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Utility of plasma fibronectin versus clinical scorings in intra-abdominal infection– Our experience

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Abstract
Even with advanced intensive care support the mortality of intra-abdominal infections are still substantial. Predicting mortality and morbidity risk based on severity of illness at time of admission is essential for early intervention and proper use of resources in developing countries. Systemic scores like APS, APACHE 2 and Sepsis scores were used to assess the measure of severity of illness in relation to physiological response in western countries. In this study, we have studied the scoring systems use in Indian population and the use of plasma Fibronectin levels in predicting mortality.
All the three scales (APS, APACHE 2, Sepsis score) can be used in predicting mortality in patients with intra-abdominal infections ($p<0.05$). Plasma fibronectin (Fn) levels have no correlation with age and gender but have significant correlation between survivors and non-survivors. Coefficient of correlation between plasma Fn levels and various scores is statistically significant ($p<0.01$). Hence any of the scores/ Fn levels can be used to determine the mortality risk based on availability.

Keywords: intra-abdominal infection, aps, apache 2, sepsis score, fibronectin

Introduction
Although the surgeons have always been concerned with the diagnosis and treatment of infection, the past decades have shown a burst of activity and investigations into the pathophysiology, diagnosis, and treatment of severe surgical infections. This has included many clinical reports as well as basic laboratory pursuits of underlying pathophysiological mechanisms of bacterial infection, bacterial virulence factors and nature of host response. The greatest efforts have been directed towards intra-abdominal infections. Mortality and morbidity resulting from intra-abdominal infections are still substantial. [1, 2, 3, 4] Mortality remains extremely high in patients suffering from advanced surgical sepsis despite recent advances in intensive care support. Those patients who succumb, frequently follow a recognizable pattern as they pass through the later stages of sepsis leading to "Multi organ dysfunction syndrome". [5, 6] Treatment available to break this downward spiral of failing organs often proves to be ineffective and the mortality usually is greater than 50 percent.
Classification of patients according to mortality risk is essential for early intervention and proper use of resources. But it is impeded by the heterogenous causes of intra-abdominal infections and the wide range severity of illness that they can cause. A measure of severity of illness was expected to provide a better basis for mortality risk classification. [7, 8, 9] Scores like Sepsis Score [7, 8], Acute Physiology Score (APS) [9] and APACHE 2 score [10, 11] helps in determining the severity of illness in case of intra-abdominal sepsis.
But the recognition of host defence failure and in particular that of reticuloendothelial system during sepsis has generated interest in underlying mechanisms. In sepsis the phagocytic process is sharply curtailed, as evidenced in both animal and human studies. [12] One major cause of reduced phagocytosis may be the loss of opsonic proteins, since decreased levels of circulating fibronectin have been demonstrated in patients with sepsis. [13, 14] Fibronectin is an alpha-2 glycoprotein which is strongly opsonic increasing the phagocytic action of RES cells by a factor of 50. Determination of plasma Fibronectin level has been claimed to be of prognostic value with persisting lower values found in survivors. [15] Others, however, have found fibronectin depletion to be merely part of generalised predominance of protein metabolism over synthesis with no prognostic value [16]. Hence an effort in this study has been made to determine the effect of sepsis on plasma fibronectin concentrations and to correlate the plasma fibronectin levels with severity of sepsis determined by Sepsis Score, Acute Physiology Score (APS) and APACHE 2 score in intra-abdominal sepsis.

Materials and Methods
Aims and objectives
1. To estimate the levels of plasma fibronectin in patients with intra-abdominal sepsis
2. To estimate the severity of illness by APS, APACHE 2 and Sepsis Score in patients with intra-abdominal sepsis.
3. To correlate plasma fibronectin levels with severity of illness and the patient outcome in terms of morbidity and mortality.

Design: Prospective Data collection and review
Setting: Emergency surgical services/ surgical ICU of a tertiary care hospital in India
Duration: August 1992 to November 1993

Inclusion criteria
a. Intra-abdominal sepsis resulting from inflammation, perforation, abscess, ischemia of intra-abdominal organs

Exclusion criteria
a. infections confined solely to the genitourinary tract
b. traumatic peritonitis

Evaluation
Detailed history, systemic examination, various laboratory investigations and vital function parameters were recorded to calculate the modified APS, APACHE 2 score and sepsis score on each patient during the first 24 hours following admission and on 3rd, 7th, and 14th day if necessary. Plasma fibronectin was measured on 0, 3rd, 7th and 14th day, if necessary, by ELISA technique. Normal human plasma fibronectin values were taken as 300-400 microgram/ml.
2.4ml of patient's blood (EDTA) was withdrawn and was frozen till assayed. Wells in a microliter plate were coated with 1 microgram of gelatin per millilitre. Immediately before the assay, the plate was washed twice with 0.9% NaCl containing 0.15% Tween-20. Fibronectin standard and unknown samples were serially diluted and 100 microliters added to each well. The optimal dilution was worked out by chekabond titration. The plate was incubated at room temperature for 3 hours and then washed three times with NaCl tween. A constant amount of enzyme labelled anti-Fn was added to each well, and the plate was again incubated. Finally, after washing, the enzyme activity was measured.

Outcome
Measured plasma Fn was correlated with severity of illness and clinical scorings. The final outcome in relation to measured plasma Fn and clinical scoring was categorised as follows:
A. Non-survivor
B. Survivor with complication
C. Survivor without complication

Statistical analysis
The results of the study were analysed by applying Student T test for probability values and Chi- square test for significance. The logistic regression equation supplied by Knaus *et al* shown in Leneshow *et al*. (1987) was applied to the data and probability of mortality risk was calculated.

Ethical consideration
The investigations planned at admission are done as a routine in all major intra-abdominal sepsis. These were repeated on day 3, 7 and 14 if only necessary for proper care of patient. Therefore, this project is justified ethically.

Results
Patients with intra-abdominal sepsis underwent relevant investigations at admission, day 3 and day 7. A total of 60 patients were included in the study of which 3 were expired before relevant investigations could be sent. Hence, a total of 57 patients were included in the study. Of which 12 patients succumbed to the illness and 45 patients survived. Of the 45, 18 survived without complications and 27 survived with complications. The overall mortality was 21% and morbidity was 47%. Smoking and alcohol consumption are the commonest risk factors (26% & 28% respectively). Duodenal perforation (35%), ileal perforation (32%) and appendicular perforation (14%) are the common aetiology for intra-abdominal sepsis. Pulmonary infections are the commonest complications. Patients with complications had a longer stay in hospital with a mean of 15 days (range, 0-63).
APS, APCAHE 2 and Sepsis Score were calculated individually and ROC was determined using multiple logistic regression analysis for each. When comparing the score values between the survivors and non survivors, survivors without complications and survivors with complications, the difference was statistically significant in all three scores individually and the correlation of coefficient values between all three scales was also statistically significant at 1% (0.01). (Table 1)
The mean plasma fibronectin concentration of control group was 300 ±100 µg/ml. The plasma fibronectin concentration in septic groups ranged from 8 to 106 µg/ml. The overall mean value of survivors was 73 ± 12.30 µg/ml. Fibronectin concentration was not statistically significant with age and gender. Comparing the values between survivors and non survivors, survivors with and without complications, results were statistically significant (p=<0.05). When serial plasma fibronectin was measured on day 3 and day 7, patients with low concentrations on admissions and found to have very low values on day 3 and day 7 eventually succumbed (Table 2). Also, patients with initial high concentration, found to have higher values on day 3 and 7 and eventually survived, thus highlighting the value of serial plasma Fn as a predictor of mortality. Coefficient of correlation was applied to find the relationship between plasma fibronectin and various scoring systems which are statistically significant (Table 3). Hence in non survivors with high APS, APACHE 2 and sepsis scores, plasma Fn concentration was found to be significant lower and vice versa.

Table 1: Correlation between APS, APACHE 2, Sepsis Score

	APS	APACHE 2	Sepsis Score
APS	1.000	0.746	0.449
APACHE 2	0.746	1.000	0.648
Sepsis Score	0.449	0.648	1.000

Table 2: Trend in Serial Plasma Fibronectin

Mean Day	Survivors without complications	Survivors with complications	Non- survivors
Day 1	77	70	21
Day 3	125	90	14
Day 7	186	119	10

Table 3: Correlation of fibronectin with APS, APACHE2 and Sepsis Score

Scoring system	r	p
APS	-0.437	<0.01
APACHE 2	-0.600	<0.01
Sepsis score	-0.262	<0.05

Discussion

Intra- abdominal infections are recognised by surgeons to be among the most difficult infections to diagnose early and treat effectively. Mortality remains extremely high in patients suffering from advanced surgical sepsis despite recent advances in intensive care support. APS, APACHE 2 and Sepsis score are scores based on physiologic response to underlying insult. The accuracy of these scores in correlating physiologic response to the outcome of abdominal infection has been prospectively validated in the ICU setting in western countries as well as Asian centres (in Hongkong). An attempt has been made in this study to determine the value of APS, APACHE 2 and Sepsis score as severity of illness classification system and Plasma Fn as a predictor of outcome of patients with severe intra-abdominal sepsis.

Knaus *et al*. [11] tested APS on 795 patients in a multicentre trial and values ranged between 0-50 with overall mean of 19 and mean of 24 in non survivors. In our study the APS values ranged between 0-47 with a overall mean of 20 and mean of 27 in non survivors.

Bohen *et al*. [4] tested the validity of APACHE 2 system in 100 patients with value ranging from 0 to 71. Mean of non survivors was 18 and survivors was 11. In our study, all results were comparable with above study. Overall mean of 10±6.85 with 18±5.04 in non survivors and 8 in survivors, serial APACHE 2 highlighted the value of score as a predictor of mortality as there was serial rise in values in day 3 and 7 in non survivors and fall in values in survivors. In our study, patients with score more than 10 had a higher risk of mortality and post-operative complications.

Elebute and Stoner [7] graded the severity of sepsis using sepsis score with a value range of 0-45. Dominioni *et al*. [17] has examined the sepsis score in more detail and have used serial sepsis score in predicting mortality. The serial score of patients who died subsequently remained high and fallen in survivors. Similar relation was seen in our study when serial SS was recorded on day 3 and 7. Sepsis score is based more on clinical variable than laboratory data and is easy to apply whereas APS and APACHE 2 are not simple to obtain and cannot be used if the assessment of chronic health status is not available.

Fibronectin is a plasma glycoprotein of importance in host defence by augmenting neutrophil and macrophage phagocytosis and participates in clearance of noxious material from circulation by RES. Low plasma levels have been reported in patients with septic complications following surgery, trauma or burn injury. Stathakis *et al*. determined normal levels of serum plasma Fn concentration as 325±70 µg/ml. Fredrik *et al* and O'Connell *et al*. studied plasma Fn levels with variables like age, gender etc and found to have no correlation. In our study also there was no correlation between age and gender. Significant correlation was found between survivors and non survivors. Serial plasma Fn levels rise in survivors and fall in non survivors which is consistent with Wilson *et al*. [18] When Fn values were correlated with APS, APACHE 2 and Sepsis score, all values were statistically significant and hence we conclude that both plasma Fn and various scoring systems (APS, APACHE 2 and Sepsis score) can predict the mortality in patients of intra-abdominal sepsis.

Limitations of the study

As intra-abdominal infections worsen at a rapid rate, the time of presentation from symptom onset determines the outcome which was included in this study. The sample size is relatively less.

Conclusion

Fifty-seven patients of intra-abdominal sepsis were studied using APS, APACHE 2, Sepsis Score and plasma Fibronectin levels were studied to determine the severity of illness and correlate this with the outcome. This prospective study validates the use of APS, APACHE 2, Sepsis Score and plasma Fn levels in assessing the severity of illness and predicting the outcome. Serial assessment using these scores can pick up patients in whom more aggressive therapy is required. Hence anyone of the above scores/ Fn levels which are easily available can be used to assess and monitor patients of intra-abdominal sepsis.

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