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Original Article

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C-Reactive Protein Trends and Prediction of Anastomotic Leak in Esophageal Atresia

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Abstract

Objective: C-reactive protein (CRP), an acute phase reactant, has been proposed as an early biomarker for anastomotic leak in such patients. ***Design:*** Retrospective, single center, observational study. ***Patients:*** A cohort of 202 postoperative patients, with serum CRP levels measured on postoperative day (POD) 1, 3, and 5. ***Methods:*** Patients were stratified according to the presence of anastomotic leak (n=41) versus no leak (n=161). Group differences were assessed, and analysis was performed to evaluate diagnostic accuracy and determine optimal cutoff values. ***Result:*** Mean CRP levels were significantly higher in patients with anastomotic leaks compared to those without, with differences becoming most pronounced after POD 3. Statistical testing confirmed significant differences at POD 1 ($p<0.01$), POD 3 ($p<1\times10^{-9}$), and POD 5 ($p<1\times10^{-15}$). ROC analysis demonstrated increasing discriminatory power across time points: AUC 0.64 (POD1), 0.85 (POD3), and 0.94 (POD5). Optimal CRP cutoffs were identified as 2.7 mg/dl (POD1, sensitivity 61%, specificity 70%), 6.7 mg/dl (POD3, sensitivity 68%, specificity 89%), and 7.5 mg/dl (POD5, sensitivity 93%, specificity 98%). ***Conclusion:*** Elevated postoperative CRP levels, particularly on POD3 and POD5, are strongly associated with the occurrence of anastomotic leak. A CRP threshold of approximately 7 mg/dl on POD3 may serve as an early warning indicator, while levels above 7.5 mg/dl on POD5 provide excellent diagnostic accuracy. Routine CRP monitoring can therefore facilitate earlier detection and timely intervention in patients with anastomotic complications.

Keywords: ***tracheoesophageal fistula, diagnosis, c-reactive protein, anastomotic leak, neonates.***

Introduction

Esophageal atresia with tracheoesophageal fistula (EA/TEF) is a congenital anomaly of esophagus with incidence of 1 in 3000 to 5000 live births [1]. EA/TEF is classified of the presence and location of tracheoesophageal fistula (TEF). Type 'C' being the most common, in which there is proximal esophageal atresia with fistula between distal esophagus and trachea, which makes around 85% of EA/TEF cases [2]. Although great progress has been made in the neonatal intensive care which has significantly reduced the mortality and morbidity associated with prematurity, sepsis or pneumonia. Anastomotic leak (AL) and associate congenital anomalies especially complex cardiac anomalies are still important cause of mortality in immediate postoperative period.

Anastomotic leak is defined as esophageal dehiscence caused by poor anastomotic healing after esophageal reconstruction surgery. Anastomotic leak increases length of stay (LOS) and is a fatal complication of esophageal reconstruction surgery [3]. Thus, there is a need for biological marker to predict this dreadful complication before its manifestation, this may facilitate prompt intervention and potentially reduce the severity of the complication, and improving the final outcome.

The study aims to evaluate the role of C-reactive protein (CRP), a biological marker of inflammation, in predicting adverse event like AL after esophageal reconstruction surgery in EA/TEF type C patients. Temporal association of variation in CRP levels postoperatively and anastomotic leak is to be determined, which may help in early prediction of AL.

Methods

This is a prospective, single center observational study on Esophageal atresia with tracheoesophageal fistula patients (n=201) managed over a period of 12 months (April 2024 to March 2025) was conducted after clearance from the Institute Ethics Committee.

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All patients with EA/TEF type-C, who have undergone single stage primary repair by esophageal anastomosis were included in study. Patients with other congenital anomalies along with EA/TEF, AL leak detected before postoperative day (POD) 3, and length of hospital stay <3 days were omitted from the analysis.

Observation parameters included the patient's demographics (age at presentation, sex and birth weight), clinical, laboratory and radiological parameters. Data was recorded in predesigned excel (Microsoft® Excel version 16.48; Microsoft 365 subscription) charts. Baseline serum CRP levels were assessed prior to surgery. Follow-up CRP levels were assessed at POD 1,3, and 5. Contrast esophagography was done on POD 5 using water soluble contrast agent.

Anastomotic leak was defined as clinical leak (saliva in draining intercoastal chest tube) or leak demonstrated by esophageal contrast study (esophagography).

Statistical Analysis was performed using SPSS (version 26.0 for Windows). Data were expressed in Mean and range. Data analysis was done using Mann-Whitney U test, Chi square test and Student's t-test were applied. A probability of $P < 0.05$ was considered statistically significant. The trend of levels of CRP were studied, and the temporal relationship of changes in values with anastomotic leak were analyzed.

Results

The study cohort comprised of 202 patients with EA/TEF type C. The general features of the patients with risk factors were listed in Table 1. There were 98 male and 104 females. Mean gestational age was 36.11±.05 weeks, and mean birth weight was 2.3±.05 kg. The incidence of Anastomotic leak was 20.3% (41 out of 202). Out of 41 leak patients, 9, 10, and 22 were identified on POD 4, POD 5 and POD 6 respectively. The study showed gender had no impact on the anastomotic leak (p value = .75). Birth weight had been inversely related to anastomotic leak (p=.002825) while more the gap length, more was the risk of anastomotic leak (p=.01904). Higher the post-natal age higher the chances of anastomotic leak (p=.038).

The baseline serum CRP level (n=202) was 0.98mg/dl (min: <0.5mg/dl; max: 10.3mg/dl). The reference level for serum CRP being <1.0 mg/dl. Around 28.2% (57 in 202) patients had levels above baseline. The baseline CRP levels in both groups, leak and non-leak, were not discriminatory.

In non-anastomotic leak group (n=161), there was 2 times increase in levels on POD 1(mean: 2.3mg/dl; min: <0.5mg/dl; max: 14.2mg/dl); the peak CRP was observed on POD-3 (mean: 3.6mg/dl; min: <0.5mg/dl; max: 9.8mg/dl) followed by a subsequent decline on POD 5 (mean: 2.3mg/dl; min: <0.5mg/dl ; max: 10.3mg/dl) [**Figure 1**]. In anastomotic leak group (n=41) , a three-fold increase in levels was seen on POD 1(mean: 3.3mg/dl; min: <0.5mg/dl; max: 9.4mg/dl); on POD-3 (mean: 8.6mg/dl; min: 1.4mg/dl; max: 17.8mg/dl) and on POD 5 (mean: 13.9mg/dl; min: <0.5mg/dl ; max: 25.8mg/dl) [**Figure 1**]. Mean CRP values in the leak group were consistently higher than in the non-leak group across all postoperative days (p<.001).

The CRP level of 2.7mg/dl or above, had modest sensitivity (61%) and specificity (70%) to detect the possibility of anastomotic leak. On POD-3 the predictability of anastomotic leak significantly increases with a CRP level of 6.7mg/dl or more with a sensitivity of 68% and specificity of 89%. A CRP level of 7.5mg/dl or above, on POD 5 detects leak with sensitivity of 93% and specificity of 98%, making it a reliable marker, with a very few false positives [**Figure 2**].

Table 1: General characteristics of the patients with the risk factors

Characteristics	Anastomotic leak	Non-Anastomotic leak	Overall	*p* value
Sex				
Male	19	79	98	.75
Female	22	82	104	
Gestational age (weeks)	36.02±.04	36.14±.06	36.11±.05	.0.0853
Post natal age (days)	1.5	2	1.9	.035
Birth Weight (kg)	2.13±.01	2.35±.06	2.30±.06	.002825
Gap Length (cm)	1.39±.15	1.20±.06	1.24±.06	.01904

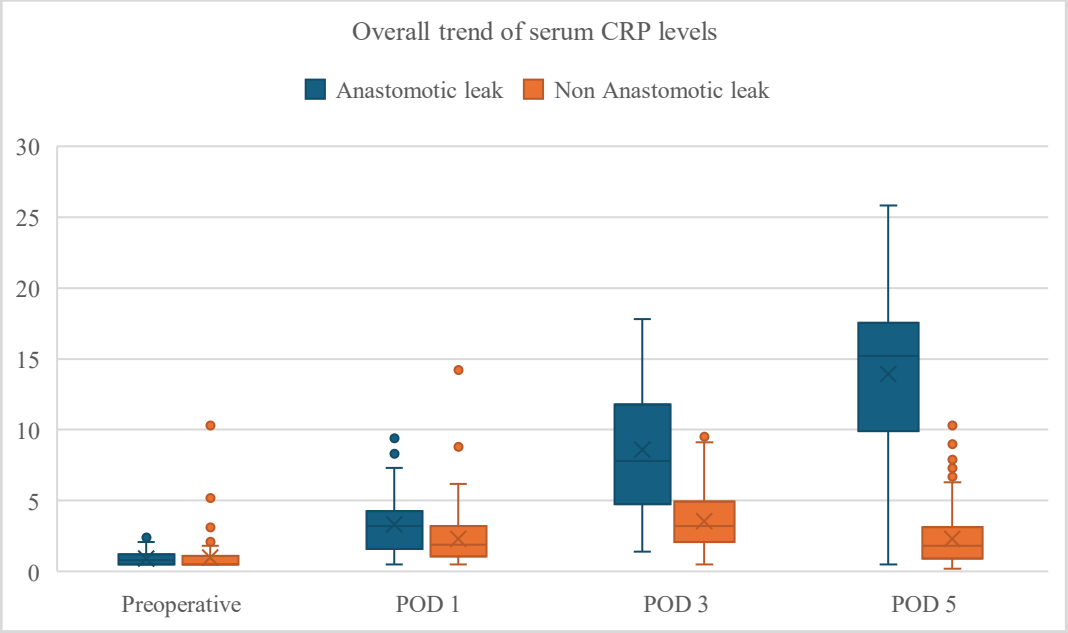

Figure 1: Trend of Serum CRP levels in two groups in study cohort

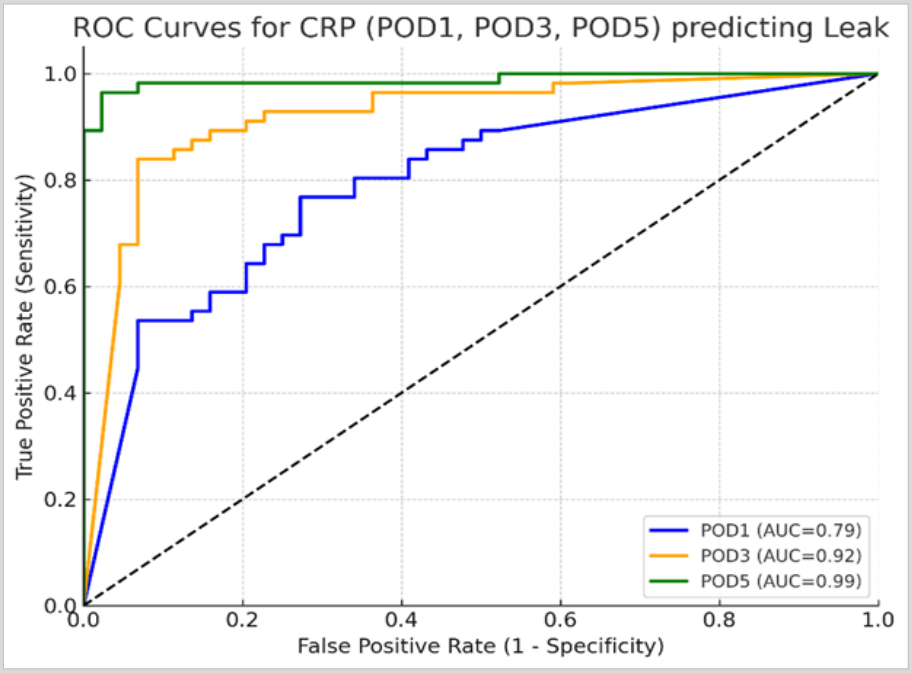

Figure 2: ROC curve depicting sensitivity and specificity of serum C-reactive protein between leak and non-leak group on POD1, 3, and 5.

Discussion

Anastomotic leak is the most dreaded complication of EA/TEF repair surgery. Although the overall survival has improved dramatically due to advances in neonatal intensive care, anesthesia, and surgical technique, postoperative morbidity continue to be significant [4]. Anastomotic leak repair has its own complications in the form of increased risk of sepsis, prolonged hospital stay, and subsequent stricture formation [5]. Risk factors contributing to leak development include long gap EA necessitating excessive mobilization of the esophagus, increased anastomotic tension, ischemia of esophageal ends, prematurity, low birth weight, and presence of associated anomalies, particularly congenital heart disease [6,7].

In our study, it was observed that the mean birth weight (with standard deviation) of patient developing anastomotic leak was 2.13±.01 kg which was less than the mean of birth weight in the non-leak group, 2.35±.06, and it was statistically significant (P=.002825). Lower birth weight may be associated with poorer peripheral circulation and lower cardiac output, which may lead to a poor blood supply at the local anastomotic site [8]. Additionally, a Turkish study also found a significantly higher incidence of anastomotic leak in lower birth weight group as compared to normal birth weight groups [9]. Another study also reported that birth weight was lower in leak group then non leak group [10].

Long-gap EA/TEF management is difficult [11]. Anastomotic leakage risk is more in long gap EA/TEF. Usually there is an extensive mobilization of the esophageal stump, which may hamper the vascular supply to the esophagus and invariably impair the healing ability of anastomotic site [12]. In order to prevent anastomotic complication during repair of EA/TEF, the surgeon should take utmost care that, anastomotic repair has to be under lower tension [13]. In this study, the mean gap length in leak was more than that of non-leak group, and the difference was statistically significant (1.39±.15 vs 1.20±.06, P=.01904). Suggesting, long gap being an independent risk factor for anastomotic leak.

These above risk factors help in predicting anastomotic leak in pre and perioperative period. In the post operative period, anastomotic leak may present as excessive drainage of saliva in intercoastal chest tubes, sepsis or pneumothorax [14]. Radiological confirmation is commonly achieved by contrast esophagography performed on Postoperative day 5-7, demonstrating extravasation at the anastomotic site [15]. In early presentation of anatomic disruption, when saliva is present in chest tube, this sets in the inflammation caused due to salivary pooling. Alternatively, if the leak is mild or the chest tube is occluded, an inflammatory cascade may occur before the clinical manifestation; in these situations, a contrast esophagogram is the only way to confirm the leak. Hence early detection is critical, as delayed recognition often results in severe sepsis, prolonged intensive care stays, reoperation, or even death. Consequently, there is a need of identification of biochemical markers that can provide early warning of postoperative complications, particularly anastomotic leaks and may help in improvising upon the final outcomes.

CRP, in an acute phase reactant produced predominantly by hepatocytes in response to interlukin-6 stimulation, is one of the most widely studied biomarkers for postoperative infections and inflammatory complications. CRP rises 6-12 hours after the onset of systemic inflammation, peaking around 48 hours and then gradually declines in the absence of ongoing insult [16]. In adult gastrointestinal surgery, levels beyond the POD-3 correlate strongly with anastomotic leak and other septic complications. Conversely, an uneventful postoperative course is typically associated with decline in CRP levels after their expected early peak [17-19]. This temporal pattern has been exploited to develop predictive cut offs and algorithms for clinical use. However, there are very few studies correlating temporal relation of CRP levels with anastomotic leak.

According to this study, patients with EA/TEF had higher baseline CRP levels. This could be related to the varying degree of chest involvement in these patients due to aspiration of saliva and chemical pneumonitis related to regurgitation of gastric secretions and bile through the fistulous tract [20]. A rise in CRP levels following surgery is related to the major surgical insult from the reconstructive procedures [21,22]. Transient endotoxin or bacteremia is also possible following surgery of the esophagus and associated procedures such as insertion of red rubber catheter in the upper pouch to help

identification or passage of a trans anastomotic feeding tube through the nasogastric route [22]. In this study CRP levels rises on POD-1 and POD 3 in both the leak and non-leak groups. However, the difference in the rise of CRP levels from POD-1 to POD-3 was significantly more in leak group. Thereafter, in non-leak group, CRP level fall after peaking on POD 3, but continues to rise in leak group.

In patients with leak, CRP levels on POD 1, the cut off levels at 2.7mg/dl were observed to predict anastomotic leak with 61% sensitivity and 70 % specificity. CRP levels cutoff at 6.7mg/dl on POD-3 had a 68% sensitivity and 89% specificity in predicting the anastomotic leak. On POD-5 CRP level cut off at 7.5mg/dl predicts anastomotic leak with a sensitivity of 93% and specificity of 98%. This shows that there is an increased chance of anastomotic leak with increase in CRP levels.

A study of temporal relationship between rising CRP levels preceding the clinical manifestation of adverse event like anastomotic leak which is subtle in the initial days. A rise in serum CRP reflects changes happening at cellular and molecular levels which build up gradually to become manifest clinically over 24-48 hours. The additional window afforded by CRP based monitoring of the patients of esophageal atresia following surgery may be translated into early recognition of complications and timely institution of intervention.

The use of CRP like any other biomarker has its own limitations. In surgical neonates, the rise in CRP is a combined effect of inflammatory response elicited by the surgical trauma and sepsis. Unless we have means to differentiate between the two factors or to quantify the magnitude of each, it is important that the trend of CRP be considered for main clinical decisions rather than the absolute values of this biomarker. Furthermore, clinical decisions should be based on an overall assessment of the patient including the clinical, laboratory and radiological parameters. An optimal balance between the conventional and novel biomarkers of sepsis and surgical complications is likely to yield positive results. Larger, well formulated studies and multicentric trials are required to formulate clinical protocols for optimal utilization of CRP in the management of patients of EA/TEF.

Conclusion

Serial postoperative CRP measurement is a reliable tool for the early detection of anastomotic leaks. A CRP > 6.7 mg/dl on POD 3 is highly predictive of leakage and may be used as clinical trigger for further investigation or early intervention. Routine CRP monitoring could improve postoperative safety and outcomes. CRP monitoring, by virtue of its accessibility, low cost and reliability, holds promise as an integral component of postoperative surveillance protocols aimed at reducing morbidity and mortality from anastomotic leaks.

Declaration

Ethical Approval and Consent to participate

This is a retrospective, observational, single center study so consent not taken.

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Consent for publication

Taken from all authors.

Conflict of Interest

None

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Authors' Contributions

AP: Data acquisition, initial intellectual content development and principal investigating author
VC: Data acquisition, initial intellectual content development and principal investigating author.
NT: Manuscript preparation, final intellectual content development and corresponding author
AJ: Manuscript preparation, final intellectual content development and corresponding author
AJB, AC, PG: Data interpretation, manuscript integrity appraisal and critical reviewing author
AKK: Initial study conception, study design, and final version approving author.

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