through the most lateral subcostal cannula using a grasper. The Callot was dissected. The cystic artery and cystic duct were severed after double clips were applied. Next, using endo-scissors and electrocautery, the gallbladder was removed from the

infundibulum and separated from the liver. It was through the subxiphoid incision that the gallbladder was delivered. Nasogastric drainage did not occur in any of the patients before to, during, or following the procedure. None of the patients received local anesthetics at the trocar sites.

After achieving anesthesia, the start time of surgery was recorded corresponding to the skin incision given for the primary laparoscopic port, and the end of surgery was also noted corresponding to the end of skin closure time. After full recovery from anesthesia and clinically stable, patients are shifted back to the surgery ward. While in the ward, the patients were kept under close monitoring of vital signs and for any postoperative complications. Paracetamol was given in postoperative period to all patients. The nurses on duty record the time when the patient compliant of nausea and or vomiting in PACU and in the ward during the first 24 hours of the postoperative period. Rescue antiemetic with ondansetron or metoclopramide was administered for patients with PONV.

Post operative nausea and vomiting

PONV is defined as the onset of nausea or vomiting within 24 hours of operation.[10] Rapid peritoneal distension, response reflex-activated neurogenic pathways, and splanchnic pressure and manipulations are thought to be the causes of post-laparoscopic cholecystectomy PONV.[6-14] Laparoscopy requires the formation of a pneumoperitoneum, which causes mechano-receptor stretching, elevated serotonin (5HT) production, and PONV.[7-15] The incidence of PONV was the main outcome.

Patient allocation and data collection

All the patients at our facility who had ELC under general anesthesia were chosen and allocated into two groups. The following information was gathered: age, ASA physical state, history of smoking, alcohol use, and underlying conditions.

Sex, age, ASA physical status, body mass index (BMI), prior medical history, surgical duration, preoperative neutrophil and lymphocyte count, NLR, and PLR were all taken from electronic medical records. The NLR and PLR were calculated after a thorough analysis of the inflammatory markers. By dividing the absolute neutrophil and platelet counts by the lymphocyte count, the NLR and PLR were calculated.

We classified the laparoscopic cholecystectomy patients into groups with and without PONV. The identification of factors for PONV was done using logistic regression analysis. The significance level was established at p value =0.05.

RESULTS

Data of total 146 patients was retrieved. Out of the total 127 patients were female. There was no significant difference in baseline characteristics of the two groups except PLR and NLR. The mean age in the study group was 39.6 years. The mean weight was 59 kg (SD-11.6). Mean BMI was 24.6 (SD-4.1). The mean duration of surgery in the study was 65 minutes (SD-28). On comparison of means between the two groups NLR and PLR shows a significant difference (Table 1). The student t-test was utilised to assess parametric values. The Mann-Whitney U test was utilised to compare nonparametric values. The χ^2 and Fisher exact tests were used to compare side effects, gender, and ASA status. $P<0.05$ was regarded as statistically significant. The area under the receiver operating characteristic curve (ROC) was used to evaluate the predictive value of NLR and PLR for PONV. P values of less than 0.05 on both sides were regarded as statistically significant.

Table 1: Comparison of demographic details and clinical findings in two groups.

	PONV	No PONV	P value
n	39	107	
Age (years)	39.66	39.65	0.996(t)
Sex (females)	34	93	0.967(c)
Weight	60.02	59.7	0.896(t)
BMI	24.8	24.62	0.815(t)
Smoking (Y/N)	0/39	3/104	0.291(c)
Alcohol (Y/N)	1/38	2/105	0.793(c)
Previous surgery (Y/N)	11/28	29/78	0.895(c)
NLR	2.85	2.16	0.016(u)
PLR	152.51	133.65	0.047(u)
Duration of surgery	68.07	64.11	0.411(u)

Variance inflation factor (VIF) was calculated and no significant multicollinearity detected.

PONV was considered the dependent variable, and age, Duration of surgery, BMI, preoperative NLR, and PLR

level were assigned in the univariate logistic regression analysis. The results showed that increased preoperative NLR was an independent risk factor for the development of PONV ($p<0.05$) (Table 3). The ROC showed that NLR could significantly predict PONV (AUC: 0.631, 95% CI: 0.094-0.710, $p<0.05$). PLR could not significantly predict PONV (AUC: 0.608, 95% CI: -0.001-0.003, $p=0.56$) (Figures 1 and 2).

Using index of union method, cut off value of NLR was estimated to be 2.05 (sensitivity 58%, specificity 57%) and cut off value of PLR was 110.7 (sensitivity 60%, specificity 61%).

Table 2: Multicollinearity diagnostics.

Parameters	Tolerance	VIF
Age	0.840	1.190
BMI	0.863	1.159
Duration of surgery	0.948	1.055
N/L ratio	0.937	1.068
P/L ratio	0.984	1.016

Table 3: Univariate logistic regression analysis of factors associated with the occurrence of PONV.

				Wald test	
	Estimate	**Standard error**	**Odds ratio**	**Wald statistic**	**P value**
P/L ratio	0.000	0.002	1.000	0.018	0.893
N/L ratio	0.477	0.195	1.612	6.016	0.014
duration of surgery	-0.002	0.007	0.998	0.046	0.831
BMI	0.009	0.052	1.009	0.027	0.869
Age	-0.009	0.018	0.991	0.251	0.617

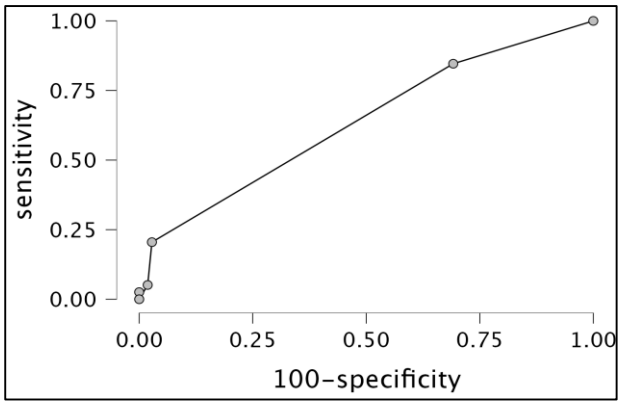

Figure 2: ROC plot of PONV diagnosis predicted by NLR.

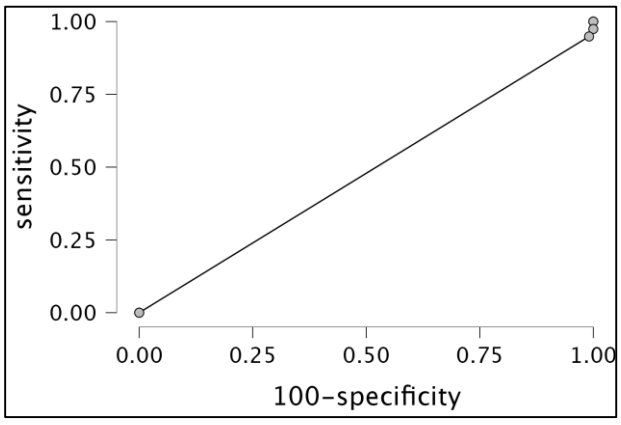

Figure 3: ROC plot of PONV diagnosis predicted by PLR.

DISCUSSION

One of the most often performed minimally invasive procedures is laparoscopic cholecystectomy. PONV is a common postoperative symptom. The incidence of PONV is 10%–30% after surgery under general anaesthesia and approximately 4% under spinal anaesthesia.[13]

Most of the patients experience PONV after LC, especially during the first 24 hours. The autonomic nervous system regions associated with vomiting are located in the hindbrain at the level of the medulla oblongata. Chemo-sensitive receptors track down chemicals in the blood and send this information to the nearby solitary tract nucleus in the hindbrain area.[16] Through blood circulation, inflammatory mediators can impact the centres responsible for nausea and vomiting. NLR and PLR have been employed as inflammatory markers in prior research to predict the prognosis of several disorders, including heart disease, vascular disease, and tumours.[17-19] Predicting the severity of cholecystitis is crucial for therapeutic intervention in order to promote an early recovery and avoid unfavourable surgical outcomes. In order to forecast the likelihood of postoperative problems, we examined the values of the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR).) Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are systemic inflammatory biomarkers that have recently been studied for their predictive value in a variety of inflammatory and septic conditions, including septic shock, diabetic foot ulcer, acute appendicitis, and spontaneous bacterial peritonitis.[20,21] These biomarkers are inexpensive and simple to calculate using the complete blood count (CBC), and several studies have found a

strong correlation between the length of postoperative stay and the degree of inflammation in chronic cholecystitis. Nevertheless, there is still conflicting evidence regarding the clinical significance of these biomarkers and their cut-off value that could be used in therapeutic management.

The cut-point value of NLR in our study was 2.05 which was similar to previous studies.[22,23]

In individuals undergoing maxillofacial surgery, antiemetic requirement in the group with NLR>2 was significantly higher, suggesting that high NLR is a predictor of PONV.[24] In 433 patients and 160 controls, Tayfur et al examined the connection between the platelet-lymphocyte ratio and hyperemesis gravidarum and found that the high NLR and PLR had statistically significant predictivity for the development of hyperemesis gravidarum.[25]

In the study by Karaca et al, patients undergoing breast reduction surgery can have PONV predicted by NLR and PLR. The results showed that the success of PLR in predicting PONV in patients undergoing breast reduction surgery was higher than NLR. This was contrary to our study where the N/L ratio was superior in predicting PONV. The cut-off values of NLR and PLR were 1.97 and 137.2 respectively.[26] Whereas in our study the cut-off values of NLR and PLR were 2.05 and 110.7 respectively. The small sample size may have contributed to this outcome. Therefore, extensive prospective research is required to validate this.

Altun et al retrospectively divided the patients undergoing septorhinoplasty surgery into two groups based on their NLR levels below and above two. They evaluated the groups' postoperative nausea and vomiting, antiemetic needs, and requirements at recovery time and found statistically significant differences between both groups.[2]

An increase in preoperative NLR was found to be an independent risk factor for PONV ($p<0.05$) by Feng et al, who investigated the effectiveness of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting the incidence of nausea and vomiting following total knee arthroplasty. NLR strongly predicted the occurrence of PONV, according to ROC analysis (cutoff value: 2.20, ROC: 0.711, $p<0.001$). Consequently, PONV was not significantly predicted by the PLR.[27]

We frequently employ ondansetron 8 mg to reduce PONV, as do other antiemetic medications.[28] Thirty-nine individuals in our cohort experienced vomiting, and patients with NLR>2.05 had a significantly greater incidence of PONV. Combination therapy is better than monotherapy, and there is currently solid evidence to support the recommendation of using two or more antiemetics to prevent PONV.[29]

This research has limitations. First, the study was retrospective in nature, the sample size was limited, and we only examined data from one centre. Second, patient-reported responses were used to determine the severity of preoperative nausea and vomiting.

CONCLUSION

PONV is one of the elements lowering patient treatment quality and satisfaction. The study's findings demonstrated that preoperative NLR might be taken into account in considering antiemetics use to prevent postoperative nausea and vomiting. However, considering the retrospective nature of this study further research are required on a larger sample to verify this finding.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gupta AK, Rajput D. Neutrophil-to-lymphocyte ratio as predictor of nausea and vomiting after elective laparoscopic cholecystectomy. Int J Res Med Sci 2025;13:1190-5.