Clinical Study

Eosinopenia as a Prognostic Marker in Patients with Peritonitis

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Introduction. Eosinopenia has been, recently, found to have strong association with inflammatory-syndrome-associated bacterial infectious diseases. This prompted us to investigate its use as a prognostic marker in perforation peritonitis patients. **Methods.** A prospective study of perforation peritonitis patients admitted to the surgical wards at a teaching hospital in Central India was conducted. Jabalpur prognostic score (JPS, a simplified prognostic score for developing countries), C-reactive protein (mg/dL) levels, and absolute eosinophil counts (cells/cmm) were measured on admission. Their correlation with inpatient mortality was evaluated. **Results.** 94 consecutive patients were studied, peptic ($n = 55$) followed by ileal, colonic, and appendicular perforations were the commonest cause of peritonitis. 13/94 died; ileal perforations had the highest ($n = 6/34$, 17.6%) mortality. When correlated with mortality, univariate analysis showed JPS, CRP, and AEC to be accurate prognostic markers ($P < 0.00001$), while multivariate analysis showed only AEC to be accurate ($P = 0.03$). At a cut-off value of 8, JPS showed sensitivity of 77%, a specificity of 85.1%, positive predicted value (PPV) of 55%, negative predicted value (NPV) of 95%, and area under receiver operating curve (AUROC) was 0.86. CRP level, at a cut-off value of 7.4, yielded sensitivity of 92.3%, specificity of 79%, PPV of 41%, NPV of 98%, and AUROC was 0.93. At a cut-off value of 45, the sensitivity of the AEC was 92.3%, specificity of 92.5%, PPV 85%, NPV of 99%, and AUROC was 0.96. **Discussion.** Eosinopenia on admission is a prognostic marker of mortality in patients with peritonitis.

1. Introduction

Peritonitis is the commonest cause of sepsis in patients admitted in surgical wards in developing countries. Cost constraints prevent routine use of expensive tests like procalcitonin assay in developing countries. Many recent reports have shown eosinopenia as a marker for sepsis [1–5]. This prompted us to prospectively assess the diagnostic value of eosinopenia as a prognostic marker in perforation peritonitis patients.

2. Material and Methods

This prospective study was performed on patients with peritonitis consecutively admitted from July 2008 to September 2009, to General surgery wards in, NSCB government Medical College, Jabalpur, Madhya Pradesh, India. Study protocol was approved by the hospital ethics committee, as per hospital regulations. Informed consent was not taken because this observational study did not require any deviation

from routine medical practice. Children under the age of 14 years were not included in this study.

Details of each case were recorded with special reference to following factors: age, comorbid illness, perforation operation interval, preoperative blood pressure, preoperative heart rate, and serum creatinine. All blood samples were drawn pretreatment at the time of admission. These parameters constitute the Jabalpur prognostic score (JPS), a simplified prognostic score for developing countries as it does not use expensive and sophisticated investigations (Table 1) [6]. Definitions of co-morbid illness were according to the APACHE II scoring system [7].

Blood samples were taken in tubes containing ethylene diaminetetraacetic acid anticoagulant on admission and sent for examination. The white blood cell count, the absolute eosinophil cell count (AEC), and the C-reactive protein (CRP) level were recorded on admission to the ward. AEC was done by using Neubauer counting chamber. To determine the CRP level, blood samples were drawn into green-top vacutainer tubes containing heparin as anticoagulant and measured by a latex agglutination test.

TABLE 1: Jabalpur prognostic score [6].

Factor	Score						
	0	1	2	3	4	5	6
P-O interval (Hrs)	<24	25–72	73–96	97–120	>120	—	—
Mean systolic BP (mm Hg)	70–109	—	50–69 or 110–129	130–159	<49 or >160	—	—
Heart rate/min	70–109	—	55–69 or 110–139	40–54 or 140–179	<39 or >180	—	—
Serum creatinine (mg/dL)	0.6–1.4	—	1.5–1.9	2.0–3.4	>3.5	—	—
Age (years)	<45	—	45–54	55–64		65–74	75 or more

P-O interval: perforation-operation interval.

Comorbid illness, if present, is given a score = 5, none if not (Definitions of co-morbid illness were according to the APACHE II scoring system) [7].

Total score: perforation operation interval score + age score + blood pressure score + heart rate score + creatinine score + comorbidity score.

Maximum score possible is 27.

All patients underwent conventional surgery after optimizing their condition. For gastroduodenal perforation, surgery included patch omentopexy, peritoneal lavage, and drainage. Ileal perforations were repaired/exteriorized/resected; proximal diversion stoma was done as needed and decided by operating surgeon, peritoneal lavage, and drainage [8]. Appendicular perforations were managed by appendicectomy, peritoneal lavage and drainage. Colonic perforations were managed by resection with anastomosis/repair of perforation and proximal defunctioning stoma formation as needed, peritoneal lavage and drainage. Post-operatively, all patients were managed in the general surgical wards, as intensive care and/or ventilator support is rarely available.

Patients were followed post operatively in terms of duration of stay in hospital, any morbidity and mortality (defined as “in hospital mortality,” any death occurred in the same hospitalization). Survival or inpatient mortality was considered the end point in this study.

Data were processed and analysed using software SPSS 11.5 for Windows. All values were expressed as mean $\pm$ standard deviation/median. Mean (for normally distributed samples) and median (for not normally distributed samples) of various parameters were compared using *t*-test or Mann-Whitney tests, respectively, amongst survivors and nonsurvivors. Logistic regression test and ANOVA (analysis of variance) test were used for multivariate analysis.

Cut-off values were calculated that represented the best discrimination as derived from the receiver operating characteristic (ROC) curve. Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of each parameter were calculated according to standard methods using these cutoffs. ROC analysis was carried out for diagnostic accuracy of various parameters as expressed by area under the receiver operating characteristic curve (AUROC); an AUROC 1.0 was considered perfect discrimination and 0.5 was considered equal to chance. The critical levels of significance of the results were considered at 0.05 levels.

3. Results

94 consecutive patients (82 male) were prospectively included in this study. Age of patients ranged from 16 years to 75

years (mean = 36.9, SD = 13.9). Other than eosinopaenia, we did not find any significant changes in other components of complete blood count. Demographic details of these patients with their JPS, CRP, and AEC values are given in Table 2. Peptic perforations were commonest (55/94, first part duodenum $n = 5/55$ /prepyloric $n = 50/55$), followed by ileal (34/94) and colonic perforations (3/94, 2 caecal perforations and 1 sigmoid, all due to volvulus). Ileal perforations were mostly due to typhoid (26/36) or trauma (6/36). Appendicular perforations were only 2 in numbers. Ileal perforations had the highest (17.6%, 6/34) mortality (Table 3).

All three parameters, JPS ($t = 5.7$, $DF = 17$, $P = 1.1 \times 10^{-5}$), CRP ($t = 6.6$, $DF = 13$, $P = 8.5 \times 10^{-6}$), and AEC ($t = -13$, $DF = 38$, $P = 6.3 \times 10^{-13}$), correlated strongly with mortality, as both mean and median scores of survivors ($n = 81$) were significantly different from those who died ($n = 13$, 13.8%), as seen in Table 4 and Figure 1.

An increasing JPS correlated with increasing mortality (Figure 2). Further analysis of data showed that increasing JPS also correlated with increasing CRP, and decreasing AEC (Figure 3). Mean/median values of CRP and AEC differed significantly ($P < 0.0001$) between survivors and those who died in middle- and high-risk groups (Table 4). Similar comparison could not be made in low risk group as there was no mortality in this group. On multivariate analysis only AEC ($P = 0.03$) was found to be significant determinant of mortality (Table 2).

When prognostic accuracy of JPS, CRP, and AEC was compared, AEC was found to have the highest discriminative value, with an AUROC of 0.96 (95% CI = 0.94–1.0), followed by CRP (AUROC = 0.93, 95% CI = 0.89–1.0) and JPS (AUROC = 0.86, 95% CI = 0.79–0.96) as seen in Table 5. Cut-off values for each were calculated on the basis of ROC and were chosen at the point of highest sensitivity and specificity. At a cut-off point of <45, AEC had the highest sensitivity (92.3%), highest specificity (92.5%), and highest predictive value of positive test (85%), highest predictive value of negative test (99%), lowest false positive % (2%), and lowest false negative % (8%) (Table 5).

4. Discussion

Eosinopenia, *per se*, is very rare [9] and has been traditionally associated with enteric fever [10–12]. A rapid and

TABLE 2: Demographic data of patients with perforation in the present study.

Parameter	Survivors (N = 81)						Dead (N = 13)						D'Agostino and Pearson omnibus normality test	P value (t-value) (df = 92) Unpaired t-test comparing means	P value (Mann- Whitney test comparing medians)	Multivariate Analysis (logistic regression test)
	Mean (SD)	Range	95% CI	Median	Mean (SD)	Range	95% CI	Median	Mean (SD)	Range	95% CI	Median				
Age (years)	37.4 (14.2)	16–75	34.2–40.6	35	34 (11.7)	22–65	26.9–41.1	30	Not normal	0.42 (0.8)	0.47	0.47				
M:F	70:11				10:3											
Perforation-operation interval (hours)	83.8 (47.4)	12–240	73.2–94.3	80	102.8 (54.0)	40–240	70.1–135.4	102	Not normal	0.19 (1.3)	0.12	0.42				
Mean blood pressure (mm Hg)	81.4 (16.9)	40–118	77.6–85.1	84	59.7 (20.5)	40–94	47.3–72.1	60	Normal	<0.0001 (4.1)	<0.0012	0.63				
Heart rate	103.1 (13.1)	72–140	100.3–106.1	100	114.4 (11.1)	100–140	107.7–121.2	112	Normal	0.0043 (2.9)	0.003	0.73				
Creatinine (mg/dL)	1.21 (0.43)	0.6–3.2	1.1–1.3	1.0	1.67 (0.45)	0.7–2.6	1.3–1.9	1.7	Normal	0.0007 (3.5)	0.001	0.43				
Co-morbid illness	2/13 (15.3%)					2/81 (2.4%)										
AEC (cells/mL)	73.4 (17.9)	38–110	69.4–77.4	72	35.5 (7.6)	24–55	30.7–40	34	Not normal	<0.00001 (7.4)	<0.00001	0.03				
CRP (mg/dL)	6.9 (0.5)	5.2–8	6.7–7.0	7	8.9 (1)	7.2–10.2	8.2–9.5	9.1	Normal	<0.00001 (9.9)	<0.00001	0.24				
JPS	4.8 (2.6)	38–110	4.2–5.3	4	9 (2.4)	5–14	7.5–10.4	9	Normal	<0.00001 (5.3)	<0.00001	0.41				

AEC (cells/cmm): absolute eosinophil count.
CRP (mg/dL): C-reactive protein.
JPS: Jabaipur prognostic score.

FIGURE 1: Box and whisker's plot showing JPS, CRP, and AEC values of survivors and those who died. Median is shown as horizontal line. 25th–75th percentile and 5th–95th percentile are depicted by box and error bars, respectively. The dots represent the outliers.

TABLE 3: Causes of perforation in the present study and their JPS, CRP, and AEC values.

Perforation type	<i>n</i>	Died (%)	JPS			CRP			AEC		
			Mean	(SD)	Range	Mean	(SD)	Range	Mean	(SD)	Range
Peptic	55	7 (12.7)	5.3	3.1	0–14	7.1	1	5.2–10.2	69.6	21.6	24–110
Ileal	34	6 (17.6)	5.2	2.7	1–11	7.1	0.9	5.8–10	65.7	22.1	28–105
Appendicular	2	0	6.5	0.7	6–7	7.2	0.28	7–7.4	50.5	3.5	48–53
Colonic	3	0	6.3	5	2–12	6.8	0.4	6.4–7.3	79.3	6.1	74–86

AEC (cells/cmm): absolute eosinophil count.

CRP (mg/dL): C-reactive protein.

JPS: Jabalpur prognostic score.

TABLE 4: Comparison of different parameters between survivors and those who died and their significance.

	Survivors (N = 81) Mean (SD, 95% CI)	Dead (N = 13) Mean (SD)	Survivors (N = 81) Median	Dead (N = 13) Median	t-test (df)	P value	D'Agostino and Pearson omnibus normality test	P value Mann-Whitney test comparing median (nonparametric test)
JPS	4.8 (2.6, 4.1–5.3)	9 (2.4, 7.5–10.4)	4	9	5.7 (17)	0.000001	Normal	<0.00001
CRP	6.9 (0.5, 6.7–7)	8.9 (1, 8.2–9.5)	7	9.1	6.6 (13)	0.0000008	Normal	<0.00001
AEC	73.4 (17.9, 69.4–77.4)	35.5 (7.6, 30.7–40)	72	34	–13 (38)	0.000000000000006	Not normal	<0.00001

AEC (cells/cmm): absolute eosinophil count.
CRP (mg/dL): C-reactive protein.
JPS: Jabalpur prognostic score.

TABLE 5: Prognostic accuracy of different parameters.

Parameter	JPS	CRP	AEC
Cut-off value	>8	>7.4	<45
Sensitivity % (95% CI)	77 (46.1–94.9%)	92.3 (63.9–99.8%)	92.3 (63.9–99.8%)
Specificity % (95% CI)	85.1 (76–92%)	79 (68.4–87.2%)	92.5 (91.3–99.7%)
Predictive value of positive test %	55	41	85
Predictive value of negative test %	95	98	99
Area under ROC (95% CI)	0.86 (0.79–0.96)*	0.93 (0.89–1.0)*	0.96 (0.94–1.0)*

* $P < 0.0001$.

Note: sensitivity, specificity, and predictive values were calculated for the cutoff, which represented the best discrimination as derived from the ROC curves.

AEC (cells/cmm): absolute eosinophil count.

CRP (mg/dL): C-reactive protein.

JPS: Jabalpur prognostic score.

FIGURE 2: Bar diagram showing correlation of increasing JPS with increasing mortality.

persistent decrease in the numbers of circulating eosinophils is a distinctive aspect of physiological response to acute inflammation [13–15]. It has been speculated that eosinopenia may be the result of migration of eosinophils into the inflammatory site itself due to release of small amounts of the chemotactic factors of acute inflammation into the circulation [13]. The precocity and precision with which the eosinophil trend follows the phases of the infection underline the value of the assay of these cells as a reliable parameter for monitoring acute infection [15]. Many recent studies have found eosinopenia to be quite accurate marker of bloodstream infections in critically ill patients [1–3]. Abidi et al. found eosinopenia a better marker than CRP, but others found CRP and procalcitonin assays better markers than eosinopenia [1–3].

However, some authors have questioned its capacity to discriminate infection from controls [4, 5]. These observations only confirm that testing for goodness of fit with the data, to which it is being applied, is a must for any prognostic scoring system or biomarker. Geographical variation in the different patient subsets makes such testing and validation mandatory. Since each surgical/medical unit serves a different patient population, each score system/biomarker must

be calibrated and may have different cut-off values (disease or setting specific) in the individual hospital to ensure that the model is applicable for the patient material involved, before it is accepted as quality standard [16, 17]. Clearly, the septic syndrome is far too heterogeneous and complex to be reduced to a single cutoff of any surrogate marker. Different microbes might induce distinct responses, resulting in a variable up/downregulation of circulating biomarkers and mediators [18].

Ours is the first study using eosinopenia as a marker for survival in patients with peritonitis. Sepsis-related research in developed countries is focused on refining the use of procalcitonin, widely acknowledged as the most promising biomarker for sepsis [19, 20]. Other efforts include starting national/international level educational programs and registries to improve outcome after severe sepsis [21–23]. On the other hand, developing countries are struggling to find affordable ways to identify the high-risk patient, who then can be offered intensive therapy from limited resources [24, 25]. JPS was developed in response to this need as it does not use expansive investigations, making it a user-friendly risk stratification system and therefore can be used at a wider scale. Addition of AEC can identify patients with better prognosis at higher JPS (Figure 3) but small sample size in high-risk group limits the significance of this observation.

We have used ROC/AUROC to compare the diagnostic accuracy of JPS, CRP, and AEC (Table 5) as it compares test accuracy over different thresholds for positivity and provides tools to select optimal models for decision making [26].

Limitations of our study include small sample size in high-risk group from a single centre. Cost and methodological constraints prevented us from getting culture for fungal infections, which have been shown to affect prognosis adversely in our patient population [27].

AEC allows timely identification of patients at high risk for sepsis-related mortality in patients with peritonitis. As eosinophil count is routinely done as part of complete blood count, it does not entail any extra effort or expenditure. Hence, AEC not only has the necessary sensitivity and specificity but also has the “ease” and “cost effectiveness” not seen with other markers for sepsis. The concept is clinically very appealing and warrants larger prospective studies.

FIGURE 3: Bar diagram showing mean serum CRP and AEC levels at various JPS levels. Mean (SD) is shown inside the boxes. Unpaired t -test and its significant value are shown on the top of bars. Y error bars are showing range of data.

Conflict of Interests

The authors declare that they have no conflict of interests.

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