

Early Prediction for Persistent Inflammation-Immunosuppression Catabolism Syndrome in Surgical Sepsis Patients

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Objective: To find the predictors for persistent inflammation-immunosuppression catabolism syndrome in ICU surgical septic patients.

Design: Single center observation study.

Participants: Inclusion: 1) patients ≥ 18 , 2) admitted to the ICU after major surgery or transferred to the ICU within 48 hours after the diagnosis of sepsis following the definition of sepsis-3.0. Exclusion: 1) pregnant or lactating patients, 2) patients with severe immune deficiency, 3) patients that expired within 14 days after the diagnosis of sepsis.

Results: A total of 169 participants were included. After propensity score matching, PICS patients were found to have higher intensive care unit (ICU) mortality (32.4% vs 12.4%, $p=0.046$), 90-day mortality (32.4% vs 9.1%, $p=0.006$), and ICU-acquired infection rate (44.1% vs 12.7%, $p<0.001$), and longer ICU stays (29 vs 11 days, $p<0.001$) comparing to non-PICS patients. In multivariate logistic regression, it demonstrated that the SOFA score, Charlson co-morbidity index (CCI), albumin level on the ICU day 1, and lymphocyte count on the ICU day 3 were statistically significant. Sensitivity analysis was conducted with the receiver operating characteristic curve for a combination of the four parameters and the area under the curve was 0.838 (95% confidence interval 0.774–0.901).

Conclusion: The chronic disease condition and decreased immunity in the early course of sepsis were crucial for PICS. The combination of CCI, SOFA score, albumin level on ICU Day 1 and lymphocyte count on ICU Day 3 can be early predictor for PICS.

Keywords: sepsis, persistent inflammation-immunosuppression catabolism syndrome

Introduction

Sepsis is one of the most devastating disease processes and contributes to a high mortality in the intensive care unit (ICU).^{1–3} Surgical sepsis, defined as sepsis that requires surgical intervention for source control or sepsis within 14 days of a surgical procedure, is recognized as an engine for the development of post-operative morbidity and mortality.⁴

The rate of surgical sepsis increased from 0.7% in 1997 to 1.3% in 2006, and the rate of severe surgical sepsis increased from 0.3% in 1997 to 0.9% in 2006.⁵ Although the incidence of sepsis in surgical patients is increasing,^{1,3} the overall outcome of sepsis has greatly improved over the last 20 years with the implementation of evidence-based ICU management of diseases.^{6,7} However, in a study on the long-term outcomes of sepsis, one-third of patients with sepsis developed a chronic critical illness, and these patients were at a high risk of poor function and death over 1-year period.⁸

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Chronic critical illness is clinically characterized as persistent but manageable organ failure, impaired life activity, mechanical ventilation dependence, malnutrition, prolonged ICU stay, and eventually death.⁹ The underlying pathophysiologic syndrome was termed persistent inflammation-immunosuppressive catabolism syndrome (PICS).¹⁰ Patients surviving sepsis with PICS have impaired physical function, need high resources to support their lives, and are usually with irreversibly poor long-term outcomes.¹¹ PICS has been reported in patients with major trauma, pancreatitis, and intestinal fistula, but minimal data exist on patients with sepsis associated with major surgery.^{12–14}

Unfortunately, although PICS has received more attention regarding the management of surgical patients with septic complications, methods to predict its occurrence and change the course of the disease remain unclear. According to the definition, PICS are diagnosed over 14 days after sepsis onset, so it is crucial to find risk factors to recognize this population and apply strategy to prevention. The purpose of this report is to describe the character of PICS patients in the early stage of sepsis and to seeking risk factors to predict the PICS.

Methods

Study Design

We performed this study by review the electronic medical records involving surgical patients admitted to our 30-bed intensive care unit from January 2015 to June 2019 at a teaching hospital. This study was conducted in accordance with the Declaration of Helsinki. The study design and possible ethic issues related to this study were reviewed and approved by the ethics committee of Ruijin Hospital affiliated Shanghai Jiao Tong University School of Medicine.

Patient Eligibility

The inclusion criteria were set as: patients must be 18 years old or older and were admitted to the ICU after major surgery or transferred to the ICU within 48 hours after the diagnosis of sepsis following the definition of sepsis-3.0 from a surgical department. The exclusion criteria were any of the following: pregnant or lactating patients, patients with severe immune deficiency, and patients that expired within 14 days after the diagnosis of sepsis.

Severe immune deficiency¹⁵ was considered in this study if the patient received chemotherapy in the past 28 days, had a blood neutrophil count less than $1 \times 10^9/L$, took

a dose of prednisone greater than 20 mg per day or an equivalent dose of other steroids for more than 14 days, had HIV infection, underwent transplantation, or had active tuberculosis.

Definition of Sepsis and PICS

In this study, sepsis was defined according to the Sepsis-3.0 guidelines¹⁶ and surgical sepsis was delimited as sepsis requiring surgical intervention for source control or sepsis within 14 days after a surgical procedure.⁴

PICS was diagnosed according to the following criteria: On the day of PICS diagnosis, the patient's ICU stay ≥ 14 days with a body weight reduction of 10%, body mass index (BMI) of 18 or less, blood C-reactive protein level of 150 ug/dL or above, blood lymphocyte count of $0.8 \times 10^9/L$ or less, pre-albumin level of 100 mg/L or less, and albumin level of 30 g/L or less.¹⁷ An ICU-acquired infection was defined as an infection (or suspected infection) that occurred 48 hours after ICU admission.

Data Collection

The ICU admission demography was collected from a review of medical records including the age of the patients, gender, body weight, diagnosis at ICU admission, reasons for ICU admission, chronic co-morbidities, and BMI. Laboratory parameters comprising the blood neutrophil count, blood lymphocyte count, C-reactive protein levels, albumin levels, pre-albumin levels, and procalcitonin levels measured on post-ICU admission days 1, 3, and 7 were also extracted from the medical records.

Upon admission to the ICU, the sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE II) score, and CCI were all calculated such that they could be obtained from the medical record review. For evaluation of the outcome, the data were further stratified into ICU mortality, ICU stay duration in days, hospital mortality, hospital stay duration in days, 90-day mortality, 28-day mortality, and the incidence of ICU-acquired infection.

Statistical Analysis

SPSS version 22.0 (IBM) was used for propensity score matching (PSM) and all calculations in this study. PSM was used to reduce the bias in measuring patient's outcome. Data are presented as frequency, percentage, mean with standard deviation, median, or the 25th/75th percentiles. Fisher's exact test and the Kruskal–Wallis test were used for comparison of the categorical and continuous

variables, respectively. Statistical significance was defined as a two-tailed P value of less than 0.05.

In the PSM, the patients were matched at a ratio of one PICS patient to two non-PICS patients based on age, CCI, BMI, gender, and SOFA score. Multivariate stepwise logistic regression models were created to determine the independent risk factors (determinable within 72 hours of sepsis onset) for the development of PICS. The variables included in the models were those with statistical significance in the univariate analysis or clinical relevance. Diagnostic performance was evaluated using the area under the curve (AUC). Lastly, the Kaplan-Meier curve was used to evaluate survival.

Results

Demographics

Following the study design, a total number of 169 patients were enrolled in this study with a mean age of 65 years, a median BMI of 22.85, and a ratio of men versus women of 2.6:1. Among the 169 patients, 146 (86.4%) underwent gastrointestinal surgery before the development of PICS. The top three infection sources for sepsis were intra-abdominal infections (56%), lung infections (11.83%), and a combination of hematogenous infection and intra-abdominal infection (10.64%) (Table 1). The most common deteriorated organ in septic patients was the lung (60.95%), followed by the liver (41.42%). Malignancies were diagnosed in 46% of patients.

Mortality of PICS Patients

PICS was diagnosed in 27.8% (47/169) of the included patients. Before PSM, patients with PICS possessed higher APACHE II scores (22 vs 19.5), SOFA scores (11 vs 9), and CCI (4 vs 2) than non-PICS patients. Moreover, in comparison with non-PICS patients, PICS patients not only had higher ICU (36.2% vs 8.2%), 28-day (10.6% vs 1.6%), and 90-day (38.3% vs 6.6%) mortality, they also stayed in the ICU longer (29 vs 12 days). Using PSM, the patients were matched with a 1:2 ratio (PICS vs non-PICS) based on age, CCI, BMI, gender, and SOFA score. After matching, 89 patients were included in each cohort, and the PICS patients were found to have higher ICU mortality (32.4% vs 12.4%), 90-day mortality (32.4% vs 9.1%), and ICU-acquired infection rate (44.1% vs 12.7%) (Table 2). The Kaplan-Meier curve showed that the PICS patients had particularly high 90-day mortality (Figure 1).

Table 1 Characteristics of Patients

	N=169
Age (Median IQR)	65 (54–76)
Male, n (%)	122 (72.19%)
BMI (Median IQR)	22.85 (19.46–25.08)
Surgery, n (%)	
Gastrointestinal	
Tumor	78 (46.15%)
ERCP	8 (4.73%)
Emergence	60 (35.5%)
Orthopedics	5 (2.96%)
Urinary	5 (2.96%)
Neurology	4 (2.36%)
Lung	4 (2.36%)
Primary sepsis diagnosis	
Intra-abdominal	96 (56%)
Lung	16 (11.83%)
Blood	9 (5.32%)
Urinary	2 (1.18%)
Surgical site	2 (1.18%)
Intra-abdominal + Blood	18 (10.64%)
Lung + Blood	2 (1.18%)
Intra-abdominal + Lung	4 (2.36%)
Lung + Blood + Intra-abdominal	3 (1.78%)
Other	13 (7.69%)
Organ dysfunction, n (%)	
Renal	70 (41.42%)
Respiratory	103 (60.95%)
Circulation	55 (32.54%)
Coagulation	54 (31.95%)
Chronic comorbidity	
Neurologic	17 (10.06%)
Chronic Heart Failure	14 (8.28%)
Tumor	67 (39.64%)
Respiratory	9 (5.32%)
Hypertension	75 (44.37%)
Cirrhosis	7 (4.14%)
Chronic Kidney Disease	9 (5.32%)
Others	8 (4.73%)
Sepsis severity score	
APACHE II, median (IQR)	20 (15–27)
CCI, median (IQR)	2 (1–3)
SOFA, median (IQR)	10 (6–13)

Laboratory Evidence for PICS

Patients with PICS displayed a lower albumin level (25 vs 28 g/L), a lower lymphocyte count (0.6 vs 0.7 $\times 10^9/L$) on the first day after ICU admission, and a lower lymphocyte count (0.6 vs 0.8 $\times 10^9/L$) and neutrophil to lymphocyte

Table 2 Propensity Score Matching and Outcomes for Patients

	Before Propensity Score Matching			After Propensity Score Matching		
	PICS	Non-PICS	P-value	PICS	Non-PICS	P-value
	N=47	N=122		n=34	n=55	
CCI	4 (2–5)	2 (1–3)	<0.001 ^a	3.17±1.4	2.8±1.6	0.937 ^b
SOFA	11 (9–15)	9 (6–12)	0.003 ^a	10.97±4.33	10.87±4.53	0.683 ^b
BMI	22.2 (19.5–26.2)	23.0 (20.2–25.0)	0.994 ^a	23.08±4.78	22.91±4.01	0.147 ^b
Age	67 (56–78)	65 (51–76)	0.413 ^a	65±16	65±15	0.641 ^b
APACHE II	22 (17–28)	19.5 (15–25)	0.025 ^a	22.02±7.04	21.91±8.64	0.308 ^b
Male	31 (66%)	91 (74.6%)	0.338 ^a	21 (67.44%)	39 (70.90)	0.373 ^b
Outcomes						
ICU length of stay (days) (IQR)	29 (20–55) ^a	12 (8–26)	<0.005 ^a	29 (20–55)	11 (7–27)	<0.001 ^a
Hospital length of stay (days) (IQR)	55 (29–77) ^a	43 (23–69)	0.089 ^a	43 (25–76)	54 (26–81)	0.387 ^a
Mortality, n (%)						
ICU mortality	17 (36.2%)	10 (8.2%)	<0.001 ^c	11 (32.40%)	8 (12.4)	0.046 ^c
Mortality 28 days	5 (10.6%)	2 (1.6%)	0.024 ^c	4 (11.76%)	2 (3.63%)	0.067 ^c
Mortality 90 days	18 (38.3%)	8 (6.6%)	<0.005 ^c	11 (32.40%)	5 (9.1%)	0.006 ^c
ICU-acquired infection	18 (38.29%)	14 (11.47%)	<0.001 ^c	15 (44.1%)	7 (12.7%)	0.001 ^c
Bacteria	15 (31.91%)	14 (11.47%)	0.003 ^c	12 (35.3%)	7 (12.7%)	0.012 ^c
Fungi	3 (6.38%)	0 (0.00%)	0.005 ^c	3 (8.8%)	0 (0.00)	0.102 ^c

Notes: ^aMann–Whitney test (U-test). ^bStudent Test (t test). ^cChi-square test.

ratio (NLR) (16.9 vs 10.5) on the third day compared to the non-PICS patients (Table 3).

Prediction of the Development of PICS

Univariate logistic regression was first performed to compare the laboratory results between patients with and without PICS. Afterward, multivariate logistic regression was performed on the APACHE II score, CCI, SOFA score, albumin level on day 1, lymphocyte counts on days 1 and 3, and NLR on day 3 after ICU admission to determine their statistical significance. The results showed that the albumin level on day 1, lymphocyte count on day 3, SOFA score, and CCI were statistically significant (Table 4). Lastly, sensitivity analysis was performed with the receiver operating characteristic (ROC) curve for the CCI, SOFA score, albumin level on day 1, lymphocyte count on day 3, and a combination of the four parameters. The results showed that the AUC of the combined predictors was 0.838 (95% confidence interval 0.774–0.901) (Table 4).

Patient and Public Involvement

Patients and members of the public were not involved in the design of this study.

Discussion

A substantial portion of surgical patients who were admitted to the ICU for septic complications progressed to CCI, which can subsequently develop into PICS. Gentile et al¹⁷ first characterized PICS clinically as: ICU stay > 14 days, C-reactive protein > 150 Kg/dL, total lymphocyte count < $0.80 \times 10^9/L$, weight loss > 10% during hospitalization or BMI < 18, creatinine height index < 80%, albumin level < 3.0 g/dL, pre-albumin level < 10 mg/dL, and retinol-binding protein level < 10 µg/dL. Following these criteria, we identified 47 PICS patients from among 1452 patients admitted to our ICU over a period of 4 years.

In this study, we found that PICS patients had higher incidences of ICU mortality, 28-day and 90-day mortality, and ICU-acquired infection. We further identified the CCI, SOFA score, albumin level on the first day, and lymphocyte count on the third day following ICU admission as risk factors for the development of PICS. We confirmed that the combination of the CCI, SOFA score, albumin level on day 1, and lymphocyte count on day 3 was a prognostic predictor for PICS. Taken together, PICS is a deteriorating syndrome that increases the mortality rate

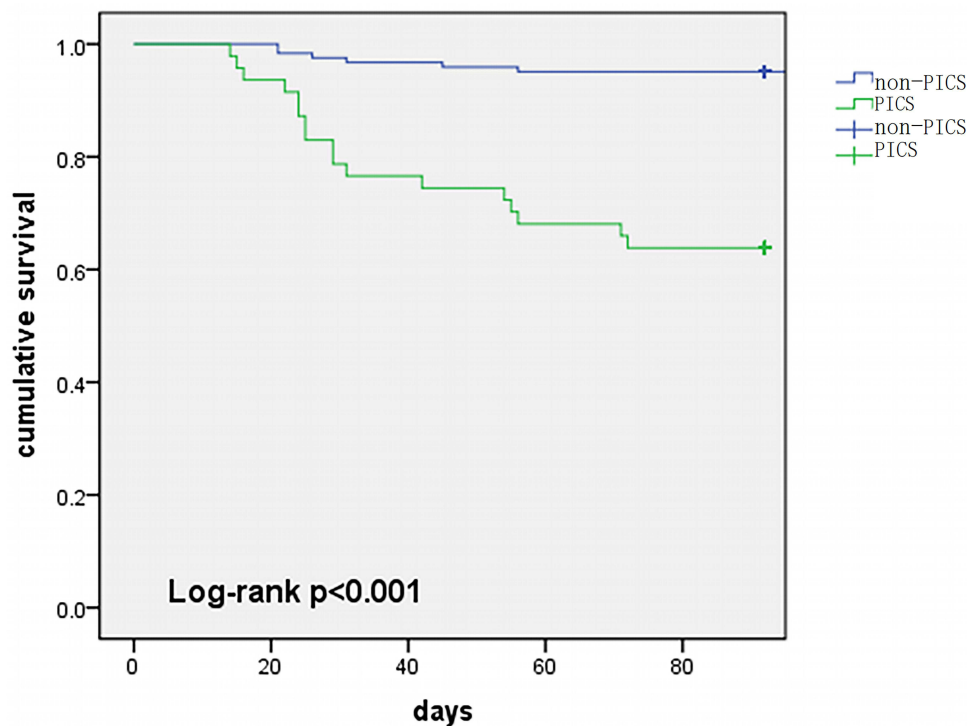


Figure 1 The Kaplan-Meier survival curve for mortality within 90 days. Log-rank $p < 0.01$: PICS group had a lower survival rate than non-PICS group.
Abbreviation: PICS, persistent inflammation-immunosuppression and catabolism syndrome.

in surgical patients suffering from sepsis, which is consistent with the findings in previous reports involving septic patients with major trauma, pancreatitis, or intestinal fistula.^{9–11}

One of the predominant pathophysiologies of PICS is multiple immunological determinants, which can

subsequently promote adaptive immunosuppression. We found our PICS patients not only had a higher incidence of ICU-acquired infections, also displayed lower lymphocyte count on the third day after the onset of sepsis, indicating the existence of immune deficiency in the early stages of sepsis, which is consistent with the recent

Table 3 Laboratory Parameters of Patients

	PICS (n=47)	Non-PICS (n=122)	P-value
Day 1			
CRP (mg/l)	95.6 (68.3–170.8)	120 (49.0–208.3)	0.426
PCT (ng/dl)	5.6 (1.5–23.7)	2.3 (0.78–17.37)	0.118
Neutrophil count ($\times 10^9/L$)	10.1 (6.7–15.1)	11.0 (6.3–15.8)	0.920
Lymphocyte count ($\times 10^9/L$)	0.6 (0.4–0.8)	0.7 (0.4–1.1)	0.040*
NLR	17.6 (12.5–26.6)	15.7 (7.4–24.0)	0.159
Albumin (g/L)	25.0 (22.0–30.0)	28 (24.0–34.0)	0.035*
Pre-albumin (g/L)	76 (56–114)	85.0 (50.5–118.0)	0.783
Day 3	n=47	n=122	
CRP (mg/L)	138 (99.1–222.8)	131 (73.2–195.6)	0.370
PCT (ng/dl)	4.8 (1.4–16.7)	2.4 (0.6–17.6)	0.101
Neutrophil count ($\times 10^9/L$)	10.3 (7.7–15.0)	9.2 (5.5–13.6)	0.273
Lymphocyte count ($\times 10^9/L$)	0.6 (0.4–0.8)	0.8 (0.5–1.2)	0.002**
NLR	16.9 (10.3–26.4)	10.5 (7.2–17.9)	0.001**
Albumin (g/L)	30.0 (26.5–32.0)	29.0 (27.0–32.0)	0.839
Pre-albumin (g/L)	67.0 (48.0–101.0)	81.0 (57.0–113.8)	0.107

Notes: All with Mann–Whitney (U-test). * $p < 0.05$. ** $p < 0.01$.

Table 4 The Result of Logistic Regression and ROC Curve

		P-value		OR (95% CI)	
Univariate					
APACHE II		0.027		1.050 (1.005, 1.09)	
Lymphocyte day 1		0.025		0.407 (0.186, 0.894)	
Lymphocyte day 3		0.01		0.295 (0.116, 0.752)	
Albumin day 1		0.118		1.040 (0.990, 1.092)	
NLR day 3		0.38		1.005 (0.993, 1.017)	
SOFA Score		0.004		1.126 (1.038, 1.221)	
CCI		<0.001		1.833 (1.466, 2.290)	
Multivariate					
Albumin day 1		0.013		1.081 (1.016–1.149)	
Lymphocyte day 3		0.016		0.222 (0.64 0.757)	
SOFA Score		0.032		1.118 (1.015–1.230)	
CCI		<0.001		1.911 (1.494–2.443)	
ROC curve					
	AUC	95% CI	P-value	Regression Coefficient	
CCI	0.770	0.688–0.853	<0.001	0.616	
SOFA	0.649	0.560–0.738	0.003	0.115	
Albumin day 1	0.605	0.508–0.701	0.035	0.076	
Lymphocyte day 3	0.348	0.260–0.436	0.002	–1.701	
Combined predictor	0.838	0.774–0.901	<0.001		

understanding of sepsis and PICS,⁷ and suggesting that the lymphocyte count on the third day can be accepted as a surrogate predictor to for the occurrence of PICS in the early stage of sepsis. Myeloid-Derived Suppressor Cells (MDSCs), a cluster of cells with immunosuppressive functions, are believed to play an important role in the development of PICS.¹⁷ Some unidentified genes involved in immune suppression may also be expressed early in the development of PICS.¹⁸ But neither MDSC nor genes are now available clinically in ICU. The lymphocyte count on the 14th day after ICU admission is one of the major criteria for PICS diagnosis. In our study, the lymphocyte count on the 3rd day can be used for predicting the PICS occurrence in the early stage of sepsis.

Charlson comorbidity index was widely used to describe the underline chronic comorbidities of patients.¹⁹ Chronic conditions had been considered to associate with immune insufficiency to infection in pathological backgrounds such as tumors, and diabetes,²⁰ COPD,²¹ chronic heart disease.²² Thereby, septic patients with higher Charlson comorbidity index had more complicated outcome,^{23,24} which is reasonable in the case of PICS.

SOFA score was used as another mean to evaluate and stratify sepsis.¹⁶ The higher the score, the greater severity of

sepsis was. In our study, SOFA score on ICU admission was suggested to be a predictor for the onset of PICS, indicating the extent of severity of sepsis projects to the dysfunction of organs and immune system in the early stage, which may expedite the complex pathologic process of PICS.

Albumin and pre-albumin levels are widely used to reflect catabolism, but pre-albumin may be more associated with inflammation.²⁵ Our study showed a significantly lower level of albumin on the first day after ICU admission in the PICS group. This finding was consistent with the catabolic nature of PICS and indicated that catabolism occurs in the early phase of sepsis long before the onset of PICS.

In order to build a model to predict the onset, development, and prognosis of PICS, four parameters were selected to reflect the differences in the pathophysiological nature of the syndrome. SOFA indicates the severity of sepsis, the CCI reflects the comorbidities with the primary illness, the lymphocyte count indicates the status of early immunosuppression, and the albumin level is associated with the extent of catabolism. Each of these four parameters showed the ability to predict PICS, but the results from our study suggested that a combination of the four parameters has an even better predictive capacity for the development of PICS.

Our study has several limitations. First, it is a single-center cohort study with a small sample size, which can unavoidably generate sampling bias. Factually, only a few reported studies on PICS can be found in the literature, and none of them estimated the incidence of PICS in critically ill patients in the ICU. Thus, we were unable to predict the sample sizes for our study. Second, since the pathogenesis and pathophysiological nature of PICS still require further clarification, the parameters and biomarkers that were selected as surrogate predictors for the development of the disease may not truly reflect the complicated nature of PICS. Third, tumor cachexia have similar clinical manifestations to patients with PICS, and the inclusion of tumor surgery patients (nearly 40%) may have an impact. In our study, the BMIs of the patients were 22.85 (19.46–25.08). This showed there is few patient with tumor cachexia, and it seemed to have little impact on our result. We thought further study needed to further understand PICS in such population. Thus, we advocate more well-designed studies, such as randomized controlled trials with a larger number of participants to improve the understanding of the pathogenesis and pathophysiological characteristics of PICS as well as for other related diagnostic and therapeutic issues.

Conclusion

In this study, we found that the chronic disease condition and decreased immunity in the early course of sepsis were crucial contributing factors to the development of PICS. A combination of the CCI, SOFA score, albumin level on the first day, and lymphocyte count on the third day following ICU admission can be a potential predictor for the development of PICS.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Hong-ping Qu on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ruijin Hospital Ethics Committee of Shanghai Jiaotong University School of Medicine, China.

Formal informed consent was obtained from the patients or their next of kin.

Consent for Publication

Consent for publication was obtained from the all the authors.

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Disclosure

The authors declare that they have no competing interests.

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