



The clinical utility of pre-operative neutrophil-to-lymphocyte ratio as a predictor of outcomes in patients undergoing elective laparoscopic cholecystectomy

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Abstract

Background In recent years, there has been an increasing trend towards day-case surgery for patients undergoing laparoscopic cholecystectomy (LC). We investigated the predictive value that pre-operative neutrophil-to-lymphocyte ratio (PNLR) had on surgical outcomes.

Methods A review of all patients who underwent LC during a 6-year period in a single institution was performed and PNLN recorded. A PNLN cutoff value of 3 was utilised. We compared operation time, length of stay (LOS), and conversion to open between those with PNLN less and greater than 3.

Results A total of 567 patients underwent elective LC. Those with PNLN>3 had associated prolonged operation time ($p < 0.005$), prolonged LOS ($p < 0.005$), and higher rates of conversion to open surgery ($p < 0.005$).

Conclusions PNLN correlates with outcomes following LC. It is useful in delineating patients that have higher risk of conversion or prolonged length of hospital stay and is helpful in assessing suitability of day-case surgery.

Keywords Laparoscopic cholecystectomy · Minimally invasive surgery · Neutrophil-to-lymphocyte ratio · Surgical outcomes

Introduction

Since first being reported three decades ago [1], laparoscopic cholecystectomy (LC) has transformed the management of symptomatic gallbladder disease. Early studies observed reduced hospital stay, better cosmesis, and reduction in healthcare expenses [2, 3]. Therefore, it was quickly adapted as the gold standard of operative management [2–4].

Increasingly over the last decade, there has been a major drive to expand day-case surgery volume. As a result, the

feasibility of offering LC as a day-case procedure (DCLC) has been advocated [5–7]. Several randomised control trials examining LC as a day-case procedure have supported its implementation [8–10].

However, patient selection and suitability are ‘key’ factors to ensure successful management. Identifying pre-operative outcome predictive factors can improve patient counselling, facilitate convalescence planning, and optimise patient expectations. These factors can improve patient safety by allowing the surgeon to anticipate complications and can benefit in healthcare cost reductions. To date, there remains no optimal haematological biomarker or score that accurately predict outcomes such as length of stay (LOS) or post-operative complication rates following LC.

Pre-operative neutrophil-to-lymphocyte ratio (PNLR) is a simple, inexpensive marker of subclinical inflammation that has been investigated in several inflammatory conditions [11–16]. In a state of inflammation, arachidonic acid metabolites and platelet-activating factor cascades lead to a neutrophilia. Concurrently, there is a corresponding suppression of the cytolytic activity of immune cells such as lymphocytes, activated T

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cells, and natural killer cells. This is reflected as a lymphopenia [17]. The use of PNLR has previously been shown to successfully predict outcomes in patients with undergoing LC for acute cholecystitis [16, 18]; however, the application of PNLR to patients awaiting elective LC remains unexplored.

The aim of this study was to evaluate the role of PNLR in predicting post-operative LOS and outcomes in patients undergoing LC.

Methods and materials

All consecutive patients who underwent LC at our institution over a 6-year period were reviewed. Ethical approval was sought and granted by Galway University Hospital's Research Ethics Committee. All patients underwent LC as an elective procedure having had either a previous admission for acute cholecystitis (> 6 weeks prior to admission for surgery) or a diagnosis of symptomatic gallstones. All patients who had an admission for acute cholecystitis in the 6 weeks prior to their procedure had their surgery rescheduled to allow adequate time for resolution of inflammation, as was the practice in the institution.

A pre-operative anaesthetic assessment unit was attended by all patients within 6 weeks of surgery, where patient readiness for anaesthesia and surgery were assessed. Blood sampling, including full blood count, was performed on all patients. All patients also underwent pre-operative abdominal ultrasonography. An American Society of Anaesthesiologists (ASA) Physical Status Classification Score was applied to these patients to evaluate surgical risk. Patient demographics, haematological and biochemical markers, operation time, intra and post-operative (30-day) complications, and LOS were recorded. Histological reports were also assessed. From November 2011, day-case LC was introduced to the institution. Strict parameters were maintained if a patient was to be considered for same day discharge. These criteria are detailed in Table 1 [19]. For patients deemed suitable, a minimum post-operative observation period of at least 4 h was implemented prior to discharge.

Each patient's PNLR was derived from bloods samples from the pre-operative anaesthetic assessment unit attendance. The PNLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. A PNLR value of 3, which has been previously identified to predict outcomes following LC for acute cholecystitis was utilised as the cutoff value to compare outcomes [16, 18]. The patient cohort was then divided into two groups, Group A (PNLR<3) and Group B (PNLR>3).

Statistical analysis

Statistical analysis was performed using SPSS Version 20 (IBM Corporation, New York, NY, USA) and the

Table 1 Parameters to be satisfied if patient is to be considered for same day discharge

Criteria for same day discharge

- Vital signs comparable with those on admission.
- Orientated in time, place, and person.
- Minimal nausea.
- Has achieved their optimal mobility.
- Has passed urine post-operatively.
- No evidence of any complications.
- Patient and relatives are happy for discharge.
- Patient lives within 1 h drive of the hospital.
- Has a responsible adult who can take them home and be with them for the next 24 h.
- Adequate pain control and supply of oral analgesia.
- Written and verbal instruction given about post-operative care.
- Understands how to use all medications supplied (including written information).
- Knows to contact a member of the team if any new symptoms develop.

'ModelGood' package for R 3.1 (R Foundation for Statistical Computing, Vienna, Austria). Comparisons of continuous variables were performed using parametric Student's *t* test or ANOVA. The relations between categorical binary variables were studied using chi-square. A multivariable logistic regression was performed to assess the effects of PNLR score, gender, ASA score and age on the likelihood of conversion to open surgery or requirement of overnight hospital admission. A two-tailed *p* value of less than 0.05 indicated statistical significance.

Results

During the study period, 567 patients underwent LC. The majority were female ($n = 452$, 79.7%). Mean (median, range) age was 45.9 years (43.1 years, 14.9–86.6). Mean (\pm SD) age of females was 43.4 (\pm 15.6) years compared to 55.4 (\pm 15.2) years for male gender. Mean (median, range) weight was 79.2Kg (42.9–140.8). Mean (\pm SD) duration of surgery was 86.1 (\pm 31.9) minutes and median (range) length of hospital stay was 2 days (0–31). Twenty-four cases had conversion from laparoscopic to open cholecystectomy (4.2%). Of these 24 patients, 13 (54.2%) had a previous history of abdominal surgery. Adhesions were cited as the most common cause for conversion. Histopathological analysis observed that 543 (95.6%) of patients had chronic cholecystitis. Of those ($n = 24$) who did not have chronic cholecystitis, 95.8% ($n = 23$) had gallstones identified. Occult gallbladder carcinoma was noted in 4 patients (<0.01%), 2 of which had a conversion to open procedure. Conversion rate was significantly lower (1.97%) in patients under 45 years ($n = 306$) than those over

45 years (7.4%, $n = 261$). There was no peri-operative or 30-day mortality.

Pre-operative neutrophil-to-lymphocyte ratio

Mean (\pm SD) PNLR in female patients was significantly lower (2.95, \pm 3.2) compared to males (3.78, \pm 3.51). The mean (\pm SD) PNLR for non-smokers ($n = 476$) was 3.22 (\pm 3.5). This was significantly lower in smokers (2.6, \pm 1.57) ($p = 0.009$). The mean (\pm SD) PNLR for those with histologically confirmed chronic cholecystitis ($n = 543$) was 3.16 (\pm 3.33), which was significantly higher than those without chronic cholecystitis 2.36 (\pm 1.49) ($p < 0.05$).

PNLR subgroup comparisons

Four hundred fourteen patients (73.0%) had a PNLR of ≤ 3 (group A), while 153 patients (27%) had a PNLR of > 3 (group B). A breakdown and comparison of demographic details of the two groups is highlighted in Table 2.

ASA subgroup comparison

Five hundred six (89.2%) patients had a pre-operative ASA classification score (Table 3). LOS was significantly shorter in those with an ASA score of 1, when compared to those with a score of 2 and a score of 3 ($p < 0.001$). Procedural length for patients with an ASA score of 1 was significantly shorter than those with an ASA of 2 and 3 ($p = 0.015$). Conversion rates were significantly lower in those with an ASA score of 1 than those with an ASA of 2 or an ASA of 3 ($p = 0.001$).

PNLR as a predictor for suitability for day-case surgery

Since the introduction of day-case laparoscopic cholecystectomy (DCLC) in November 2011, 252 patients have undergone LC. For this subgroup, the median (range) length of stay was 1 (0–13) days. Of these, 44.4% ($n = 112$) have been discharged as DCLC. A further 41.7% ($n = 105$) were discharged day 1 (D1) post-operation. The remainder ($n = 35$) had a median (range) length of stay of 4 (2–13) days.

Of those successfully discharged as DCLC, 83.9% ($n = 94$) had a PNLR of less than 3. Of the remaining 18 patients in this group, the median (range) PNLR was 3.4 (3–10.1). Of those who were discharged D1 post-op, 75.2% ($n = 79$) had a PNLR of less than 3. Of the remaining 26 patients, the median (range) PNLR was 4.5 (3–19). Finally, of the patients ($n = 35$) with a length of stay greater than 1 day, 48.5% ($n = 17$) had a PNLR of less than three, which was significantly lower than those discharged as DCLC or discharged D1 ($p < 0.001$).

Multivariate regression analysis

Multivariate analysis was carried out for all variables found to be significant on univariate analysis; PNLR score, patient gender, ASA score, and age.

Multivariable regression analysis—conversion to open surgery

There were significant individual associations identified between conversion to open surgery and PNLR and age. Patients with a PNLR of > 3 were more likely to undergo conversion to open surgery than those with a PNLR < 3 (OR .0134 CI 0.51–0.351, $p < 0.001$). Patients aged older than 45 years were more likely to undergo conversion to open surgery than younger patients (OR 2.708 CI 1.065–6.886, $p = 0.036$).

Multivariate analysis—day case vs. overnight hospital admission

On multivariate analysis of day case and overnight hospital admission, there was a significant association identified between PNLR and overnight hospital admission. Patients with a PNLR score > 3 were more likely to require admission post-operatively (OR 2.041 CI 1.194–3.487, $p = 0.009$). It was also found that female patients required admission more often than men post-op (OR 0.679 CI 0.965–2.924, $p = 0.067$). Patients over the age of 45 years were less likely to require overnight admission on multivariable analysis (OR 0.481 CI 0.299–0.773, $p = 0.003$).

Discussion

The timing of LC for symptomatic gallbladder disease remains controversial. A meta-analysis published recently comparing early LC (operating within 24 h of presentation) with delayed LC (day 7–45) identified favourable outcomes such as a shorter total length of stay, a decreased incidence of wound infections, and decreased cost. It also identified that there was with no difference in the rates bile duct injuries, bile leaks and conversions [20]. However, a transition from elective to acute LC has not been universally accepted [21, 22]. Considering a large number of these patients are undergoing LC as an outpatient, the value of having a preadmission predictor of outcomes cannot be underestimated. We have shown that a PNLR > 3 is associated with adverse patient outcomes. It is predictive of prolonged length of stay, prolonged operation time, and higher intraoperative complications. Our results also reiterate the value of the ASA score, in predicting outcomes in elective surgery.

Inflammation or infection is associated with an upregulation of the innate immune response and inflammatory

Table 2 Patient demographics

Patient demographics (<i>n</i> = 567)		NLR < 3 (<i>n</i> = 414)	NLR > 3 (<i>n</i> = 153)	
Age (years)	Median (range)	44.7 (14.9–86.6)	48.8 (19.5–82.3)	<i>p</i> = 0.007
Gender (female)	Number (%)	341 (82.4)	111 (72.5)	<i>p</i> = 0.012
Smoking history	Number (%)	72 (17.4)	19 (12.4)	<i>p</i> = 0.152
Length of stay (days)	Mean (\pm SD)	2.3 \pm 2.4	3.7 \pm 4.6	<i>p</i> < 0.001
Surgery duration (minutes)	Mean (\pm SD)	82.7 \pm 29.4	94.9 \pm 36.3	<i>p</i> = 0.007
Conversion to open	Number (%)	7 (1.7)	17 (11.1)	<i>p</i> < 0.001

pathways by pro-inflammatory cytokines. This can result in a neutrophilia. Concurrently, however, there is also down regulation of adaptive immunity, including T cell activation [23]. This will be reflected as a lymphopenia on the complete blood count. The value of neutrophilia and lymphopenia count as individual prognostic markers has been identified to be of particular use in critically ill patients [24, 25]. PNLR can offer a simple combined reflection of both innate and adaptive immunity as a simple value [26]. In the patient with compromised immunity preparing for a LC procedure, a lack of active inflammation will result in a normal neutrophil reading. In this scenario, the PNLR can still prove to be of value as an impaired adaptive immunity, reflected as a lymphopenia, will result in a higher PNLR, which may alert the attending surgeon that the patient may be at a higher risk. Thus the PNLR can offer a cheap, easily calculated, indicator of patient performance prior to admission, enabling additional measures to be put in place to optimise patient outcome.

The British Association of Day Case Surgery (BADs) recommended in 2009 that 60% of all LC should be carried out as a day-case procedure [27]. This institution recorded a transition in DCLC from 0 to 44.4% (*n* = 112) when LC cases prior and subsequent to November 2011 are compared. Moreover, a total of 86.1% (*n* = 217)

patients since November 2011 were discharged by D1 post-operation. This implementation and transition to DCLC remains above par when compared with national progress which saw DCLC increase from 13% in 2010 to 21.9% in 2012. The average LOS in public hospitals, however, still exceeding 72 h [28].

In an era of ambulatory surgery, day-case surgery LC has been demonstrated to be cost effective and has favourable effects on both bed planning and healthcare expenditure [29, 30]. Moreover, it is also acknowledged that day-case LC surgery is associated with high levels of patient satisfaction [31]. The findings of this study highlight the value and importance of pre-operative counselling and the ability to predict outcomes by using simple markers. This would help delineate those patients that are low risk and suitable for consideration for ambulatory surgery. Additionally, those with elevated PNLR are at risk of prolonged length of stay or conversion and this can be useful in patient and hospital planning.

We acknowledge that this study has limitations. This is retrospective in nature and should be validated with prospective data. However, we found that a PNLR > 3 in patients undergoing elective LC can help identify those that may have a complicated operative and post-operative course.

Table 3 Breakdown of patient groups by ASA classification

ASA classification	1 (<i>n</i> = 288)	2 (<i>n</i> = 214)	3 (<i>n</i> = 12)	4 and 5 (<i>n</i> = 0)	Unknown (<i>n</i> = 53)	Total (<i>n</i> = 567)
Age (Years)	38.3 (14.9–73.9)	53.6 (16.5–86.6)	65.0 (42.3–83.3)	n/a	50.0 (15.4–79.5)	43.1 (14.9–86.6)
NLR (Mean \pm SD)	2.93 \pm 3.11	3.51 \pm 3.78	4.78 \pm 4.09	n/a	2.35 \pm 1.01	3.12 \pm 3.28
NLR < 3 <i>N</i> (%)	219 (76.0)	146 (68.2)	7 (58.3)	n/a	42 (79.2)	414 (73.0)
NLR > 3 <i>N</i> (%)	69 (24.0)	68 (31.8)	5 (41.7)	n/a	11 (20.8)	153 (27.0)
LOS (Mean \pm SD)	2.2 \pm 2.1	3.0 \pm 4.0	5.4 \pm 5.7	n/a	3.8 \pm 3.1	2.7 \pm 3.2
Duration (Mean \pm SD)	83.6 \pm 29.0	88.5 \pm 34.4	107.3 \pm 43.7	n/a	84.9 \pm 21.4	86.1 \pm 31.9
Conversion <i>N</i> (%)	11 (3.87)	9 (4.3)	2 (16.7)	n/a	2 (3.8)	24 (7.1)

Conclusion

PNLR has a clinical utility in predicting post-operative LOS and outcomes in patients undergoing elective LC. If a PNLr of greater than 3 is recorded at pre-assessment, further post-operative surgical planning is warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this was a retrospective studies, formal consent is not required.

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