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Can Neutrophil-Lymphocyte Ratio Predict Operators’ Difficulty in Early Cholecystectomies; A Retrospective Cohort Study

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Abstract

Background: Recent years have seen an increased trend toward “early cholecystectomy” following acute cholecystitis. Operators whilst performing cholecystectomy during acute cholecystitis commonly finds varying degree of inflammation ranging from soft adhesions to densely adherent gangrenous gall bladder, which is not only associated with morbidity but is often technically challenging. In this study we aim to retrospectively evaluate the role of neutrophil-lymphocyte ratio (NLR) and its association with operative difficulty and length of stay for patients who underwent ‘hot cholecystectomy’.

Methods: An anonymised retrospective single-centre cohort study using operative notes and clinical data. Chi-squared test and Mann-Whitney U-test were applied to determine significance between variables in the predetermined low NLR (<5) and high NLR (>5) groups. Multiple linear regression was applied for assessing any significant relationships between NLR and operative difficulty, length of stay (LOS) and post-operative stay (POS).

Results: Patients with a high NLR > 5 level upon admission are on average older (median 44 vs 60 years; p-value 0.003), have a longer hospital stay (median 4 vs 5 days; 0.005), their operations take longer (median 81 vs. 98 minutes; p=0.026), and operations are deemed more difficult (13% vs. 33%; p=0.035) as judged by surgeons and evident by intra operative parameters. In linear regression increased age was found to be associated with higher NLR (median 4 vs 5 days; 0.005), their operations take longer (median 81 vs. 98 minutes; p=0.026), and operations are deemed more difficult (13% vs. 33%; p=0.035). Presence of gangrene was significantly associated with both LOS and POS in regression analysis (p-value 0.044 and 0.015 respectively).

Conclusions: In performing an ‘early cholecystectomy’ a higher NLR on admission is associated with operators’ difficulty. However, a NLR cut off of 5 is not significantly linked to increased length of stay. Nonetheless, NLR on admission can be applied to stratify acute cholecystitis to plan surgery and anticipate difficult operation. NLR when combined with age can be utilised as guide to prioritise the urgency of operation and as prognostic predictor of possible post op complications.

INTRODUCTION

Acute cholecystitis is one of the common surgical emergencies. Since its introduction, laparoscopic cholecystectomy has become the preferred operative choice to remove the gall bladder. In recent years there has been a shift towards ‘early cholecystectomy’ i.e., removing the gall bladder during an acute attack of cholecystitis. It is strongly recommended by national institute of clinical excellence (NICE) to offer cholecystectomy during acute cholecystitis commonly finds varying degree of inflammation ranging from soft adhesions to densely adherent gangrenous gall bladder, which is not only associated with morbidity but is often technically challenging. In this study we aim to retrospectively evaluate the role of neutrophil-lymphocyte ratio (NLR) and its association with operative difficulty and length of stay for patients who underwent ‘hot cholecystectomy’.

CRP although are very sensitive in suggesting the presence of inflammation / infection but, cannot suggest clinical severity of condition. Investigators have found a relative lymphocytopenia in variety of infective and septic conditions, its relation to the disease severity has been investigated [7-10]. In an attempt to understand the immune response the neutrophil lymphocyte ratio (NLR) has been investigated in variety of inflammatory / infective and tumoral conditions [7-13].

As an indicator of severity of inflammation, the prognostic value of NLR in different conditions such as acute cholecystitis, acute appendicitis, and sepsis due to multiple causes requiring intensive care, has been studied [7-10,14]. Investigators have also found a higher level of plasma cytokines (IL-1ra, IL-6, IL-7, IL-8, IL-12) in patients with high NLR [13,15,16]. In this study we aim to utilise NLR as surrogate indicator of up-regulation of immune system which in turn translates into operators’ difficulty...
Definition of difficult gall bladder and cut off value for neutrophil-lymphocyte ratio NLR

Strict criteria of difficult operation was applied, difficult operation was defined as "an operation involving inflammation, empyema, adhesions, gangrene or perforation of gall bladder leading to operator’s difficulty in dissecting the Calot’s triangle with or without subtotal operation" [17-19]. All the intra operative findings attributed to difficult gall bladder were analyzed in addition to surgeon’s judgment about operative difficulty (as described in operating notes).

Lee et al. [7], described an NLR of 3 as cut off point to differentiate between and simple and severe cholecystitis. Beliaev et al. [10], have demonstrated the cut off value to be diagnostic at 3.25 and 4.17 between mild and moderate-severe cholecystitis respectively. Kelly et al. [8], described the value of NLR > 6.35 to be associated with severe appendicitis. Sharaia et al. [12], and Carruthers et al. [12], separately described NLR >5 as having prognostically predictive value in two separate tumoral processes. Patel et al. [20], describes NLR > 11 significantly associated with length of stay in acute cholelithiasis. While studying patients admitted to intensive care due to infection Liu et al. [9], found NLR as indicator of disease severity, at value of 11.11, 22.67 and 31.50 associated with sepsis, severe sepsis and septic shock respectively. An agreed cut off NLR > 5 was used to divide patient in two groups to observe how the intensity of immune response based on disease severity translates in to a difficult operation and associated morbidity.

METHODS

Study design & subjects

We retrospectively reviewed clinical data of early cholecystectomies performed in a busy district general hospital between October 2014 to September 2015. During this period, 89 patients underwent emergency laparoscopic cholecystectomies. Inclusion criteria were: emergency hospital admission; hot gallbladder confirmed through radiological diagnostic (USS 77% n=62 and CT scan 33%n=19) test pre-operatively; operated within operation during same admission. Exclusion criteria were: non-inflamed gallbladder i.e., Pancreatitis, Cholecystitis with CBD stones requiring ERCP, Operation during same admission.

Inclusion and Exclusion criteria.

Inclusion criteria
- Emergency admission
- Clinical signs suggesting Cholecystitis (Tokyo classification)
- Radiological confirmation
- Operation during same admission

Exclusion criteria
- Emergency operation done for non inflamed gall bladder i.e., Pancreatitis
- Cholecystitis with CBD stones requiring ERCP
- Requiring interventionradiology due to post physiologic status

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RESULTS

NLR < 5 group had 32 patients and NLR > 5 had 49 patients. As expected female were more in both groups. Median age was found to be 60 years in NLR > 5 group as compared to 43 years in other group (p=0.003). There was difference of one day in length of stay noticed in both groups (p=0.005) (Table 1).

Intra operative details were analyzed and we found significant difference in operative time 81 mins vs. 98 mins in two groups (p=0.026). Operators’ difficulty as judged by surgeon was also found to be significant at 33% in NLR > 5 group comparing 13% in NLR < 5 group (p=0.035). In addition it was found, there were higher in incidence of empyema, gangrene and adhesions in NLR > 5 group (Table 2). Also higher rates of conversion to open and intra operative drain insertion were seen in NLR > 5 group (Table Amongst the operations judged difficult 9% vs. 16% in respective groups were partial or subtotal cholecystectomy (partial means leaving posterior wall attached but cystic duct successfully clipped, subtotal means safe clipping of cystic duct not performed gal bladder tied or sutured at the level of hartmann’s pouch).

In multiple linear regression analysis it was found that the age is a significant factor in NLR > 5 group (p=0.036). No association of NLR > 5 was seen with either overall length of stay or postoperative stay (Table 3).

We performed further multiple linear analyses on length of stay and post operative stay in both groups. It was found that the overall length of stay and post operative stay was associated independently with presence of gangrenous gall bladder in both the groups (p=0.044 and p=0.015 respectively) (Table 4). It is important to mention no mortality in the study population with only 1 patient requiring level 3 care for respiratory complications later discharged.

DISCUSSION

It is estimated around 66,660 cholecystectomies are performed each year in UK out of which 61,220 are performed laparoscopic [21]. Overall annual cost to the NHS for performing
Table 1: Overview of variable statistics for groups NLR < 5 and NLR > 5.

<table>
<thead>
<tr>
<th>Variable</th>
<th>NLR &lt; 5 (n= 32)</th>
<th>NLR &gt; 5 (n= 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male / female)</td>
<td>22% / 78% (7 / 25)</td>
<td>39% / 61% (19 / 30)</td>
<td>0.14\textsuperscript{A}</td>
</tr>
<tr>
<td>Age (yrs, median)</td>
<td>43</td>
<td>60</td>
<td>0.003\textsuperscript{**}</td>
</tr>
<tr>
<td>Length of Stay LOS (days, median)</td>
<td>4</td>
<td>5</td>
<td>0.005\textsuperscript{**}</td>
</tr>
<tr>
<td>Post-op stay POS (days, median)</td>
<td>1.5</td>
<td>2</td>
<td>0.135\textsuperscript{A}</td>
</tr>
<tr>
<td>ASA grade (median)</td>
<td>1.5</td>
<td>2</td>
<td>0.63\textsuperscript{A}</td>
</tr>
</tbody>
</table>

*Statistically significant at p-value < 0.05; \textsuperscript{A}Chi-squared test; \textsuperscript{B}Mann-Whitney U-test.

Table 2: Intra operative variable statistics for groups NLR < 5 and NLR > 5.

<table>
<thead>
<tr>
<th>INTRA OPERATIVE FINDINGS</th>
<th>NLR &lt; 5 (n= 32)</th>
<th>NLR &gt; 5 (n= 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min, median)</td>
<td>81</td>
<td>98</td>
<td>0.026\textsuperscript{**}</td>
</tr>
<tr>
<td>Gangrene present</td>
<td>3% (n=1)</td>
<td>14% (n=7)</td>
<td>0.094\textsuperscript{A}</td>
</tr>
<tr>
<td>Pus present</td>
<td>19% (n=6)</td>
<td>27% (n=13)</td>
<td>0.39\textsuperscript{A}</td>
</tr>
<tr>
<td>Omental adhesions present</td>
<td>44% (n=14)</td>
<td>59% (n=29)</td>
<td>0.20\textsuperscript{A}</td>
</tr>
<tr>
<td>Drain required</td>
<td>28% (n=9)</td>
<td>51% (n=25)</td>
<td>0.052\textsuperscript{A}</td>
</tr>
<tr>
<td>Conversion required</td>
<td>0% (n=0)</td>
<td>10% (n=5)</td>
<td>0.059\textsuperscript{A}</td>
</tr>
<tr>
<td>Operation completed</td>
<td>91% (n=29)</td>
<td>84% (n=41)</td>
<td>0.35\textsuperscript{A}</td>
</tr>
<tr>
<td>Operation difficulty, judged ‘yes’ by surgeon</td>
<td>13% (n=4) (9% n=3 partial or sub-total)</td>
<td>33% (16% n=8, partial or sub-total)</td>
<td>0.035\textsuperscript{**}</td>
</tr>
</tbody>
</table>

*Statistically significant at p-value < 0.05; \textsuperscript{A}Chi-squared test; \textsuperscript{B}Mann-Whitney U-test.

Table 3: Multiple linear regression analysis for categorized NLR (<5 and >5).

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Standardized coefficient Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>-0.015</td>
<td>0.91</td>
</tr>
<tr>
<td>ASA level</td>
<td>0.29</td>
<td>0.036\textsuperscript{*}</td>
</tr>
<tr>
<td>Age</td>
<td>-0.094</td>
<td>0.46</td>
</tr>
<tr>
<td>Operation time</td>
<td>0.18</td>
<td>0.20</td>
</tr>
<tr>
<td>Inflamed</td>
<td>-0.12</td>
<td>0.36</td>
</tr>
<tr>
<td>Gangrenous</td>
<td>0.15</td>
<td>0.36</td>
</tr>
<tr>
<td>Pus present</td>
<td>-0.003</td>
<td>0.99</td>
</tr>
<tr>
<td>Omental adhesions</td>
<td>0.039</td>
<td>0.77</td>
</tr>
<tr>
<td>Operation difficulty</td>
<td>0.052</td>
<td>0.80</td>
</tr>
<tr>
<td>Operation completed</td>
<td>0.029</td>
<td>0.85</td>
</tr>
<tr>
<td>Drain use</td>
<td>-0.035</td>
<td>0.84</td>
</tr>
<tr>
<td>Conversion</td>
<td>0.092</td>
<td>0.51</td>
</tr>
<tr>
<td>LOS</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>POS</td>
<td>-0.13</td>
<td>0.43</td>
</tr>
</tbody>
</table>

# statistically significant, p-value <0.05

this operation is around £111.6 million [21]. NICE has given a strong recommendation to offer early laparoscopic cholecystectomy within one week of diagnosis of acute cholecystitis [1]. It has previously been shown that when performing a planned elective cholecystectomy with history of cholecystitis some patients are more of a challenge to surgeons than others. Those patient groups who initially presented as an acute cholecystitis, and subsequently underwent delayed planned elective surgery, had more conversion rates and their operation times were longer Lorenz et al. [22]. Previous attempts have been made to predict the operative difficulty during a cholecystectomy using radiological tools [2,3].

In this study we demonstrate there is a significant difference in median age between 2 study groups. An increase age was found to be associated with high NLR. It has been described that an increased age is associated with severity of cholecystitis and prolonged length of stay by Lee et al. [7] and Patel et al., [20]. It has also been observed that an increased age with high NLR is associated with non survivor group of intensive care patients admitted with sepsis [9].

Although the NLR utility to predict and estimate the
severity of inflammation has been described in the literature (12,23,24,25). To our knowledge this study is the first to describe the relation of high NLR with a difficult cholecystectomy (13% vs. 33%, p=0.035 Table 2). We appreciate that judging the operator’s difficulty of performing an operation has inherited subjective bias, care was taken to thoroughly investigate the intra operative findings. Although 13% operation were deemed difficult in NLR < 5 group 9% (n=3) were partial or subtotal, comparing to NLR > 5 group where 33% operations were judged as difficult by surgeon but only 16% (n=8) were partial or subtotal rest of all the difficult operation were complete (Table 2). In our study group no operation was abandoned and bailed out with cholecystostomy tube.

Individual parameters of operative time, inflammation, empyema, adhesions, gangrene, intra operative drain and conversion to open were analyzed between 2 groups. Significant difference was seen in operative time (p=0.026 Table 2). In multivariate regression analysis the association was not found to be independent but, longer median operation time 98 vs. 81 min (p=0.026), the increase incidence of empyema (27% vs. 19%), gangrenous gall bladder (14% vs. 3%), adhesions (59% vs. 44%), intra operative drain insertion (51% vs. 28%) and conversion to open (10% vs. 0%) in NLR > 5 group indicate that NLR >5 can be utilized as a guide to predict and plan a difficult operation.

In this study an independent association between the NLR and length of stay at cut off value of 5 could not be established. However it was interesting observation in multivariate regression to see the association of the incidence of gangrenous gall bladder with increased length of stay more importantly with post operative stay (Table 4).

Our study was limited with its retrospective cohort. There was an element of surgeons’ and experience bias however this was thought to be minimum given there was always a consultant scrubbed for a ‘hot cholecystectomy’. Due to lack of agreement at cut off value of NLR at cut off value in literature [7-10,20] the departmentally agreed cut off was utilised by the authors to divide patients in 2 groups. Moreover the overall length of stay analysis was confounded by the availability of radiological service to confirm the suspected clinical diagnosis.

After the finding of this study a prospective study in out institute is being carried out NLR > 5 is being used as a guide to inform patients of increased likelihood of difficult operation and potential complications, but also helps the operating surgeon to plan and operate with appropriate help and expertise around.

CONCLUSION

It is therefore suggested that higher NLR > 5 can be use as a guide to predict and plan a difficult cholecystectomy. NLR being simple to calculate should be used as common practice with patients presenting with acute cholecystitis. High NLR > 5 when combined with age not only predicts the operating challenge and technical difficulty but also indicates severity of underlying immune response. Its utility may also include prioritisation, planning appropriate expertise, and as guidance to inform patients in consent process of possible complication and what to expect.

REFERENCES

1. Nice Guidelines on management of acute cholecystitis.


