

Predictors of septic shock following anastomotic leak after major gastrointestinal surgery: An audit from a tertiary care institute

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Abstract

Background: Anastomotic leak is a serious complication after major gastrointestinal surgery and majority of deaths occur due to septic shock. Therefore, the early identification of risk factors of septic shock may help reduce the adverse outcomes. **Objective:** The aim of this audit was to determine the predictors of septic shock in patients with anastomotic leak after major gastrointestinal surgery. **Design:** Retrospective, audit. **Materials and Methods:** The patients admitted in the gastrosurgical intensive care unit ICU) of our institute between September 2009 and April 2012 with anastomotic leakage after surgery were identified. The ICU charts were retrieved from the database to identify the patients progressing to septic shock. A comparison of risk factors was made between the patients who developed septic shock (septic shock group) against the patients who did not (non-septic shock group). **Results:** The study sample comprised of 103 patients with anastomotic leak, of which 72 patients developed septic shock. The septic shock group had a higher APACHE II score, lower MAP, and higher HR at the time of ICU admission. They received greater transfusion of packed red blood cells during their ICU stay. Septic shock was more common after pancreaticojejunostomy and hepaticojejunostomy leaks. **Conclusion:** Presence of malignancy, chronic obstructive pulmonary disease (COPD), packed red blood cell transfusion, bacteremia, and hepaticojejunostomy or pancreaticojejunostomy leaks were independent predictors of mortality and length of ICU stay. To the best of our knowledge there are no available studies in the literature on the predictors of risk factors of septic shock in patients with anastomotic leakage.

Keywords: Anastomotic leakage, post-leak sepsis, septic shock

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Introduction

Sepsis is systemic inflammatory response syndrome (SIRS) secondary to infection, and, when associated with organ dysfunction, produces several life-threatening complications. While the occurrence of sepsis after major surgery is uncommon in healthy patients, the risk increases after emergency surgery, greater surgical insult, blood transfusions, advancing

age, and male gender.^[1-4] The extent to which the co-morbid illness increases the risk of sepsis after surgery has been studied in great detail, and many scoring systems like Charlson co-morbidity score (CCS) have been derived to measure its burden.^[5]

Anastomotic leak is a serious complication after major gastrointestinal surgery that considerably increases the mortality and morbidity.^[6] A large number of patient-related and surgery-related risk factors are known to influence anastomotic leak, but consensus is lacking on their independent role due to their mutual interdependency.^[7] However, the majority of deaths occur after anastomotic leak due to overwhelming sepsis.^[8]

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Since the progression from anastomotic leak to severe sepsis and septic shock is often rapid and fatal, the early identification of risk factors for this progression may help reduce the mortality and morbidity. The aim of this retrospective audit was to determine the predictors for developing septic shock in patients with anastomotic leak after major gastrointestinal surgery.

Materials and Methods

All the patients admitted in the gastrosurgical intensive care unit of our hospital between September 2009 and April 2012 with anastomotic leak after major gastrointestinal surgery were identified. The ICU charts of the patients were retrieved from the database and an audit was performed to identify the patients who progressed to septic shock. A comparison of the risk factors was made between the patients who developed septic shock against the patients who did not. The risk factors were primarily determined by literature search and collected from the information available in the ICU charts.

“Anastomotic leak” was defined as the leak of luminal contents from a surgical joint between two hollow viscera and was diagnosed on the basis of clinical suspicion and/or radiological investigation.

“Sepsis” was defined as SIRS such as fever, tachycardia, tachypnoea, or leucocytosis in response to a culture-proven or clinically suspected infection.

“Severe sepsis” was defined as sepsis with at least one additional sign of organ hypo perfusion or dysfunction such as cardiac dysfunction, acute lung injury, or altered mental status.

“Septic shock” was defined as severe sepsis in addition to a systemic mean blood pressure < 60 mmHg (or < 80 mmHg if previous hypertension) after an attempt at adequate fluid resuscitation or a need of systemic vasopressors to maintain a mean blood pressure > 60 mmHg (or > 80 mmHg if previously hypertensive).

“Bacteremia” was defined as a positive blood culture, excluding isolates believed to be contaminants.

Categorical data are presented as numbers (%). Quantitative data are presented as mean (SD). Statistical analyses were performed using SPSS software (version 12.0; SPSS Inc., Chicago, IL). Univariate analysis was conducted to determine the potential risk factors for the occurrence of septic shock. Chi-square tests or Fishers’ exact tests were used for qualitative variables.

The required significant level was set at a $P < 0.05$. A multivariate analysis was performed by stepwise logistic regression with sepsis as dependent variable to identify independent risk factors for the development of septic shock. The variables that were analyzed as potential predictors were selected from the literature and from the clinical experience of the researchers. The variables consisted of patient characteristics (age, sex, and smoking habit), type of the leak (esophagogastric, colorectal, and pancreaticojejunal), and severity of condition (APACHE II score, blood transfusion needs).

Results

The study sample comprised of 103 patients with anastomotic leak in the aforesaid period. Sepsis occurred in 90 patients and septic shock in 72 patients. The details of the demographic and clinical characteristics of the septic shock and non-septic shock groups are presented in Table 1. As would be expected, compared with the non-septic shock group, the septic shock group had a significantly greater derangement of physiological state at the time of ICU admission. This was reflected by a higher APACHE II score (19 ± 6 vs. 9 ± 4 ; $P < 0.05$), lower mean arterial pressure (45 ± 4.2 vs. 70 ± 6.2 ; $P < 0.05$), higher heart rate (130 ± 9 vs. 72 ± 8 ; $P < 0.05$), and a greater base deficit (-4.2 ± 5.1 vs. -2.6 ± 4.6 ; $P < 0.05$). Although the hemoglobin level at the time of ICU admission was similar (8.2 ± 1.4 vs. 9.3 ± 2.1 ; $P > 0.05$) between the groups, the septic shock group received more packed red blood cell (RBC) transfusions (47.3% vs. 27.9%; $P < 0.05$) during the ICU stay. The progression to septic shock occurred more after pancreaticojejunal (22% vs. 13%; $P < 0.05$) and hepaticojejunal anastomosis than jejunojejunal anastomosis (45% vs. 37%; $P < 0.05$). Bacteremia was more common in the septic shock group (87% vs. 34%; $P < 0.05$). Multiorgan dysfunction at the time of ICU admission was more common in the septic shock group (77% vs. 14.3%; $P < 0.05$).

Univariate analysis of septic shock and outcome

Analyses were conducted to evaluate the univariate associations between septic shock and common outcomes after anastomotic leak (i.e., in hospital mortality, 30-day mortality, ICU length of stay, and hospital length of stay). Chi-square analyses were performed to determine the association between septic shock and mortality. The septic shock group had a higher stay in hospital (17.3% versus 9.1%; $P < 0.05$) and 30-day mortality rates (15.1% vs. 8.7%; $P < 0.05$). Analysis of variance (ANOVA) was performed to evaluate the association between septic shock and ICU and hospital length of stay. It was seen that the septic shock group spent a significantly longer time in the ICU (18 ± 7 days vs. 10 ± 4 days; $P < 0.05$) and

hospital (35 ± 4 days vs. 19 ± 8 days; *P* < 0.05). The septic shock group also had a greater number of ventilator days in the ICU (11 ± 5 days vs. 4 ± 3 days; *P* < 0.05).

Predictors of septic shock in anastomotic leak

Logistic regression analysis identified malignancy, chronic obstructive pulmonary disease (COPD), liver disease, heart disease, packed RBC transfusion, presence of bacteremia, hepaticojunal anastomotic leak, colorectal fistula, and APACHE II score > 15 as significant independent predictors of septic shock in patients with anastomotic leak [Table 2].

To evaluate the predictive value of septic shock and the combined effects for outcome, the significant univariate

Table 1: Comparison of septic shock and non-septic shock patients on demographic, clinical, and anastomotic leak measurements

	Septic shock (n=72)	Non-septic shock (n=31)	P value
Age (years; mean±SD)	45±4.5	42±2.6	>0.05
Male (%)	36	40	>0.05
Smoking (%)	40	39	>0.05
Presence of co-morbidities (%)			
Malignancy	23	8	<0.05
Diabetes	34	14	<0.05
Heart disease	40	36	>0.05
COPD	19	4	<0.05
Liver disease	11	3	<0.05
APACHE II on admission (points; mean±SD)	19±6	9±4	<0.05
APACHE II mean > 15 on admission (%)	27	14	<0.05
MAP (mmHg) at admission (mean±SD)	45±6.2	70±4.2	<0.05
HR at admission (mean±SD)	130±9	72±8	<0.05
Hb (%; mean±SD)	8.2±1.4	9.3±2.1	>0.05
Platelet (count; mean±SD)	0.84±0.04	0.95±0.07	>0.05
Prothrombin time (Quick %; mean±SD)	72±23	80±22	>0.05
Base excess at admission (mmol/L; mean±SD)	-4.2±5.1	-2.6±4.6	<0.05
pRBC transfusion (%)	47.3	27.9	<0.05
Fresh frozen plasma (n; mean±SD)	2.3±0.7	1.1±0.5	<0.05
Type of leak (%)			
Oesophagojejunal	22	13	<0.05
Pancreatojejunal	21	17	NS
Hepaticojunal	45	37	<0.05
Colorectal	9	24	<0.05
Gastrojejunal	3	9	NS
Bacteremia (%)	87	34	<0.05
Multi organ failure (%)	77	14.3	<0.05
Ventilation days (days; mean±SD)	11±5	4±3	<0.05
ICU LOS (days; mean±SD)	18±7	10±4	<0.05
In hospital LOS (days; mean±SD)	35±4	19±8	<0.05
30 day mortality (%)	15.1	8.7	<0.05
In hospital mortality (%)	17.3	9.1	<0.05

APACHE II=Acute physiology and chronic health evaluation score II; LOS=Length of stay; ICU LOS=Intensive care unit length of stay; pRBC=Packed red blood cell; Hb=Hemoglobin; HR=Heart rate; MAP=Mean arterial pressure; COPD=Chronic obstructive pulmonary disease; NS=Non-significant

predictors for septic shock were entered into multiple logistic regression models. Results of these analyses are presented in Table 3. Analysis indicated that the interaction of septic shock with the variables of APACHE II > 15, bacteremia, malignancy, hepaticojunal anastomotic leak, and packed RBC transfusions were significant predictors of in-hospital mortality. The analysis also indicated that the interaction of septic shock with APACHE II > 15, bacteremia, malignancy, hepaticojunostomy leak, and liver disease was a significant predictor of the length of ICU stay, while the interaction of septic shock with APACHE II > 15, bacteremia, and hepaticojunostomy leak was a

Table 2: Predictors of septic shock (Logistic regression analysis)

Variable	CI	OR	P value
Malignancy	2.41-5.23	3.52	<0.05
COPD	1.15-3.36	1.35	<0.05
Liver disease	3.59-11.61	6.21	<0.05
Heart disease	1.29-2.37	1.23	<0.05
pRBC transfusion	3.31-5.87	2.41	<0.05
Bacteremia	2.41-8.00	4.47	<0.05
Hepaticojunostomy leak	3.09-11.23	6.11	<0.05
Colorectal fistula	4.12-9.34	4.11	<0.05
APACHE II > 15	3.19-7.27	3.27	<0.05

CI=confidence interval; OR=odds ratio; COPD=chronic obstructive airway disease; APACHE II=acute physiology and chronic health evaluation score II; pRBC=packed red blood cells

Table 3: Multiple logistic regression models for mortality, ICU length of stay, and hospital length of stay

Mortality			
Predictors	OR	CI	P value
APACHE II < 15	7.12	3.16-12.37	<0.05
Bacteremia	1.21	1.47-3.56	<0.05
Malignancy	4.94	4.20-5.81	<0.05
Hepaticojunostomy leak	9.28	7.66-11.25	<0.05
Colorectal fistula	1.21	0.98-1.52	>0.05
pRBC transfusion	3.36	1.68-5.22	<0.05
Liver disease	1.64	1.03-2.61	>0.05

ICU length of stay			
Predictors	Co-efficient	CI	P value
APACHE II < 15	9.11	4.63-12.28	<0.05
Bacteremia	3.17	2.36-7.45	<0.05
Malignancy	0.029	0.021-0.037	<0.05
Hepaticojunostomy leak	5.63	5.17-6.28	<0.05
Colorectal fistula	0.58	0.17-0.98	>0.05
pRBC transfusion	0.8	0.24-1.37	>0.05
Liver disease	-1.15	-2.39-1.04	<0.05

Hospital length of stay			
Predictors	Co-efficient	CI	P value
APACHE II < 15	20.98	19.35-23.64	<0.05
Bacteremia	6.75	6.33-7.19	<0.05
Malignancy	0.03	0.02-0.03	>0.05
Hepaticojunostomy leak	7.23	5.12-9.67	<0.05
Colorectal fistula	0.97	0.77-1.25	>0.05
pRBC transfusion	1.10	1.02-1.87	>0.05
Liver disease	0.98	0.66-1.28	>0.05

APACHE II=Acute Physiology and chronic health evaluation II; pRBC=Packed red blood cell; CI=confidence interval; ICU=Intensive care unit; OR=odds ratio

significant predictor of hospital length of stay. Based on the results from univariate and multivariate analysis, a simple scoring system for septic shock after anastomotic leak (SEPAL) has been developed. The risk of mortality can be predicted from this score. This includes APACHE II > 15 during presentation, malignancy, bacteremia, packed RBC transfusion, and hepaticojejunostomy leak. Each of the variables is given a score of 1. If the total score exceeds 3, the risk of mortality is 100% [Table 4].

Discussion

To the best of our knowledge, no prior studies have evaluated the predictors of septic shock following anastomotic leak after major gastrointestinal surgery. The present study of 103 patients of anastomotic leak had a septic shock of 69.9% ($n = 72$) with a mortality of 45.8% ($n = 33$).

Our study found a greater incidence of septic shock following anastomotic leak in patients with lower mean arterial pressure, higher heart rate, greater APACHE II score, and a higher base deficit at the time of ICU admission. This is in agreement with studies showing prolonged hypotension and microvascular ischemia predisposing to tissue ischemia and anastomotic failure.^[9] Although it is known that sepsis increases the risk of microvascular ischaemia due to excessive production of reactive oxygen species (ROS), it is not clear whether anastomotic failure itself leads to oxidative stress producing sepsis. However, the rapid progression to septic shock in this group of patients can be due to the inhibition of sympathetic nervous system and loss of baroreceptor reflex control of arterial blood pressure.^[10,11]

Our study found that the patients in septic shock group received greater packed RBC and fresh frozen plasma during the ICU stay. This suggests a more critical nature of their illness in comparison to the non-septic shock group. Telem *et al.*, found intraoperative blood loss of 200 ml or more and intraoperative transfusion requirement as major risk factors for anastomotic leakage after colorectal surgery.^[12] It is not possible to know from our study whether or not intraoperative transfusion increases the likelihood of septic shock, because we did not include the intraoperative blood

loss and transfusion requirement for analysis. However, Perner *et al.*, found that most patients with septic shock who required transfusion had higher disease severity and lower hemoglobin levels than their non-transfused counterparts.^[13] Despite this difference, the mortality was similar in both adjusted and unadjusted analyses. Some studies have shown that blood transfusions during surgery may be associated with with prolonged and difficult surgery and intraoperative hypotension, which may be independently associated with the development of sepsis after surgery.^[14,15] In our study, both the groups had similar hemoglobin level at the time of ICU admission, but there was greater requirement of transfusion in the septic shock group during the ICU stay. This mimics the findings of previous studies, although our study design and sample size does not allow us to make inference about the treatment effects.

Our study found that the presence of associated co-morbid illnesses like diabetes, malignancy, COPD, and liver disease increases the risk of septic shock. This is in agreement with a study showing higher levels of circulating biomarkers of endothelial cell adhesion (E-selectin) and vascular endothelial growth factor (VEGF) signaling (sFLT-1) in septic shock patients with diabetes.^[16] Since many of the endothelial pathways activated during sepsis remain already upregulated in diabetic patients', they can develop organ dysfunction at an earlier stage.^[17] Similarly, malignancy has been associated with increased likelihood of post-operative sepsis and as an independent predictor of death in septic shock.^[18]

A potential reason for the increased incidence of septic shock after hepaticojejunostomy and pancreaticojejunostomy leak may be the delayed diagnosis after leak. This is possible because biliary enteric anastomosis usually involves smaller ducts that are usually multiple. If the injury or stricture is above the bifurcation of right and left hepatic ducts, a small accessory duct may be missed, leading to bile leak and the subsequent sequel.^[19]

Our study found that both 30 day mortality and in-hospital mortality were higher among the septic shock patients. The following variables: APACHE II > 15, presence of bacteremia, malignancy, hepaticojejunostomy leak, and packed RBC transfusions were found to be independent predictors of mortality. Although there are limited evidences in the literature on the influence of these factors exclusively for gastrointestinal surgery, a prognostic scoring system known as Prognostic Index (PI) developed by a multivariate probit analysis was found

Table 4: Septic shock after anastomotic leakage score and mortality risk

APACHE II > 15 during presentation	
Malignancy	
Bacteremia	
Packed RBC transfusion	
Hepaticojejunostomy leak	

If the total score is > 3, the mortality risk increases to 100%; RBC=Red blood cells

to accurately predict the severity and mortality of 83 surgical patients of gastrointestinal diseases in Japan.^[20] These include age, pulse rate, blood urea nitrogen, serum albumin, serum cholesterol, and serum potassium. Although the evolution of mortality risk identification and prediction tools are limited by stratification in clinical trials, their usefulness in clinical decision making cannot be ignored. More recently, Estimation of Physiologic Ability and Surgical Stress (E-PASS), a prediction scoring system requiring nine variables was found to predict accurately the occurrence of anastomotic leak and its prognosis in various kinds of gastrointestinal procedures.^[21,22]

Roman-Marchant *et al.* found that early onset septic shock is more severe and yet has a better outcome than late-onset septic shock.^[23] This is evidenced by a shorter duration of shock, shorter length of ICU stay, and lesser mortality. Although our study did not differentiate between the early and late-onset septic shock, our results showed a higher mortality and greater length of ICU stay in the septic shock over non-septic shock group. Roman-Marchant *et al.*, found that the principal organism in early septic shock was *Streptococcus pneumoniae* and in the late septic shock was *Pseudomonas*. Since *Pseudomonas* infections normally carry a higher mortality, the higher mortality in the late septic shock can be because of the same. However, another study similar to ours found that, as compared to non-septic shock patients, septic shock patients are significantly older, have higher severity scores, have longer ICU and hospital stay, and carry longer ICU and hospital mortality.^[24] In that study, the respiratory functions, cardiovascular functions, and fungal infections were found to be strong independent predictors of death in septic shock (5.6-, 4.3-, and 2.0-fold, respectively). We also found similar results, although the presence of malignancy and liver disease emerged to be more important predictors in our study.

There are several limitations in our study. First, being a retrospective audit, it has the inherent drawbacks of its design. Some variables that may be of interest (e.g., procalcitonin and C-reactive protein) are not routinely recorded in our registry and could not be analyzed. Second, the study population includes 103 patients with anastomotic leak and 72 patients with septic shock. This is a small number with limited ability to detect an association between patient factors and sepsis. However, our study has a similar power to a study that has reported a strong association between postoperative sepsis and a high CCS.^[25] Third, our study is a single-center study in a university teaching hospital and tertiary referral centre for gastrointestinal

surgery. Our results may not apply to all hospitals with different case mix and different quality of postoperative care. The specialized nature of our study setting and our anastomotic leak is a highly selective population in any setting population limits the generalizability of our results. Fourth, our study does not consider the possible variations in the risk of sepsis due to genetic polymorphism. Various studies have shown that genetic polymorphism in the tumor necrosis factor- α promoter significantly increases the risk for severe sepsis and mortality.^[26]

To conclude, the identification of predictors for septic shock after anastomotic leak may be useful in reducing mortality, length of ICU, and hospital stay and costs. Various combinations of methods including the preoperative characteristics can be used to carry out such identification. We recommend further studies over different hospital settings.

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