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ORIGINAL ARTICLE

The role of the neutrophil:lymphocyte ratio (NLR) and the CRP:albumin ratio (CAR) in predicting mortality following emergency laparotomy in the over 80 age group

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Abstract

Introduction Emergency laparotomy in the elderly is an increasingly common procedure which carries high morbidity and mortality. Risk prediction tools, although imperfect, can help guide management decisions. Novel markers of surgical outcomes may contribute to these scoring systems. The neutrophil:lymphocyte ratio (NLR) and CRP:albumin ratio (CAR) have been associated with outcomes in malignancy and sepsis. We assessed the use of ratio NLR and CAR as prognostic indicators in patients over the age of 80 undergoing emergency laparotomy.

Methods A retrospective analysis of all patients over the age of 80 who underwent emergency laparotomy during a 3 year period was conducted. Pre and post-operative NLR and CAR were assessed in relation to outcome measures including inpatient, 30-day and 90-day mortality. Statistical analysis was conducted with Mann–Whitney *U*, receiver operating characteristics, Spearmans rank correlation coefficient and chi-squared tests.

Results One hundred and thirty-six patients over the age of 80 underwent emergency laparotomy. Median age was 84 years (range 80–96 years). Overall inpatient mortality was 19.2%. Pre-operative and post-operative NLR and CAR were significantly raised in patients with sepsis v no sepsis ($p<0.05$). Pre-operative NLR was significantly associated with inpatient ($p=0.046$), 30-day ($p=0.02$) and 90-day mortality ($p=0.01$) in patients with visceral perforation. A pre-operative NLR value of greater than 8 was associated with significantly increased mortality ($p=0.016$, AUC:0.78). CAR was not associated with mortality.

Conclusion Pre-operative NLR is associated with mortality in patients with visceral perforation undergoing emergency laparotomy. NLR > 8 is associated with a poorer outcome in this group of patients. CAR was not associated with mortality in over-80s undergoing emergency laparotomy.

Keywords CRP · Neutrophil/lymphocyte ratio · Mortality · Elderly · Laparotomy

Introduction

We live in an era of increased life-expectancy where around a quarter of people currently aged 50 and up to 12% of females currently aged 80 can expect to become centenarians.

Emergency laparotomy is associated with high morbidity and mortality with death rates ranging between 9.2 and 18.2% [2] across all ages. The elderly have an over-representation of frailty and co-morbidity and are a challenging group for surgeons to treat [31]. Mortality increases with advancing age and is an independent predictor of outcomes [3]. For those aged 80 or above, mortality significantly increases, with 30-day mortality figures ranging between 24.4 and 33.3% and 1-year mortality up to 48% [4–6]. Additionally, elderly patients often require lengthy critical care involvement and long hospital stays. Consequently, outcome prediction in these patients is valuable in guiding complex management decisions. We have identified

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this population as one which may benefit from additional prognostication to allow improved risk assessment, treatment decisions and allocation of resources.

A number of prognostic scoring tools have been devised. The most commonly used risk prediction tools are P-POSSUM and APACHE-II [6, 7]. Despite APACHE-II providing the most reliable risk prediction tool [8], it's complexity has limited it's use and surgeons pragmatically tend to use the simpler P-POSSUM (the risk tool for the United Kingdom National Emergency Laparotomy Audit). Worldwide there is ongoing interest in risk prediction in emergency surgery with several large studies alongside NELA such as the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) and the Enhanced Peri-Operative Care for High-risk patients (EPOCH) [10–12]. This interest underlines the need to develop accurate prediction tools and not solely rely on clinical judgement that underestimates mortality in very high-risk patients [9].

Inflammation-based prognostic indicators have attracted interest in multiple settings with neutrophil:lymphocyte ratio (NLR) and CRP:albumin ratio (CAR) identified as prognostic markers. These may be useful as they combine a patient's systemic inflammatory status and pathological burden. CAR has been shown to predict outcomes in cancer of the lung [14], pancreas [15], liver [16], oesophagus [17] and stomach [18]. Similarly, NLR has been shown to be associated with prognosis in cancers of the breast [19], urothelium [20], prostate [21], stomach [22] and lung [23]. Inflammation-based markers have also been identified as prognostic markers in acute settings in patients with sepsis [24–27] and in emergency abdominal and vascular surgery [28, 29]. We aimed to assess the utility of NLR and CAR in predicting the outcomes of elderly patients undergoing emergency laparotomy.

Methods

A retrospective analysis of all patients over the age of 80 who underwent emergency laparotomy during a 3 year period between 2010 and 2013 at a single centre (Wirral University Teaching Hospital, UK).

Demographic, histological, clinical, biochemical and operative data were collected and analysed by accessing patient clinical notes and electronic records. Outcome measures were in-patient, 30-day and 90-day mortality.

Sub-group analysis

Sub-group analysis was conducted by dividing the patient cohort according to cause for emergency laparotomy. Patients were divided into those with or without peritoneal contamination. Patients included in the peritoneal contamination group were patients who had peritoneal contamination with or without visceral perforation. Patients did not require formal documentation of systemic inflammatory response syndrome (SIRS) to be included in this group. A further sub-group of patients with documented visceral perforation were analysed.

Statistical analysis

Statistical analysis was conducted using the Mann–Whitney *U* Test for continuous variables. Spearman's rank correlation coefficient was utilised to assess correlation. Chi-squared test was used and receiver operating characteristics (ROC) curves were generated in analysis of mortality outcomes.

Results

Baseline characteristics

A total of 136 patients aged 80 or above underwent emergency laparotomy in a 3 year period between 2010 and 2013. 46 patients were male, 90 patients were female. Median age of this group was 84 years (range 80–96 years). Baseline characteristics of the patient cohort are shown in "Appendix Table 1". Of the 136 patients, 63 patients (46.3%) underwent emergency laparotomy where no evidence of sepsis was found. 73 patients (53.7%) underwent emergency laparotomy with intra-abdominal sepsis, of which 44 patients (57.9%) had a documented visceral perforation at the time of laparotomy. Overall mortality for patients undergoing emergency laparotomy over the age of 80 was 19.2% (26 of 136 patients). Mortality for patients without sepsis, with sepsis and with visceral perforation was 15.9% (10 of 63 patients), 21.9% (16 of 73 patients) and 25% (11 of 44 patients) respectively.

CAR and NLR trend and association with sepsis

Median pre-operative CAR and NLR values were 2.3 and 7.2, respectively. Values of both CAR and NLR increased on consecutive days reaching a peak value at post-operative day 2. Median values of both CAR and NLR proceeded to decrease on post-operative days 3 and 4. Patients with sepsis and with perforation had a significantly raised NLR when compared to patients without peritoneal contamination pre-operatively and on post-operative days 1–4 ($p < 0.05$). Similarly, CAR was significantly increased in patients with contamination and with perforation pre-operatively and on post-op days 1 and 2 ($p < 0.05$). No significant difference in CAR was seen on post-operative days 3 and 4.

CAR and NLR in predicting mortality

The CAR was not significantly different between survivors and non-survivors pre-operatively (survivors: 0.81, non-survivors: 2.6) or post-operatively (Day 1: survivors = 7.1, non-survivors = 5.28, Day 2: survivors = 10.0, non-survivors = 7.0, Day 3:survivors = 7.6, non-survivors = 6.7, Day 4:survivors = 4.5, non-survivors = 6.6).In the absence of peritoneal contamination, NLR values pre-operatively and post-operatively did not differ between survivors and non-survivors pre-operatively (survivors: 6.5, non-survivors: 7.2) or post-operatively (Day 1: survivors = 9.8, non-survivors = 8.5, Day 2: survivors = 9.0, non-survivors = 5.4, Day 3:survivors = 7.4, non-survivors = 5.3, Day 4:survivors = 8.1, non-survivors = 6.3). In patients with peritoneal contamination median NLR was increased on post-operative days 4 and 5 in those who died compared to survivors day 4 (20.75 v 10.7 survivors, $p = 0.03$), day 5 (22.7 v 8 survivors, $p = 0.012$).

Similar findings were seen in those with visceral perforation. Median NLR was increased pre-operatively in those who died compared to survivors (12.1 v median 23.1 non-survivors, $p = 0.046$) and on day 3 (13 v 25.3 non-survivors, $p = 0.003$) and day 4 (11 v 23.5 non-survivors, $p = 0.014$). (Fig. 1).

A similar relationship was seen in patients with perforation with respect to 30 and 90-day mortality. Median NLR was increased in patients who died within 30 days post-emergency laparotomy with a significant difference found pre-operatively (survivors = 12.1 v non-survivors = 16.1, $p = 0.02$) and post-operative day 2 (survivors = 13 v non-survivors = 23, $p = 0.05$) and day 3 (survivors = 11 v non-survivors = 20.9, $p = 0.02$). Similarly, median NLR was significantly increased pre-operatively in patients who did not survive to 90 days compared to those who did in patients with GI perforation (survivors = 7.5 v non-survivors = 17.2, $p = 0.01$) and on post-op day 1 (survivors = 22.2 v non-survivors = 11.6, $p = 0.023$), day 2 (survivors = 26.3 v non-survivors = 13, $p = 0.02$) and day 3(survivors = 17.5 v non-survivors = 11, $p = 0.024$).

neutrophil:lymphocyte ratio > 8 and mortality

An NLR value greater than 8 pre-operatively in patients with perforation was associated with increased in-patient

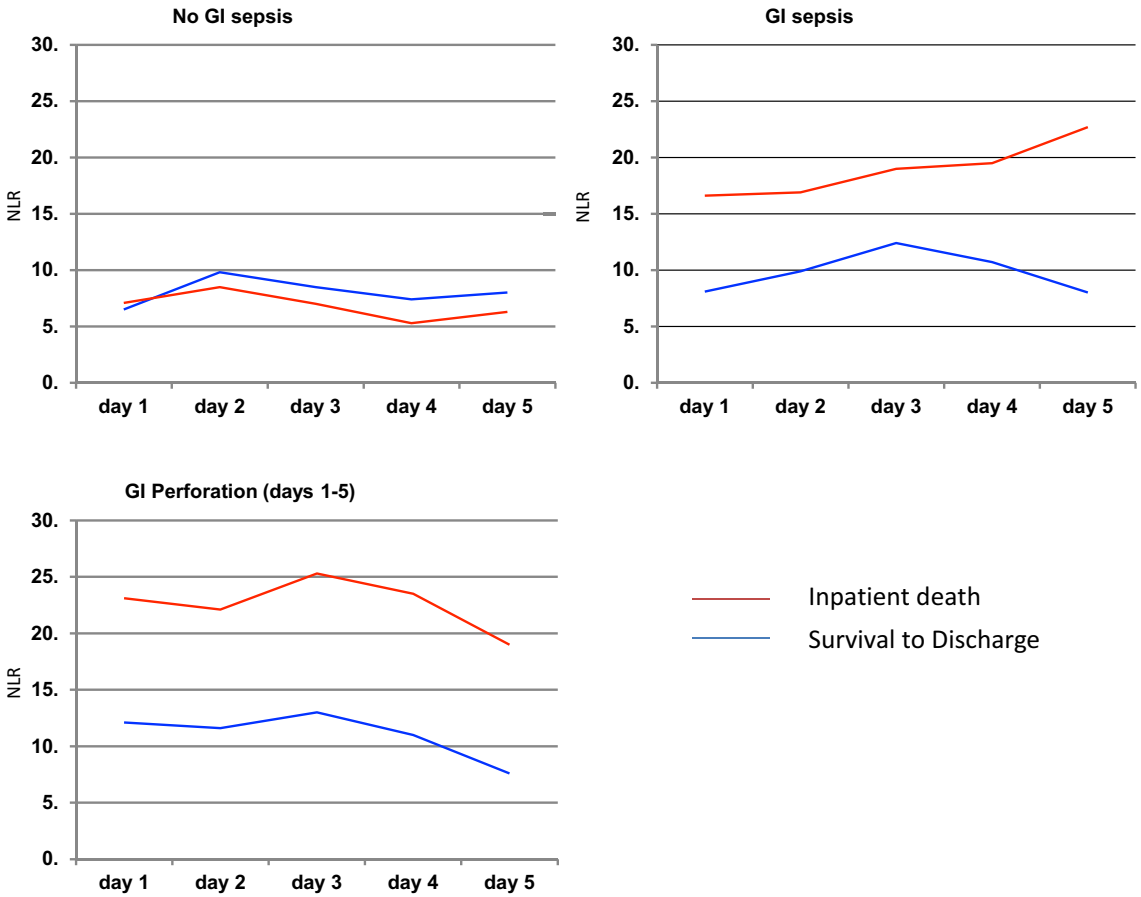

Fig. 1 NLR in patients who survived to discharge vs. patients who died whilst in hospital

and 30-day mortality (37 v 5.8%, $p=0.016$) and 90-day mortality (48.1 v 5.6%, $p=0.0025$).

Receiver operating characteristics analysis (ROC) was undertaken using NLR > 8 as a predictor of mortality. ROC analysis of NLR > 8 in patients with sepsis gave an area under the curve value of 0.70 with respect to inpatient mortality. ROC analysis of pre-operative NLR > 8 in patients with GI perforation gave an area under the curve (AUC) of 0.76 for prediction of inpatient mortality and 30-day mortality and an AUC of 0.78 for 90-day mortality (Fig. 2).

Discussion

The principal finding of this paper is that the pre-operative NLR can predict poorer outcomes in the over 80s undergoing emergency laparotomy in the presence of peritoneal contamination. Multiple initiatives are currently in existence aiming to reduce the morbidity and mortality that is associated with emergency laparotomy, and a fundamental component of this is accurate prognostication.

The NLR provides important prognostic information for decision making in these complex patients. In particular, if surgery is undertaken it can be associated with long, costly critical care utilisation that may ultimately be futile.

Many risk prediction tools exist [7, 8, 30], however, no single risk stratification system provides complete and robust prognostication, particularly in a varied, heterogenous population such as those patients undergoing emergency laparotomy. An ideal risk prediction tool would rely upon readily available parameters which are routinely assessed pre-operatively and inputted into a calculation system which is accessible and easy-to-use. Inflammation-based prognostic markers fit many of these characteristics.

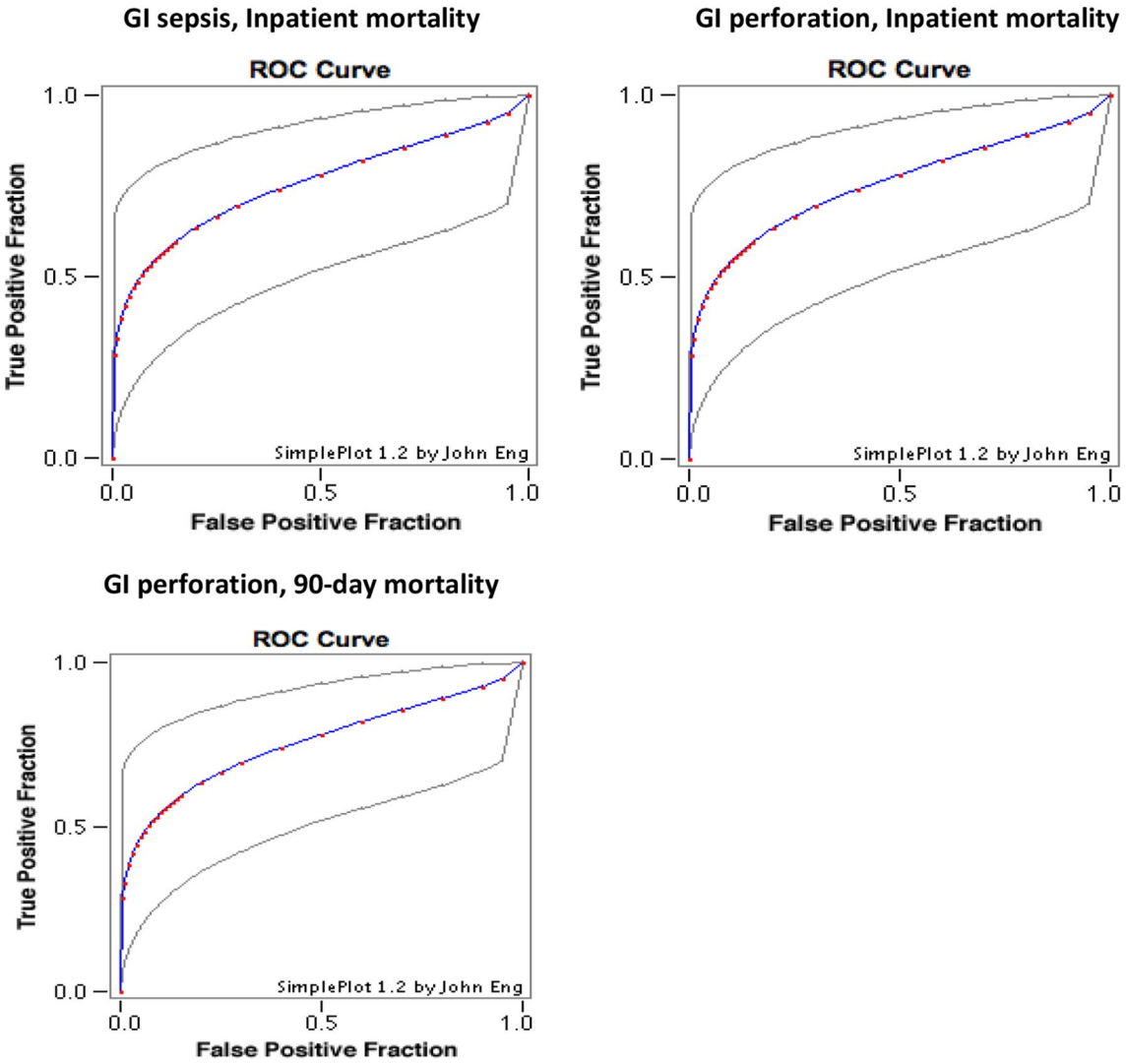

Fig. 2 Receiver Operating Characteristics curves; NLR < 8 and mortality

Previous studies have found CAR and NLR to correlate with outcomes in multiple conditions, including sepsis and in abdominal surgery [24–28]. The aim of this study was to assess their relationship to outcomes in over 80s undergoing emergency laparotomy—a group which provides surgeons with complex and difficult decision-making problems. A single study is available in the literature considering the prognostic role of NLR in patients over the age of 80 undergoing emergency abdominal surgery [28]. Our data supports findings of NLR being associated with mortality in patients over the age of 80 undergoing emergency laparotomy and demonstrates an association between NLR and 30-day, 90-day and inpatient mortality. However, we have identified an NLR cut-off value of 8 as a prognostic marker, significantly lower than NLR > 22 previously described.

In contrast to evidence in the literature and to the findings of NLR as a prognostic indicator, CAR has no association with mortality in this group of patients in terms of inpatient, 30-day and 90-day mortality. To our knowledge, this is the first finding of an NLR > 8 as a pre-operative predictor of mortality in over-80s undergoing emergency laparotomy. Furthermore, we are not aware of accounts in the literature of a direct comparison of NLR to CAR in the same population demonstrating NLR to be a superior prognostic indicator.

Our paper has several strengths and weaknesses. It is a retrospective study confined to those who underwent emergency laparotomy. Accordingly a group of comparator patients with similar pathology who did not receive surgery have not been examined. However, it is likely that these patients would not have had surgery due to an unrecoverable problem, fitness for surgery or patient wishes. In any case, these patients would not have been considered for surgery. Furthermore, the study population is limited to the over 80s and the NLR cannot be generalised to a younger population.

Our study population represents all patients who underwent surgery—this a real-world group of patients with their inherent heterogeneity, yet despite this the NLR stands out as a strong candidate as a prognostic factor. The NLR may be a surrogate marker for sepsis but it provides a simple numerator that can be used in risk prediction, possibly before clinical indicators such as shock and hypoperfusion are manifested.

We have identified NLR as a marker of outcome which may be used alone as a prognostic indicator in patients over the age of 80 undergoing emergency laparotomy. Additionally, NLR could have a potential future role as a variable in multi-variate prognostic indicators which may supercede current risk prediction tools such as P-POSSUM and APACHE-II. Further work may be done to expand the assessment of NLR as a prognostic indicator in all patients undergoing emergency laparotomy and in all patients undergoing emergency surgery.

Compliance with ethical standards

Conflict of interest Mr Gregory Simpson states that he has no conflict of interest. Ms Rebecca Saunders states that he has no conflict of interest. Mr Jeremy Wilson states that he has no conflict of interest. Mr Conor Magee states that he has no conflict of interest

Research involving human participants and/or animals For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Table 1

Table 1 Baseline characteristics of patients over 80 undergoing emergency laparotomy

Characteristics	All patients	No sepsis	GI sepsis	GI perforation
No. of patients	136	63	73	44
Male:female	46:90	28:35	18:55	17: 27
Age (median)	84 (80–96 years)	84 (80–92 years)	84 (80–96 years)	84 (80–92 years)
ASA grade				
ASA I	0	0	0	0
ASA II	20 (11.8%)	12 (19%)	8 (11%)	4 (9.1%)
ASA III	80 (59.6%)	36 (57.1%)	44 (60.3%)	29 (66%)
ASA IV	34 (26.5%)	14 (22.2%)	20 (27.4%)	10 (22.7%)
ASA V	2 (2.1%)	1 (1.6%)	1 (1.4%)	1 (2.3%)
Co-morbidity				
COPD/Asthma	21 (15.4%)	10 (15.9%)	11 (15.1%)	8 (18.2%)
Diabetes	22 (16.2%)	12 (19%)	10 (13.7%)	5 (11.4%)
Cardiovascular disease	40 (29.4%)	13 (20.6%)	27 (37%)	18 (4.1%)
Cerebro-vascular disease	11 (8.1%)	8 (13%)	3 (4.1%)	3 (6.8%)
Mortality (inpatient)	26 (19.2%)	10 (15.9%)	16 (21.9%)	11 (25%)
Median Inpatient Stay (days)	28 (4–116)	22.5 (6–93)	32 (4–116)	32 (4–116)

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