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A threshold for concern? C-reactive protein levels following operatively managed neck of femur fractures can detect infectious complications with a simple formula

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ABSTRACT

Introduction: C-reactive protein (CRP) rises in response to multiple stimuli, including surgical procedures and infections. Deviations from the predicted CRP response to a given procedure may be an early indication of a postoperative complication.

Methods: Three hundred and fifty-four patients with an operatively managed neck of femur fracture admitted over a 1-year period to an NHS Hospital Trust were included. CRP values collected during the postoperative period were retrospectively examined, and objective evidence of postoperative complications was sought. Data analysis explored daily CRP thresholds that maximised sensitivity and specificity for the detection of patients with a postoperative complication.

Results: From the 5th to the 30th postoperative day, a CRP value in excess of the threshold defined by the formula 500/d (where d represents the number of postoperative days) retrospectively detected patients with a postoperative complication with a sensitivity of 0.97 and specificity of 0.82. Patients with a CRP value above the 500/d threshold during this period had a significantly increased 30-day mortality (10.0% vs. 3.9%, RR = 2.74, $p = 0.03$).

Conclusion: Following operatively managed neck of femur fractures, a CRP value in excess of the threshold defined by the formula 500/d may indicate the presence of a postoperative complication and defines a group with increased mortality. In this context, a prompt wound review and septic screen could promote the early detection and management of infectious postoperative complications.

1. Introduction

C-reactive protein (CRP) is an opsonin [1] secreted by the liver in response to multiple stimuli. CRP has become ubiquitous as a serum marker of infection and inflammation and used widely, as suggested by the National Institute for Health and Care Excellence (and other specialty specific committees) for the detection and monitoring of infectious and inflammatory pathologies [2–4]. The doubling time of CRP in response to a stimulus is approximately 8 h [5]. CRP is therefore well placed to act as an early marker of pathology. Knowledge of the kinetics of the postoperative CRP response and recognition of deviations from expected values may therefore give an early indication of a postoperative pathology and an early opportunity to intervene. For instance, CRP elevations have been shown, albeit in a small cohort, to precede the clinical symptoms of deep wound infections following operatively managed fractures [6]. In 2008, Neumaier and Scherer [7] showed that following fracture surgery, CRP kinetics varied depending on the location of surgery, with femoral fractures generating the greatest postoperative CRP elevation. Of note, CRP values following fracture surgery tended to decrease greatly on the fourth postoperative day. Utilising this observation, a CRP threshold of 96 mg/L was calculated, which, when used after the fourth postoperative day, showed a 92% sensitivity and 93% specificity for detecting deep wound infections following fracture surgery [7]. Reassuringly, CRP responses have been shown, in an orthopaedic context, not to vary with age, gender, duration of operation, type of anaesthesia or degree of bleeding—resulting in predictable CRP responses across most patient groups [8]. Given this, and given the favourable kinetics of the CRP response to postoperative stimuli, CRP has been shown to be a more sensitive and specific marker of postoperative infections than white cell counts in multiple studies [10,11,19,20].

CRP has also been utilised by other surgical specialties: in a trial protocol with blinded daily CRP quantification and daily clinical evaluation, a group of 108 patients undergoing "dirty" abdominal procedures showed CRP elevations frequently occurred before a complication was clinically diagnosed [9]. Similarly, certain CRP cutoff values on the

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third postoperative day in a cohort of colorectal resection patients predicted anastamotic leaks with 77% sensitivity and 80% specificity, at an early "preclinical" stage. Patients that exceeded the cutoff value also demonstrated increased mortality [10]. Hoeboer et al. and Silvestre et al. showed CRP elevations often preceded the clinical diagnosis of a postoperative complication following oesophagectomy and colorectal surgery respectively [11,12]. Beyond gastrointestinal surgery, a prospective CRP surveillance study in 348 patients undergoing spinal decompression demonstrated elevations of CRP before the onset of symptoms of spinal site infection [13]. Furthermore, Toman et al. [14] examined the postoperative kinetics of CRP responses following plastic surgery, noting the absence of a decline in CRP, particularly after postoperative day 5, as a marker of complications.

The volume of data available regarding CRP responses to various surgical insults has grown significantly in recent years. The combined weight of evidence above demonstrates that CRP has been used, with success, as an early marker for the presence of postoperative pathology. Utilising knowledge of the dynamics of postoperative CRP responses, some of these studies have sought to define CRP thresholds, whereby a certain CRP value, at a certain time, can be labelled as indicative of a postoperative complication [7]. The current study seeks to reinforce previous work defining the postoperative kinetics of the CRP response following neck of femur (NOF) fracture surgery, up to the thirtieth postoperative day. Examination of postoperative complications, and their frequency, will be featured. A secondary aim is to set both useful and memorable numerical thresholds that will indicate the likely presence of postoperative complications. These biochemical data are intended to augment and complement the daily clinical examination of postoperative patients and are not intended to replace the high level of clinical vigilance required by staff caring for postoperative patients.

2. Methods

All patients with an operatively managed NOF fracture admitted over a 1-year period (01.08.2012–01.08.2013) to the Oxford University Hospitals NHS Trust were included, and data were retrospectively collected from the clinical coding department as well as biochemistry results from digital records. Patients with an elevated preoperative CRP value were not excluded. Patients were included in the "complicated" cohort if, during the first 30 postoperative days, one or more of the following criteria were met: chest radiographic evidence of consolidation, positive blood cultures (excluding single bottle coagulase-negative staphylococcal species, which were treated as contaminants), positive urine culture with symptoms, return to theatre with positive prosthetic or swab cultures, or clear documentation from the medical/surgical team of a suspected focus of infection treated with antimicrobial therapy. Patients without any of these criteria were labelled the "uneventful" cohort. Pre-existing laboratory CRP values from each participant were retrospectively collated and CRP values from 48 h preoperatively to 30 days postoperatively were tabulated. The day of operation was defined as day zero. Laboratory CRP analysis was performed using a latex-enhanced turbidimetric immunoassay technique (Diagnostics Ltd.; Siemens Advia 2400). This provides quantification of CRP (not high-sensitivity CRP) between values of 0.0 and 160 mg/L, laboratory reference range 0–8 mg/L. CRP values above 160 mg/L are not quantified in this assay. Further exclusions were then applied: patients with no CRP values available between the fifth and the thirtieth postoperative days were excluded, as well as patients with evidence of active malignancy, active rheumatoid arthritis, insufficient clinical documentation or a further surgical procedure not related to the initial orthopaedic procedure. Patients who remained after this filter became the "CRP study group". Patients were deemed to have an infectious orthopaedic complication if the parent surgical team labelled the patient with wound cellulitis, if there was persistent ooze from the wound treated with antimicrobials, if the patient returned to theatre for a washout or wound/deep tissue swabs suggested significant bacterial infection. Data analysis was performed using Microsoft Excel 2010© and Stata®. Receiver operating characteristic (ROC) curves were generated for each postoperative day and the Youden index utilised for the maximisation of sensitivity and specificity of CRP thresholds [15]. For the purpose of ROC analysis and threshold calculations, CRP data were analysed for each individual day for postoperative days 5–14; beyond day 15 (as a result of fewer CRP data points during this time), the data were grouped as follows: days 15–16, 17–18, 19–21, 22–24, 25–27 and 28–30.

3. Results

The clinical characteristics of all participants and the CRP study group are shown in Table 1. The subdivided CRP study group data are also shown, after the group has been filtered into the complicated and uneventful cohorts.

One hundred and sixty-two of the initial 684 (23.7%) patients met criteria to be described as "complicated". Five hundred and twenty-two (76.3%) showed no evidence of an infectious complication and were described as "uneventful". The frequencies of postoperative complications in the first 30 postoperative days are shown in Table 2.

In keeping with other studies, CRP values collected in the preoperative period (defined here as the 48 h preceding surgery) were modestly elevated, with a mean value of 32.7 mg/L (taken from $n = 328$ values) [7,16]. Greater preoperative CRP values did not appear to be significantly associated with increased 30-day mortality (survival group mean 31.7 mg/L vs. 30-day mortality group mean 41.5 mg/L, $p = 0.19$) (two-tailed t-test).

The maximal CRP response occurred on the third postoperative day, with a mean CRP (taken from $n = 88$ values) of 141 mg/L. This is also consistent with other studies, with maximal responses occurring on either the second or third postoperative day [6,7,17].

The group (from all participants) that met criteria for a complicated recovery had a significantly higher risk of 30-day mortality than the uneventful group (10.5% vs. 6.1% RR = 1.8, 95% CI: 1.02–3.15, $p = 0.04$) (SE ln(RR) method, as per [18]).

Of the 684 original participants, 322 patients did not have a CRP value available in the day 5–day 30 period and were therefore excluded from further CRP analysis. Additional exclusions were then applied: active malignancy $n = 4$, active rheumatoid arthritis $n = 2$, insufficient clinical documentation $n = 1$ and further surgical procedure not related to the initial orthopaedic procedure $n = 1$. This left 354 patients in the study group (hereafter referred to as the CRP study group) (see Fig. 1). This group, from the fifth to the thirtieth postoperative day, collectively received 964 CRP tests (595 in the complicated cohort vs. 369 in the uneventful cohort). In the uneventful cohort, 93.5% of CRP values were collected in the day 5–day 21 period, with only 6.5% collected after day 22. In the complicated cohort, CRP values were collected more consistently throughout the day 5–day 30 period.

A model for the decline in postoperative CRP values was sought. In particular, CRP values that distinguished the complicated cohort from the uneventful cohort most effectively were calculated (utilising daily receiver operating characteristic curve analysis with Youden index calculation) [15]. The values generated by this analysis are shown in Fig. 2. The solid line (with crosses) represents the calculated threshold, on a given day, whereby a CRP value above the line is likely to represent a postoperative complication.

Taking the line shown in Fig. 2, a memorable formula to simplify and describe this relationship that could be used by clinicians on a daily basis was sought. Multiple formulae and models were tested against the rate of decline shown by the ROC analysis that generated Fig. 2. The authors concluded that the model that was most effective and practical was the simple formula: 500 divided by the number of postoperative days (hereafter abbreviated to 500/d) (shown as a dashed line on Fig. 2). This formula can be used from the fifth to the thirtieth postoperative day. CRP values before postoperative day 5 were universally high,

Table 1
Clinical characteristics of all participants and the CRP study group (with subdivisions).

	All participants	CRP study group		
	$N = 684$	All within CRP study group, $n = 354$	Complicated cohort, $n = 150$	Uneventful cohort, $n = 204$
Mean age (years)	81.4	81.8	80.4	82.9
Female:male	3:1	2.6:1	2.1:1	3.1:1
Operation:				
Cannulated screws	140 (20.5%)	63 (17.8%)	25 (16.7%)	38 (18.6%)
Dynamic hip screw	211 (30.8%)	116 (32.8%)	48 (32%)	68 (33.3%)
Hemiarthroplasty	255 (37.3%)	143 (40.4%)	61 (40.7%)	82 (40.2%)
Hip replacement	50 (7.3%)	15 (4.2%)	4 (2.7%)	6 (2.9%)
Intramedullary nail	9 (1.3%)	5 (1.4%)	3 (2.0%)	2 (1%)
Other procedure	19 (2.8%)	12 (3.4%)	9 (6.0%)	8 (3.9%)
Cement utilised	308 (45.0%)	160 (45.2%)	68 (45.3%)	92 (45.1%)
Complications:				
Medical	140 (20.5%)	128 (36.2%)	128 (85.3%)	Nil
Infectious orthopaedic	22 (3.2%)	22 (6.2%)	22 (14.7%)	Nil
Mean length of stay in acute hospital	15.9 days	17.7 days	16.3 days	18.6 days
Dementia	133 (19.4%)	74 (20.9%)	26 (17.3%)	45 (22.1%)
30-day mortality	51 (7.5%)	26 (7.3%)	17 (11.3%)	9 (4.4%)
Number of CRP values available	1778 (day 2 preoperatively to day 30 postoperatively)	964 (day 5 to 30 postoperatively)	595 (day 5 to 30 postoperatively)	369 (day 5 to 30 postoperatively)

and attempts to find useful thresholds that separated the uneventful and complicated cohorts during this period were not successful. CRP data were not collected after 30 postoperative days, and therefore this analysis cannot comment on CRP values beyond this time.

Taking these data together, CRP data from the uneventful and complicated cohorts are shown in Fig. 3, with 500/d also illustrated.

3.1. Applying the 500/d formula

Any patient within the CRP study group, with a CRP value during the day 5 to day 30 period that was higher than the 500/d threshold, was deemed to have been "500/d positive". Utilising 500/d positivity as a retrospective screening test detected patients within the complicated recovery cohort with a sensitivity of 0.97 and specificity of 0.82. If $(500/d) + 20$ is used, specificity increases to 0.90 but sensitivity falls to 0.89.

In the uneventful cohort, as a model for the "normal" CRP response, $(500/d) - 20$ approximated the mean CRP for any postoperative day between day 5 and day 30 ($r^2 = 0.90$).

The group of patients with 500/d positivity had a significantly higher mortality in the first 30 postoperative days, when compared with 500/d negative patients (10.0% vs. 3.9% RR = 2.74, 95% CI: 1.13–6.66, $p = 0.03$) (SE ln(RR) method).

Within the CRP study group ($n = 354$), 22 patients developed local orthopaedic complications (excluding malalignment/dislocation), including wound infection ($n = 11$), infected prosthesis ($n = 3$), cellulitis ($n = 3$), haematoma ($n = 3$), wound dehiscence ($n = 1$) and chronic infection preceding surgery ($n = 1$). Utilising 500/d as a retrospective screening test detected all but one of these patients.

Table 2
Frequencies of infectious postoperative complications in the first 30 postoperative days.

Complications ($n = 162$ from 684 patients)	Frequency (%)
Lower respiratory tract infection/pneumonia/infective exacerbation of chronic obstructive pulmonary disease	62 (9.1%)
Urinary tract infection	52 (7.6%)
Unclear focus of infection/other	20 (2.9%)
Wound infection	11 (1.6%)
Intra-abdominal sepsis	4 (0.6%)
Prosthetic joint infection	3 (0.4%)
Cellulitis	3 (0.4%)
Neutropaenic sepsis	2 (0.3%)
Infected venous leg ulcer	1 (0.1%)
Necrotising fasciitis	1 (0.1%)
Line-associated infection	1 (0.1%)
Pyelonephritis	1 (0.1%)
Clostridium difficile infection	1 (0.1%)

4. Discussion

The formula 500/d, generated by this study, seeks to provide a marker to aid the interpretation of postoperative C-reactive protein values following neck of femur fracture surgery. CRP values that exceeded this threshold identified patients (when examined retrospectively) who met objective criteria for complicated recoveries and defined a group with increased 30-day mortality.

The current study questions the utility of CRP analysis in the first 3 postoperative days, as values are indiscriminately high and attempts to develop a threshold value with acceptable sensitivity and specificity for complications were not successful. Day 4 is generally the first postoperative day to show a convincing decline in CRP values. The absence of this decline may be the earliest biochemical indication of a postoperative complication. Beyond day 4, the detection of complications through CRP quantification therefore becomes more viable. Utilising this, Neumaier and Scherer showed that a CRP value above 96 mg/L on, or beyond, the fifth postoperative day detected postoperative deep wound infections following limb fracture surgery with a sensitivity of 92% and specificity of 93% [7]. This shows great similarity to the threshold generated by the current study's 500/d formula, which uses a day 5 threshold of 100 mg/L. In addition, similar work from Scherer et al. (2001) yielded a deep wound infection CRP threshold of 140 mg/L on the fourth postoperative day [6]. Although the current study did not find a day 4 threshold with adequate sensitivity or specificity for complications, the interpolated 500/d day 4 threshold of 125 mg/L again shows good concordance with other publications. Furthermore, Neumaier and Scherer made the recommendation that a CRP value exceeding the 90th centile of values taken from an uneventful cohort in the postoperative period was suspicious for complications and should be investigated. The values published within Neumaier and Scherer (2008) for the 90th centiles (data available for days 5, 6 and 12 postoperatively) show excellent concordance with 500/d thresholds from the current study.

One limitation of the current study is the entirely retrospective nature of the analysis; no influence upon blood sampling or CRP analysis in the laboratory was made. CRP values were available only if requested, by the clinical team, during the inpatient stay. As a result of the increasingly ubiquitous use of CRP analysis in each venous sample, the volume of data available was large. Granted, the use of CRP for the detection and monitoring of infectious complications meant many more CRP values

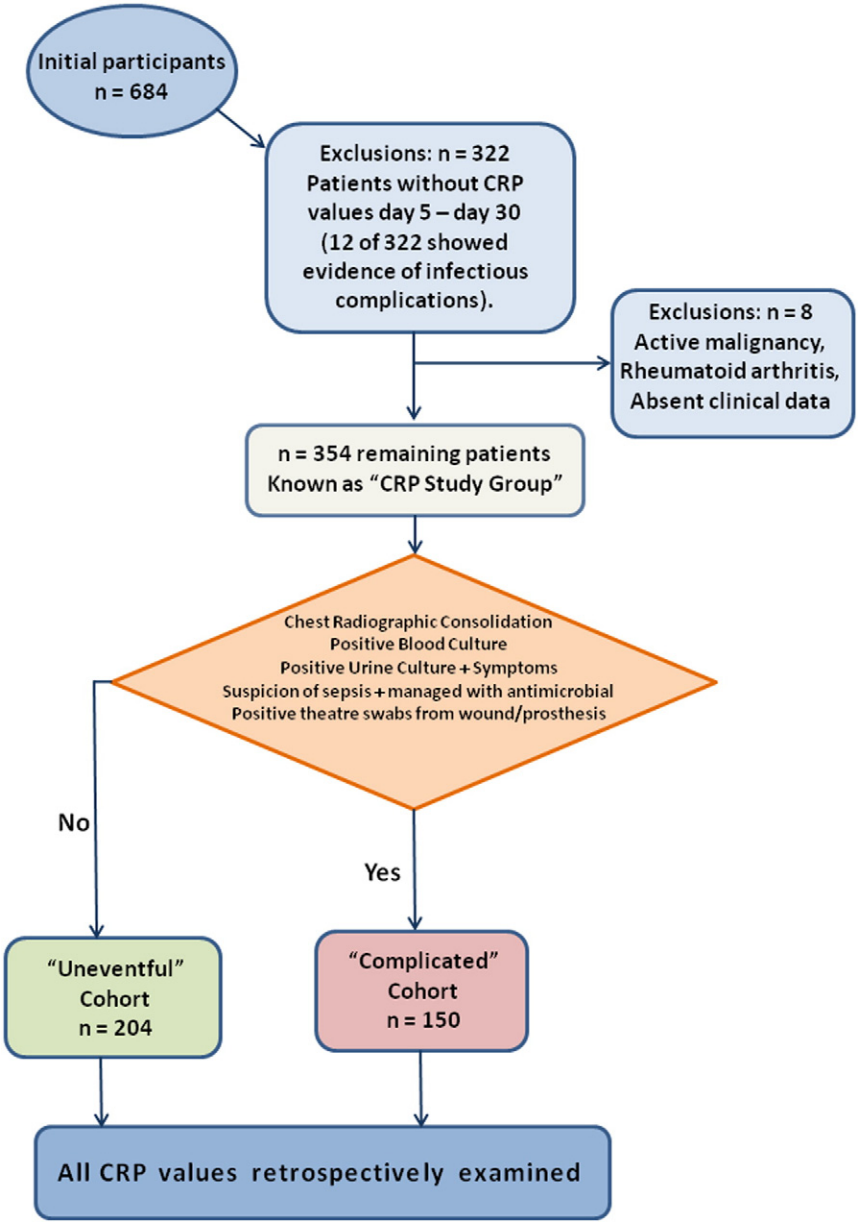

Fig. 1. Flow diagram of participants, cohort criteria and exclusion criteria.

were available where there was greater clinical suspicion of infection, or indeed existing clear evidence of a complication. Patients without a CRP value available during postoperative day 5–day 30 were excluded. This group was large (322 in total), and their exclusion may introduce bias. However, the frequency of infectious complications (using the same objective criteria shown in Fig. 1) in this group was 3.7% (12 of 322),

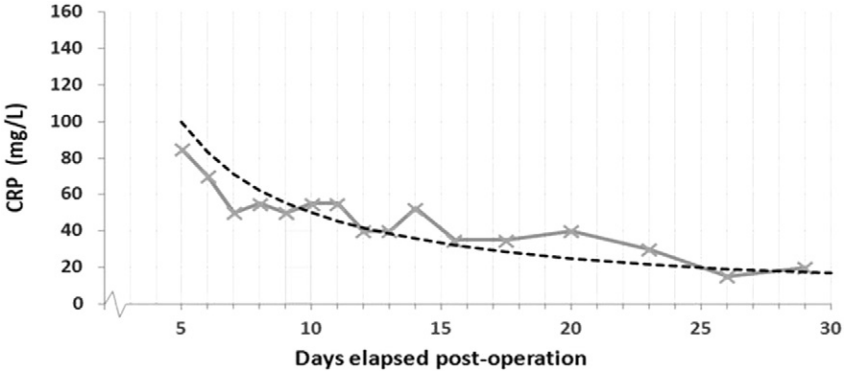

Fig. 2. ROC-generated CRP thresholds (solid line with crosses), 500/d approximation (dashed line).

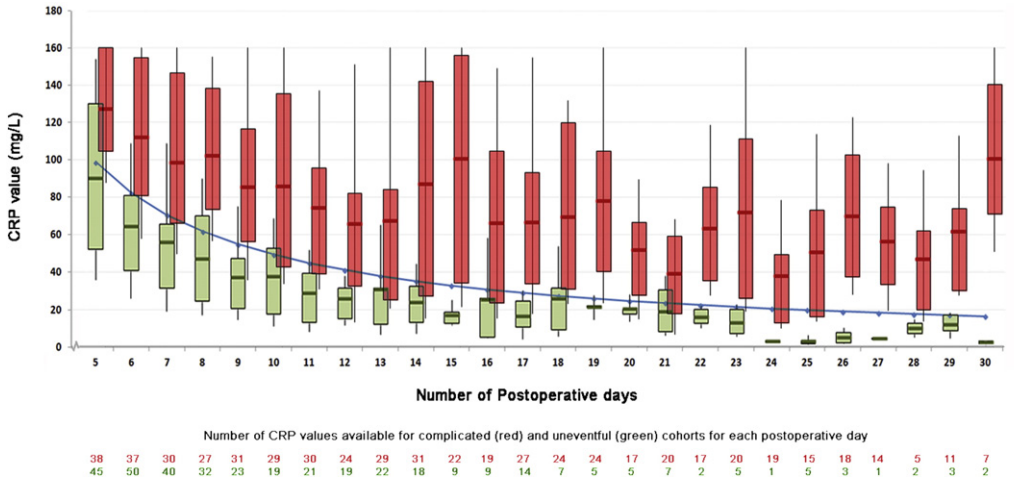

Fig. 3. Day 5–day 30 CRP values from uneventful cohort (green) vs. complicated cohort (red) showing the 10th, 25th, mean, 75th and 90th centiles. The 500/d is represented by the solid line (with circle markers). Total CRP values collected: 964.

compared with over 40% in the CRP study group. It is likely that the clinical team requested fewer CRP tests in this group because their recoveries were relatively free from infectious complications. Whilst this group may have added to the volume of CRP data available (if CRP tests had been requested), the influence this group would have had, if included, on the CRP study group and calculations made thereafter appears to be minimal. It should also be noted that far fewer CRP values were available for analysis after the 22nd postoperative day, particularly within the uneventful group. Given that the majority of patients without postoperative complications have been discharged by day 22, this relative paucity of CRP values is not unexpected. As a result, generalisations from this small collective of CRP values taken between day 22 and day 30 postoperatively should be interpreted with caution.

A valid criticism of the current study is the lack of examination of the temporal nature of the CRP screening test: the point in time at which a patient crosses the 500/d threshold is not clear. Equally, the point in time when a given postoperative complication became clinically evident is also unclear. However, with the weight of literature, covered in the introduction, showing CRP elevations are very likely to be early indicators of pathology, this potential weakness is somewhat diminished [6,9–14]. The methodology (with a binary outcome for a "complicated" vs. "uneventful" postoperative period) also falsely elevates the sensitivity of the retrospective screening test by utilising the entire day 5 to day 30 period to detect CRP elevations at any point in the natural progression of a postoperative complication. As a result, a negative/positive predictive value of a single CRP value cannot be accurately calculated from this data set.

Previous studies have demonstrated that peak CRP response differs between various surgical interventions for NOF fractures [21]. No such association in peak response was detected in the current study, although with a CRP assay ceiling of 160 mg/L the current study is ill-equipped to corroborate this finding. As a result, 500/d was applied to all participants in this study, irrespective of their surgical procedure. It remains that 500/d may benefit from iterations and adjustments for different surgical procedures following NOF fracture.

Patients with a high preoperative CRP, who are frequently excluded from similar studies, were included, on the basis that high preoperative CRP values were felt to be unlikely to significantly influence CRP values on or after day 5 postoperatively. The current study aims to reduce exclusion criteria, such that any findings can generalise to a greater number of orthopaedic patients.

Conventional CRP analysis is based upon the examination of the trend of multiple readings. The current study does not refute the utility of multiple CRP values taken intermittently, but this approach typically takes more than 24 h, at a potentially critical time in a patient's recovery. The postoperative period is, biochemically speaking, a dynamic time; therefore, a dynamic threshold for biochemical markers seems entirely appropriate. The 500/d seeks to provide some additional meaning to a single CRP value in the postoperative period, which, when added to a thorough clinical examination, could help to make informed decisions.

The postoperative NOF fracture patient group typically represents a large proportion of orthopaedic inpatients. The mean length of stay in 2013 in acute hospitals in England following NOF fracture was 15.6 days, with a further 6.9 days in post-acute and rehabilitation beds [22]. Add to this a postoperative complication rate of 20–25% [16,17,23,24] and a formula such as 500/d, which is easily calculated and may aid the early detection of infectious postoperative complications, becomes a potentially valuable everyday tool for clinicians caring for orthopaedic inpatients.

However, further validation of this concept, including prospective analysis, is necessary. The validation of the concept could occur outside of the NOF fracture cohort, with the potential for the expansion of this model for CRP analysis to other surgical specialties and procedures.

5. Conclusion

In this retrospective study, from the fifth to the thirtieth postoperative day, the formula 500/d detected, with good sensitivity and specificity, patients with an objectively complicated recovery and defined a group with significantly increased mortality following NOF fracture surgery. Although there can be no replacement for vigilance and thorough clinical assessment, exceeding the 500/d threshold should prompt an increased index of suspicion for infectious complications following NOF fracture surgery.

Contribution of authors

GC: conception of study, data collection, analysis and writing of manuscript. JH: data collection, analysis and writing of manuscript. AC: statistical analysis and writing of manuscript.

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There are no sources of funding to report. The authors have no conflicts of interest. Due to the entirely retrospective nature of the audit's data collection and full patient anonymisation, full institutional review board permissions were not felt to be necessary. Advice was taken from the Caldicott representative at the host institution regarding patient data protection, and the decision that review board permissions were unnecessary was sustained. This study was carried out in full compliance with UK law.

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