ORIGINAL ARTICLE

DO SERUM ACUTE PHASE REACTANTS PREDICT CLINICAL OUTCOME IN EMERGENCY GENERAL SURGICAL ADMISSIONS?

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Background: Identifying general surgical patients at risk of poor outcome can be a diagnostic challenge. This study aimed to determine the significance of admission serum acute phase reactants in predicting emergency general surgical outcome. **Methods**: An electronic database containing all acute general surgical admissions over two years was analysed to correlate admission acute phase reactants (including C-reactive protein (CRP), absolute neutrophil count (ANC) and serum albumin) with outcome. Study endpoints included: cross-sectional imaging, surgery, intensive care admission, in-hospital mortality and length-of-stay (LOS). **Results**: A total of 9738 patients were enrolled in the study. Elevated CRP (n= 4635; 47%) was associated with: advanced imaging 17% vs 30% (p=0.0001), surgery 15% vs 28% (p=0.0001), ITU admission 3% vs 7% (p=0.0001) and mortality 0.5% vs 2% (p=0.0001). A cut-off level of >150 mg/L was most significant. Abnormal ANC (n= 4104; 42%) was significant in predicting advanced imaging 15% vs 55% (p=0.0001), surgery 17% vs 27% (p=0.0001), and ITU admission 3% vs 8% (p=0.0001). Hypoalbuminaemia (n= 1392; 14%) was associated with a 12-fold rise in mortality 0.5% vs 6%. Normal CRP, ANC with hypoalbuminaemia was a strong negative predictor of mortality (0.015% vs 1.24%), while an abnormal combination was associated with mortality of 8%. **Conclusion:** Admission acute phase reactants are useful to enhance acute surgical patient stratification during clinical decision making. An admission CRP above 150 should alert the clinician of a potentially high-risk patient who may require prompt intervention. A combination of abnormal results has the highest in-hospital mortality.

Keywords: General surgery; C-reactive protein; Serum albumin; Neutrophils; Acute abdomen; Emergency Treatment

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INTRODUCTION

Acute abdomen presents with a rapid onset of severe abdominal symptoms that requires emergency hospital admission. It may indicate potentially life-threatening intra-abdominal pathology requiring urgent surgical intervention and accounts for approximately 10% of patients presenting to the emergency department.[1] The differential diagnosis is wide, with early diagnosis and management essential to reduce the length of hospital stay, morbidity and mortality. Prompt assessment may distinguish patients who require an operation from those who are managed conservatively.[2] Even in experienced hands the clinical diagnosis is uncertain in at least one third of patients.[3] Readily available tests are used first, followed by radiological imaging and invasive investigations to confirm the clinical diagnosis.[4–6] Indiscriminate use of computed tomography risks ionising radiation exposure, contrast induced nephropathy, and associated higher costs.

Acute phase response variables, such as C-reactive protein (CRP), absolute neutrophil count (ANC) and low albumin have been used routinely for their recognised diagnostic value and to monitor clinical progress.

Most studies reporting about the value of inflammatory markers in patients with an acute abdomen have focused upon individual inflammatory markers in specific conditions such as appendicitis, diverticulitis or pancreatitis; relatively few studies have assessed their diagnostic role in the broader category of acute general surgical emergencies presenting predominantly with acute abdominal pain.

The aim of this study was to determine significance of admission levels of acute phase reactants in predicting the overall course of surgical admissions.

MATERIAL AND METHODS

This observational study was conducted in the West Midlands at a busy district general hospital. Data was retrospectively collected from a prospectively maintained comprehensive electronic medical record system (Soarian Clinical Systems). The study

population included all patients over the age of 18 who were admitted to the surgical admission Unit (SAU) predominantly with acute abdominal pain under general surgery between January 2016 and December 2017. The SAU receives referrals in order of frequency from A&E, general practitioners and in-patients from other specialties.

The CRP level is measured in milligrams per litre (mg/L); with a normal physiological CRP level lying below 5.0 mg/L. Some healthy adults may show elevated CRP up to 10 mg/L.

CRP levels were further divided into arbitrary categories to enable statistical evaluation: less than10 mg/dL (<10), 10–20 mg/L, 21–40 mg/L, 41–150 mg/L and over 150 mg/l. Significant neutrophilia was considered an absolute neutrophil count (ANC) of more than 7.7x10^9 and WBC count of less than 4x10^9 was defined as leukopenia. A serum albumin level of 35 grams per litre (g/L) was considered as the lower limit of normal.

The main outcome measures chosen were the number of patients undergoing advanced diagnostic imaging including computed tomography (CT) and magnetic resonance imaging (MRI), surgical intervention, ITU admission, length of hospital stay, and in-hospital mortality. We also assessed whether aggregated combination of individual markers will increase their diagnostic or predictive value.

Variables were summarized as frequencies and percentages, means, medians, standard deviations and inter-quartile ranges as appropriate. Categorical variables were analysed using the chi-squared test. Comparisons of means were examined using a t-test when normally distributed and the Mann-Whitney U test where data was non-parametric. A p value of <0.05 was considered to be statistically significant. Statistical software SPSS-19 and Microsoft Excel were used to store and analyse the above data where appropriate.

RESULTS

A total of 11744 adult patients were identified in the study period, 2006 patients were excluded who did not have all the three inflammatory markers done, and 9738 were selected for the study. Of 9738 patients, 4204 (48%) were male, 5534 (52%), median age 48 years old (range 18–97 years). Admission sources included, Accident and Emergency 5729 (53%), General Practitioner 2973 (28%), and other internal in-patient referrals 2069 (19%). Figure 1 shows overall journey of emergency surgical patients.

Significance of individual and combination of acute response variables on main outcome measures are shown in table-1.

Univariate analysis showed that CRP was found to be significant in predicting whether a patient would undergo advanced imaging (p=0.0001), surgery (p=0.0001), ITU admission (p=0.0001) and mortality (p=0.0001). The proportionate diagnosis of main surgical conditions (inflammatory and malignant) was significantly higher in patients who had raised CRP. A cut-off level of >150 mg/L was most significant. At CRP level of more than 150 mg/dL, an acute surgical patient was 3 times more likely to undergo advanced imaging, almost three times more likely to need surgical intervention, seven-fold increase chance of needing ITU admission and ten time increase in mortality compared to a patient who has normal CRP.

Patients with high ANC and Leucopoenia were three times more likely to have advanced imaging, twice as likely to under undergo surgical intervention, ITU admission. ANC does not predict mortality but leucopoenia predicts a ten-fold increase in mortality. Low serum albumin is more significant in terms of mortality; a twelve-fold increase in mortality compared to patients with normal albumin levels. Individual and combination of markers have high negative predictive value; particularly all three markers have highest negative predictive value in terms of mortality. A combination of two markers does not particularly alter the sensitivity or positive predictive value (PPV).

Table-2 shows sensitivity, specificity and predictive values of acute phase response variables. Univariate analysis has shown no significant correlation of any marker with the length of hospital stay. Results are displayed in figure-2.

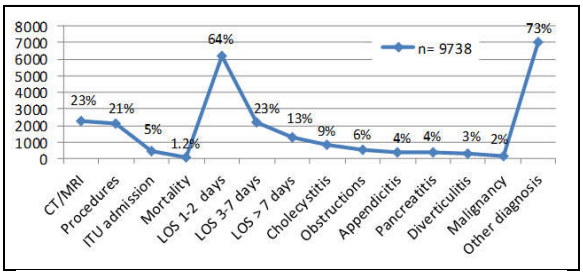

Figure-1: Overall journey of emergency surgical patients

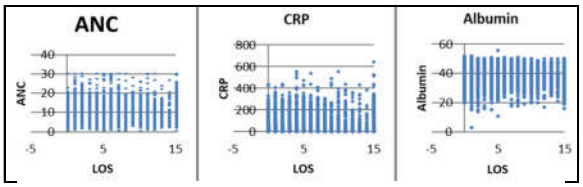

Figure-2: Effect of individual serum markers on length of hospital stay (LOS) in days.

Table-1: Effects of individual variables and in combination on outcome measures

Acute response variable (s)	Total number (n = 9738)	Advanced imaging (CT/MRI)	Surgical intervention	ITU admission	Mortality	*p*-value
CRP						
CRP <10	5103 (53%)	873 (17%)	776 (15%)	135 (3%)	25 (0.5%)	0.0001
CRP ≥10 overall	4635: (47%)	1371 (30%)	1315 (28%)	342 (7%)	96 (2%)	
CRP 10-40	2466 (25%)	583 (24%)	601 (24%)	130 (5%)	24 (1%)	
CRP 41- 150	1585 (16%)	477 (30%)	481 (30%)	119 (8%)	42 (3%)	
CRP >150	584 (6%)	311 (53%)	233 (40%)	93 (20%)	30 (5%)	
ANC						
≤7.7 x 10^9	5523 (57%)	856 (15%)	937 (17%)	145 (3%)	34 (0.6%)	0.0001
>7.7 x 10^9	4104 (42%)	2244 (55%)	1122 (27%)	323 (8%)	9 (0.2%)	
Leukopenia	111 (1%)	29 (26%)	32 (20%)	9 (8%)	7 (6%)	
Albumin						
≥35 G/dL	8346 (86%)	4013 (48%)	1647 (20%)	317 (4%)	44 (0.5%)	0.0001
<35 G/dL	1392 (14%)	509 (37%)	444 (32%)	160 (11%)	77 (6%)	
CRP + ANC						
Normal	3517 (36%)	441 (12%)	482 (14%)	54 (2%)	10 (0.3%)	0.0001
Abnormal*	2518 (26%)	896 (36%)	828 (33%)	242 (10%)	65 (3%)	
CRP + Albumin						
Normal	4806 (49%)	800 (17%)	685 (14%)	114 (14%)	16 (0.3%)	0.0001
Abnormal**	1095 (11%)	427 (39%)	371 (34%)	139 (13%)	68 (6%)	
ANC + Albumin						0.0001
Normal	4937 (51%)	723 (15%)	744 (15%)	103 (2%)	17 (0.3%)	
Abnormal***	695 (7%)	321 (46%)	268 (39%)	109 (16%)	53 (8%)	
All 3 combinations						0.0001
Normal	3297 (34%)	397 (12%)	426 (13%)	477 (14%)	5 (0.015%)	
Abnormal	618 (6%)	292 (47%)	245 (40%)	98 (16%)	49 (8%)	

* CRP ≥10, ANC >7.7, **CRP ≥10, albumin <35 G/dL, *** ANC >7.7, albumin <35 gm/L

Table-2: sensitivity, specificity and predictive values of acute phase response variables.

Acute response variable (s)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
Advanced imaging						
CRP ≥10	61	57	30	83	1.41	0.68
CRP 10-40	40	69	24	83	1.29	0.87
CRP 41-150	35	79	30	83	1.67	0.82
CRP >150	26	94	53	94	0.43	0.68
ANC >7.7^9	72	73	54	85	2.66	0.38
Albumin	11	83	37	52	0.65	1.10
CRP + ANC	67	65	36	87	1.91	0.51
CRP + albumin	35	86	39	83	2.50	0.76
ANC + albumin	31	92	46	85	0.39	0.76
CRP+ANC+ albumin	42	90	47	88	0.47	0.64
Intervention						
CRP ≥10	63	57	28	85	1.47	0.65
CRP 10-40	44	70	24	85	1.47	0.94
CRP 41-150	38	80	30	85	1.9	0.74
CRP >150	23	57	40	85	0.53	1.35
ANC >7.7^9	55	60	27	83	1.38	0.75
Albumin	21	88	32	80	1.75	0.90
CRP + ANC	81	64	33	86	2.25	0.30
CRP + albumin	35	85	34	86	2.33	0.76
ANC + albumin	26	11	39	86	0.29	6.73
CRP+ANC+ albumin	37	89	40	85	3.40	0.71
ITU admission						
CRP ≥10	72	54	7	97	1.57	0.52
CRP 10-40	49	68	5	97	1.53	0.75
CRP 41-150	45	77	8	97	1.96	0.71
CRP >150	41	91	20	97	0.46	0.64
ANC >7.7^9	70	58	8	97	1.67	0.52
Albumin	34	87	11	96	2.62	0.76
CRP + ANC	81	60	10	98	2.02	0.32
CRP + albumin	55	83	13	98	3.24	0.54
ANC + albumin	51	89	16	98	4.63	0.55
CRP+ANC+ albumin	17	84	16	86	1.10	0.99
Mortality						
CRP ≥10	79	53	2	99.5	1.68	0.40
CRP 10-40	49	68	0.8	99.5	1.53	0.75
CRP 41-150	63	77	3	99.5	2.74	0.48
CRP >150	55	90	5	99.5	5.5	0.50
ANC >7.7^9	32	57	0.3	99.4	0.74	1.20
Albumin	64	86	6	99.0	4.47	0.42
CRP + ANC	87	59	3	99.7	2.12	0.22
CRP + albumin	81	82	6	99.6	4.50	0.23
ANC + albumin	76	88	8	99.6	6.33	0.64
CRP+ANC+ albumin	91	85	8	99.8	6.10	1.10

DISCUSSION

The liver predominantly produces CRP; it is a sensitive systemic marker of inflammation and tissue damage, acting via the complement pathway.[7] High levels are seen in infective and inflammatory conditions, malignant tumours and ischaemia. Serum levels start rising 4–6 hours after the stimulus, with an increase rapidly proportionate to the severity of the condition, and peak within 48 hours. The plasma half-life of CRP is 19 hours; therefore, serum levels fall quickly once inflammation subsides, and return to baseline within a few days.[8,9] The major role of neutrophils is to protect the body against infectious agents. During established infection, the neutrophil count remains elevated, with equal numbers in the marginal and the circulating pool.[10] Albumin is the most abundant plasma protein and the main regulator of plasma oncotic pressure. It is also regarded as an acute phase protein, which is known to fall with systemic inflammatory response syndrome due to increased capillary permeability.

Acute abdominal pain remains a diagnostic challenge. Initial blood tests including CRP, WBC count, ANC and serum albumin are routinely requested on admission for most patients but they are all non-specific. It is extremely difficult to predict the course and eventual outcome of such patients. Specific imaging like computed tomography helps in making an accurate diagnosis and facilitates appropriate treatment.[11,12] Studies have shown some conflicting results on the negative predictive value of the inflammatory markers in specific surgical conditions[13–15] however raised inflammatory markers have been shown to be associated with high likelihood of positive findings on CT scan, as well as high surgical morbidity and mortality[15–17]. CT scan is widely available and known to reduce negative laparotomy rate.[18] However, resources out of normal hours may be limited, whilst the risks of ionising radiation to younger or pregnant patients should be taken into account.[19]

Inflammatory marker testing is cheap and easily accessible in all surgical admissions. Overall baseline mortality in our patient cohort was 1.24%. Patients presenting with a normal admission CRP or albumin demonstrated a decreased mortality of 0.5%; with an isolated normal ANC a marginally higher mortality rate of 0.6% was identified.

A central finding of this study was that where individually elevated, each acute phase reactant was associated variously with significantly increased incidence of radiological imaging, surgical intervention, ITU admission and mortality.

For example, where serum CRP was raised beyond 150 (6% of patient cohort), an operation became almost three times more likely, escalation to an intensive care unit almost seven times more likely and risk of mortality rose four times compared with baseline mortality. Leucopoenia appeared in just 1.1% of the patient cohort but was associated with a 6% mortality rate compared with the baseline population of 1.24%. Isolated hypoalbuminaemia accounted for 14% of patients, with risk of admission to an intensive care environment rising from 4% to 11% and risk of mortality rising to 5.5% - compared to 0.5% with a normal albumin.

Interestingly, in combination these adverse prognostic associations appeared magnified. For patients with all three markers (CRP, ANC and albumin) elevated there was a highly significant increase in mortality (8%), compared to patients whose baseline inflammatory markers were normal (0.015%). To further quantify this the patient population presenting with a trio of normal reactants were 100 times less likely to die than the baseline population, and 8 times more likely to die when all were abnormal.

Therefore, it seems inflammatory marker testing may be used to simply aid stratification of those patients potentially needing surgery, ITU admission or at higher risk than normal of dying. In such high-risk patient groups, early diagnosis and treatment can be facilitated by prioritising early clinical and radiological assessment when resources are challenged.

CRP testing is otherwise used to stratify patients with acute pancreatitis and is known to predict outcomes such as severity of attack, likelihood of pancreatic necrosis and in-hospital mortality.[20] It is also widely used as a predictor of anastomotic leak and other post-operative septic complications in patients undergoing elective colorectal surgery, and is therefore an aid in the safe discharge of these patients.[21] Finally, CRP is a well-known adjunct in identifying patients with increased disease activity that will end up needing a colectomy in the context of inflammatory bowel disease as well as predicting their response to biological therapy.[22]

Identifying complex surgical patients who have higher morbidity and mortality at an earlier stage will allow the resources to be directed appropriately and earlier intervention has the potential to reduce morbidities and prolonged hospital stay.

CONCLUSIONS

This study was carried out to help identify higher risk patients using both isolated and a combination of acute phase response variables. We have demonstrated that obtaining admission acute phase reactants allows patient stratification to be performed

prior to clinical assessment. We would suggest patients presenting on an acute surgical take with a CRP >150, leucopenia, or the trio of abnormal CRP, albumin and ANC are assessed promptly as they represent high risk surgical patient populations who may require surgery or are at risk of adverse outcomes.

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AUTHORS' CONTRIBUTION

SUK: Substantial contribution to conception, design, interpretation of data, drafting, revising, and final approval to be published. JYS: Substantial contribution to design, interpretation of data, drafting, and revising the manuscript. AP: Substantial contribution to design, interpretation of data, drafting, and revising the manuscript. MA: Substantial contribution to design, interpretation of data, drafting, and revising the manuscript. SZ: Substantial contribution to design, interpretation of data, drafting, and revising the manuscript. PWW: Substantial contribution to conception, design, interpretation of data, drafting, revising, and final approval to be published

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