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Original Article

Diagnostic accuracy of CRP in the drainage fluid for early detection of anastomotic leakage in colorectal surgery – a pilot study

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Abstract

Introduction: Anastomotic leak (AL) in colorectal surgery remains a source of concern, as it jeopardizes patient recovery and increases morbidity, particularly if not detected early. The CRP in the drain fluid has barely been investigated as a new predictive marker of AL that would improve treatment outcomes.

Materials and methods: A prospective pilot study conducted in our department included patients undergoing emergency colorectal surgery and primary anastomosis for benign and malignant disease. The CRP values of the drainage fluids and serum were measured on postoperative day 3 (POD3). The preoperative levels of albumin were also measured. Patients were followed for 2 months after their surgery, for the presence of clinical or subclinical AL. The accuracy of the CRP in the drain on POD3 to predict the incidence of AL was investigated. Secondary outcomes included the relation of the drain's CRP to that of the serum and the incidence of AL in patients with low preoperative albumin levels.

Results: Of the 188 patients who were treated for malignant and benign diseases of the small and large bowel, 56 were included in the study, 12 of whom were found to have an anastomotic leak. The estimated average C-reactive protein (CRP) level in drain fluid on postoperative day 3 (POD3) was significantly higher in the anastomotic leak (AL) group (t-test, t=−6.969, $p<0.001$). After examining the ROC curves, we defined a cut-off value for drain CRP of 77.65 mg/dL. This value demonstrated 91.7% sensitivity and 90.9% specificity in predicting AL. Furthermore, the odds of AL increased by 10.9% (95% CI [4.4%, 17.7%]) with each additional unit of CRP measured in the drain fluid.

Conclusions: Maintaining a simple and cheap-to-measure prognostic factor of AL would be valuable in diminishing the devastating results of delayed leak identification. The CRP in the drain fluid seems a significant prognostic marker. We hope that the inclusion of more patients will confirm our results and highlight their significance.

Keywords

anastomotic leakage, colorectal cancer, CRP, drain

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PENSOFT.

Introduction

Anastomotic leak (AL) constitutes one of the most fearful complications in general surgery. Its incidence remains difficult to measure, with researchers reporting numbers between 2%[1] and 24.7%[2], depending mainly on the site of the anastomoses. In 2018, the European Society of Coloproctology (ESCP) published a large-scale study, which included 4248 patients who underwent colectomy for left-sided cancers and reported an incidence rate of AL of 7.3%.

Although an experienced surgeon can reduce the likelihood of this devastating complication, its impact on morbidity and mortality of the patient necessitates prompt and targeted diagnosis for effective treatment. This is the reason why researchers have turned their attention to potential prognostic factors of AL, such as CRP plasma levels[3], procalcitonin levels[4], and intraoperative blood glucose levels[5].

According to a few researchers, CRP levels in the drainage fluid appear to be a promising prognostic biomarker for AL.[6-9] So far, higher CRP levels in the bloodstream have been linked to postoperative complications in general surgery, but these associations are not specific. The CRP values in the peritoneal fluid could bridge this gap between sensitivity and specificity and constitute a useful indicator of AL, allowing us to achieve better patient outcomes.

AIM

Our study aims to test this hypothesis and explore the correlation of the drainage's CRP to that of the plasma. This way, we could propose a cut-off value for the drain CRP, and constitute the basis for future research, to create combined scores that would achieve even higher accuracy.

Materials and methods

A prospective collection of data was conducted from February 2023 until March 2025. Inclusion criteria were patients treated urgently for malignant as well as benign diseases, in whom an entero-enteric, entero-colic, colono-colonic, or colorectal anastomosis was conducted, and who all had intraperitoneal drains.

Patients who, despite having a drain, did not exhibit any fluid in it on POD3 were excluded from the study.

The peritoneal fluid was collected from the drainage bag on POD 3 and was put in a Wasserman test tube, which was then handed to the laboratory, immediately after collection. CRP in the drainage fluid and CRP and albumin levels in the serum were measured using the standardized laser nephelometry technique. Our laboratory's normal reference range for CRP is <5 mg/L, and for albumin 3.2-4.8 g/dL.

Two independent researchers curated the collected data, and a statistician conducted all statistical analysis and data processing. Variables examined were the primary disease, the type of surgery, and the fashion of anastomosis, the CRP values in the drainage fluid and the serum on POD3 (mg/dL), and the preoperative albumin levels (g/dL). The normality of the data was tested using the Kolmogorov-Smirnov test of normality. The skewness was calculated as 0, and the kurtosis was −1.2, with the value of the K-S test statistics (D) being 0.0676 and the p-value 0.96994, indicating that the data followed a nearly normal distribution. The mean and the standard deviation were calculated for all continuous variables, between the groups of low and high CRP in the drainage fluid.

The two groups were compared using a t-test, and the correlations examined were based on the Pearson's correlation factors.

Postoperatively, the patients were followed up during their hospital stay for signs of anastomotic leak diagnosed clinically when enteric fluid was apparent in the drainage bag, or via a CT scan when the leak was suspected. Patients were reevaluated in the Clinic on PODs 15, 30, 45, and 60, with clinical examination and routine blood tests, in which the CRP in the serum was calculated. One patient was diagnosed two months after her discharge, as she demonstrated a persistent thrombocytosis.

Unfortunately, our study demonstrates some heterogeneity in its sample, as patients suffering from different diseases and having different types of anastomoses were included. However, most of the participants had anastomosis including the colon.

Categorical variables such as the type of anastomosis, and the fashion of anastomosis are described in **Tables 4, 5.1**. Their correlation to the appearance of anastomotic leakage was tested using Fisher's exact test.

ROC curves were used to describe the sensitivity of the CRP in the drainage fluid on POD3 as a predictive factor of AL.

Results

Out of 188 patients who underwent elective or emergency surgery and the creation of an enteric or colonic anastomosis, 56 were finally included in the current study. The rest were either treated electively (96/188), did not have a drain (19/188), or had a drain but no fluid was able to be collected on POD3 (17/188).

Anastomotic leak was defined as any defect in the intestinal wall seen on a radiographic study (either a CT scan or an X-ray) as a leakage of a contrast agent outside the lumen, or as a pelvic abscess close to the anastomosis, or a fistula involving the anastomosis site. For asymptomatic patients, the integrity of the anastomosis was confirmed through either an X-ray after the administration of Gastrografin (for right-sided colectomies and ultra-low resections) or an endoscopic study (for anterior resections and left-sided resections).

The drains remained in place for three to five days postoperatively and were removed as soon as source control

was achieved for the patients.

All leaks were detected between POD 4 and 15, except for one patient who was diagnosed almost 2 months postoperatively due to a persistent thrombocytosis, which led to the conduction of an abdominal CT scan. There were no clinical anastomotic leakages before POD3.

Descriptive analysis

A sample size of 56 participants who underwent colorectal surgery, aged 42 to 91 years old except for a 16-year-old patient, participated in the research. Patient demographics are presented in **Table 1**.

Most patients were treated for malignant disease, with right colon cancer (15/56) and sigmoid cancer (15/56) being the most common diagnosis. One patient with Crohn's disease was included in the study, while the 16-year-old girl who presented with a ruptured ileal diverticulum was later diagnosed with Berardinelli-Seid syndrome. Patients' diagnoses and operations conducted are described in **Table 2**.

Their CRP levels were measured three days postoperatively, regarding fluids of their abdominal drains, with a mean equal to 57.62 mg/L, and regarding their blood, with an average of 125.96 mg/L. Their albumin level was also measured one day before surgery with a mean value of 2.70 g/dl, as shown in **Table 3**. According to **Table 4**, the most frequent type of anastomosis was side-to-side, performed in 69.64% of the patients, whilst in 73.21% of cases, a circular stapler was used as a suture technique. Finally, 12 (12/56, 21.43%) of the patients presented anastomotic leak as a complication.

Table 1. Patient demographics

Men		30 (54%)
Women		26 (46%)
Age (years)	Range	16-91
	Mean	69.7
	Median	72
Clinical presentation	Hemorrhage	15 (27%)
	Large bowel obstruction	27 (48%)
	Small bowel obstruction	11 (19.6%)
	Anal prolapse	1 (1.8%)
	Small bowel diverticulum rupture	2 (3.6%)
Comorbidities	Diabetes mellitus	17
	Dyslipidemia	20
	Epilepsy	2
	Arterial hypertension	30
	Cardiac disease*	12
	Ca other than the GI*[2]	6
	Hypothyroidism	5
	COPD*[3]	7
	Berardinelli-Seip Syndrome	1

*Cardiac disease includes heart failure, valvular disease, and coronary artery disease

*[2]GI: gastrointestinal system, cancers included in this category: breast cancer, kidney cancer, urinary bladder cancer, pheochromocytoma

*[3]COPD: chronic obstructive pulmonary disease

Table 2. Primary disease and treatment strategy

Primary disease	Right colon cancer	15 (26.8%)
	Transverse colon cancer	2 (3.6%)
	Left colon cancer	4 (7.2%)
	Sigmoid cancer	15 (26.8%)
	Rectal cancer	6 (10.8%)
	Adhesions	3 (5.4%)
	Small bowel diverticulum rupture	2 (3.6%)
	Anal prolapse	1 (1.8%)
	AVM* of large bowel	1 (1.8%)
	Diverticulitis	4 (7.2%)
	Strangulated hernia	2 (3.6%)
	Chron's disease	1 (1.8%)
Operation	Right colectomy	21(37.5%)
	Left colectomy	5 (8.9%)
	Sigmoidectomy	17 (30.4%)
	Low anterior resection	8 (14.3%)
	Segmental enterectomy	5 (8.9%)

*AVM: arteriovenous malformation

Table 3. Statistical characteristics of the CRP and albumin levels

	Mean	**Std. deviation**
CRP measured in drain fluid (mg/L)	57.62	32.56
CRP measured in blood (mg/L)	125.96	85.49
Albumin level (g/dL)	2.70	0.66

Table 4. Statistical characteristics of the surgical procedure and possible complications

		N	**%**
Type of anastomosis	Side-to-end	10	17.86%
	End-to-side	6	10.71%
	Side-to-side	39	69.64%
	Side-to-side, End-to-end	1	1.79%
Suture technique	Circular stapler*	41	73.21%
	GIA stapler	15	26.79%
Anastomotic leakage	No	44	78.57%
	Yes	12	21.43%

*Some of the anastomoses conducted with the circular stapler refer to right-sided resections, with a part of them being side-to-side anastomoses.

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Inferential analysis

Tables 5.1 and **5.2** present the statistical analysis of the appearance of anastomotic leakage and patients' characteristics. There appears to be no statistically significant difference between the type of anastomosis or the suture technique and the complication, evidently, from the high p values (Fisher's exact test, for the type test statistic =1.167, p=0.898, for the technique p=0.715). Furthermore, according to **Table 5.2**, the only measure that has a statistically significant difference in the presence or not of anastomotic leakage is CRP measured in drain fluid, specifically the patients that present the complication had a higher estimated average of CRP after abdominal drain on the third postoperative day, shown in **Fig. 1** (t-test, t=−6.969, p<0.001) No statistically significant differences between the two groups of patients were detected regarding the albumin level (p=0.923) or CRP measured in blood (p=0.066).

A logistic regression model indicated a statistically significant and independent effect of CRP measured in drain fluid, while the effect of albumin levels did not reach statistical significance. The Odds Ratio of AL increase by 10.9% (95% CI [4.4%, 17.7%]) for each unit of higher CRP measured in drain fluid (p=0.001). However, albumin levels were not a statistically significant predictor of AL (OR=6.40, 95% CI [0.96, 42.92], p=0.056).

The correlation between the two measurements of CRP is statistically significant and positive (r=0.528; p<0.001) indicating that higher CRP measurements in the drain are expected for higher CRP measurements in the blood. The relationship is described in **Fig. 1** (scatterplot 1).

To evaluate the accuracy of using CRP to diagnose anastomotic leakage in patients undergoing colorectal surgery, we examined ROC curves and defined a cut-off value for CRP at 77.65 mg/L (range 77.65 to 79.5 mg/L). This value demonstrated 91.7% sensitivity and 90.9% specificity. The area under the curve (AUC) was estimated at 0.900, with a 95% confidence interval ranging from 0.754 to 1.045.

Examining the model's ROC curve demonstrates a sensitivity of 91.7% and a specificity of 95.5%. The AUC was estimated to be 0.939, with a 95% CI ranging from 0.847 to 1.000 **(Fig. 2)**.

Discussion

Anastomotic leakage is one of the most debated topics in general surgery. Currently, it is defined as any defect in the intestinal wall that is visible in a radiographic study, most commonly a CT scan, and involves the leakage of a contrast agent outside the lumen.[10] However, this definition is difficult to apply in everyday practice for the accurate diagnosis of leaks.

Therefore, many authors have provided additional commentary on this definition based on their experience. In 2020, the Italians made a significant addition when they defined AL as not only a leak of intraluminal content, but also "a pelvic abscess close to the anastomosis, even without any evident communication with the colonic lumen."[11]

This is an interesting statement that has the potential to alter the incidence rates of AL among surgeons. Nonethe-

Table 5.1. Statistical analysis of anastomotic leakage and patients' characteristics

		Anastomotic leakage				Fisher's exact test	*p*
		No		Yes			
		N	%	N	%		
Type of anastomosis	Side-to-end	7	70.00%	3	30.00%	1.167	0.898
	End-to-side	5	83.33%	1	16.67%		
	Side-to-side	31	79.49%	8	20.51%		
	Side-to-side, End-to-end	1	100.00%	0	0.00%		
Suture technique	Circular stapler	33	80.49%	8	19.51%	-	0.715
	GIA stapler	11	73.33%	4	26.67%		

Table 5.2. Statistical analysis of the anastomotic leakage and the patients' characteristics

	Anastomotic leakage	N	Mean	Std. deviation	t	*p*
CRP measured in drain fluid (mg/L)	No	44	46.03	19.26	−6.969	**<0.001**
	Yes	12	100.14	36.62		
Albumin level (g/dL)	No	44	2.70	0.67	−0.097	0.923
	Yes	12	2.72	0.67		
CRP measured in blood (mg/L)	No	44	115.02	80.51	−1.875	0.066
	Yes	12	166.06	94.71		

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
Step 1[a]	CRP measured in drain fluid	0.078	0.023	11.983	1	0.001	1.082	1.035	1.131
	Constant	−6.758	1.800	14.093	1	0.000	0.001		
Step 2[b]	CRP measured in drain fluid	0.103	0.031	11.354	1	0.001	1.109	1.044	1.177
	Albumin levels	1.857	0.971	3.660	1	0.056	6.404	0.956	42.922
	Constant	−13.452	4.465	9.078	1	0.003	0.000		

a. Variable(s) entered on step 1: CRP measured in drain fluid.
b. Variable(s) entered on step 2: albumin levels.

Scatterplot 1. Correlations		
		CRP measured in blood
CRP measured in drain fluid	Pearson correlation	0.528
	Sig. (2-tailed)	**<0.001**
	N	56

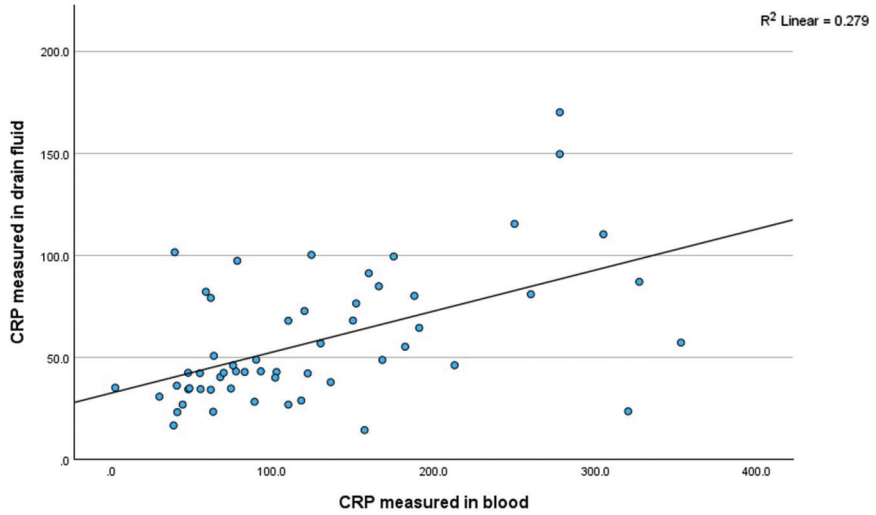

Figure 1. Statistical analysis of anastomotic leakage and CRP level in drain fluid.

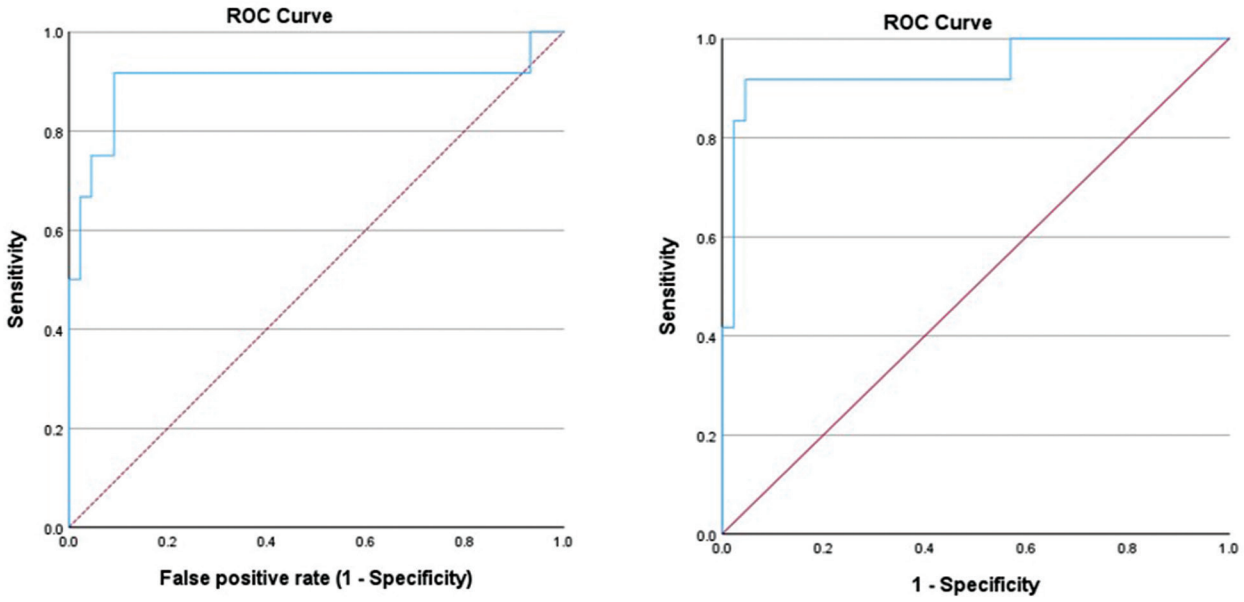

Figure 2. Accuracy of the CRP in drain fluids of patients in predicting anastomotic leakage.

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less, the concept seems correct, as it is not uncommon to treat patients with postoperative intra-abdominal abscesses, anastomosis-related fistulas, or persistent anastomosis strictures, even without evident or obvious symptoms.[11]

Due to its high morbidity, it is important to diagnose AL early in the postoperative period. The most accurate tool for predicting AL thus far seems to be the Dutch Leakage Score (DULS), created by Den Dulk et al.[12] This score combines thirteen clinical parameters, each of which is assigned 1 or 2 points. The final score ranges from a minimum of 1 to a maximum of 20 points. A score higher than 4 indicates a high likelihood of AL, with a sensitivity of 97%. However, since the parameters of this score practically describe an inflammatory response that could be triggered by several factors during the postoperative period, its specificity remains low (53.5%).

The same goes for the modified DULK score, a simplified version of the previous one, containing only four parameters (respiratory rate >20/min, deterioration of the clinical condition, abdominal pain, other than wound pain, and serum CRP >250 mg/L) to make it easier to calculate and more useful in everyday practice.

If someone calculated the DULK and the modified DULK scores of our study's population, they would be positive in most patients demonstrating AL. Nonetheless, they would also be positive in many elderly patients, with minor respiratory or urological complications.

The use of peritoneal fluid CRP values to predict anastomotic leakages is a relatively new concept that is viewed with skepticism by many due to the creation of the Enhanced Recovery After Surgery (ERAS) protocol for general surgery.[13] However, the ERAS protocol was initially designed for elective cases and shows differences in outcomes for patients undergoing emergent surgery. Specifically, the World Society of Emergency Surgery (WSES) reports that using drains is justified in cases of contaminated pelvises and advises removing the drains as soon as source control is achieved.[14]

A systematic review conducted by the Kapodistrian University of Athens' MIS group[15] (Minimally Invasive Surgery) on the use of CRP in the drainage fluid as a predictor of AL in general surgery found that patients with anastomotic leakage had higher CRP values in their drain fluids than those who did not. With measurements taking place on the third or fourth postoperative day, the mean drain CRP in the AL group was 167.7 mg/L, in contrast to 83.76 mg/L in the non-AL group. This was the first indication that the drain's CRP could be used to distinguish patients with an AL from those who did not. However, the study could not set a specific cut-off value, as the heterogeneity of the population included was significant.

Our findings are consistent with the literature, which suggests that patients with anastomotic leakage have higher CRP levels in their drainage fluid on POD3 than those without. The heterogeneity of our population was much smaller than that of the existing research, highlighting the significance of our findings.

Another debatable matter is the relationship between the drain and the serum CRP levels. In our study and the literature[7,9], there is a correlation between the two variables (moderate correlation, as indicated by the Pearson correlation factor). This means that higher CRP levels in the drain are accompanied by higher CRP values in the plasma. This finding could be misleading, as one might argue that in this case, we do not need to measure the drainage CRP to predict AL. However, research has shown that the accuracy of serum CRP in predicting AL is low, mainly based on its staying at high levels after several postoperative days, and when combined with other biomarkers such as procalcitonin.[16,17] Furthermore, all researchers agree on the significant lack of specificity of the serum CRP in diagnosing AL. Even Mišić et al.[18], who, in a series of 59 patients undergoing colectomy, indicated that the serum CRP was increased earlier during abnormal anastomotic healing and could predict AL, while the drain's CRP levels remained high for a longer period and was a poorer predictor, demonstrated a peak sensitivity of 70%.

On the contrary, using the drainage fluid's CRP, we reached a specificity of 90% in predicting AL. This allows us to recommend this variable as a new effective predictive marker, but we can also assume that combining it with others, such as procalcitonin or possibly proinflammatory cytokines in the peritoneal fluid, will result in a combined score that will even more accurately predict a leak.

A possible explanation for the increased CRP in the peritoneal fluid arises from the inflammatory response triggered by the tissue damage around the anastomosis site. CRP's role in host immunity is to promote phagocytosis by macrophages. It does that by enabling the binding of surface lysophosphatidylcholine of dead or dying cells and bacteria, thus activating the complement.[19] Its plasma half-life is 19 hours, so if no inflammatory process progresses, it quickly resolves after surgery.

In a meta-analysis by Wright et al.[20], seven studies explored the role of inflammatory cytokines in the peritoneal fluid, detecting AL. Among others, TNFa and interleukin-6 demonstrated the highest significance between the POD2 and POD6. In addition, the role of several metalloproteinases such as MMP-9 was investigated in anastomotic healing and was positively correlated with complications such as AL and anastomotic stricture.

All this data suggests that we have several biomarkers that we could combine to achieve maximum accuracy in diagnosing AL. Nevertheless, CRP remains the cheapest and easiest to measure by all laboratories worldwide.

Conclusions

Our findings indicate that C-reactive protein in the peritoneal fluid of patients undergoing colorectal and small bowel surgery can accurately predict abdominal leakage. This could enable clinicians to change their course of action early after surgery, protecting their patients from the negative

consequences of AL, including reoperation.

However, our study has some limitations, such as the relatively small sample size and the heterogeneity of our population. However, to our knowledge, this is one of the few existing studies in the literature that provides proof that CRP in drainage fluid can predict AL.

We hope to lay the groundwork for larger-scale future studies that will better validate the significance of our findings.

Authors' contributions

Conceptualization: I.K.; study design: I.K. and G.A.; original draft: I.K. and G.A.; data collection and processing: N.P.; project manager: P.G. and A.R.

Ethical approval

All patients have given an informed, written consent on their admission day, for the use of their medical data for research purposes. The current study protocol was approved by the Hospital's Ethics Committee.

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Competing interests

The authors have declared that no competing interests exist.

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