“Fistura Score” as a Predictive Instrument for Anastomotic Leak

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Abbreviations:

AL: anastomotic leak,

CKD: chronic kidney disease,

CHF: congestive heart failure,

eGFR: estimated glomerular filtration rate,

GIST: gastrointestinal stromal tumor,

AF: atrial fibrillation,

Se: sensibility,

Sp: specificity,

PPV: predictive positive value,

PNV: predictive negative value,

OR: odds ratio,

USP: United States Pharmacopeia.

Rezumat

“FISTULA SCORE” - instrument predictiv pentru fistula de anastomoză

Introducere: O anastomoză patentă este rezultatul tehnicii chirurgicale adaptată la terenul pacientului. Cunoscându-se posibilele efecte dramatice pe care le poate avea o fistulă post-anastomotică asupra pacientului și a personalului medical, identificarea factorilor de risc pentru apariția acesteia reprezintă o prioritate în alegerea tehnicii chirurgicale adoptate.

Material și Metode: Folosirea de scoruri multifactoriale permite cuantificarea pacientului la risc, creșterea gradului de suspiciune și inițierea precoce a tratamentului adecvat. A fost studiată corelația dintre diverși potențiali factori de risc și prezența unei fistule de anastomoză. FISTULA SCORE reprezintă un instrument de departajare a riscului ce include 12 variabile (clinice, paraclinice, terapeutice), cu o semnificație statistică bună (Se = 79.5%, Sp = 90.2%).

Rezultate: Din cei 508 pacienți incluși în studiu, 39 au dezvoltat fistule de anastomoză (7.68%, 95% CI: 5.67-10.32), apărute în zilele 2-10 postoperator, cu o valoare medie de 6 zile. “FISTULA SCORE” se bazează pe atribuirea riscului pentru fiecare variabilă studiată, având scopul de a identifica pacienți ce pot dezvolta fistule de anastomoză și în unele situații de a schimba strategia terapeutică sau chirurgicală. În grupul de pacienți cu fistula de anastomoză, scorul mediu a fost de 5.06 puncte (DS=1.95 puncte), în timp ce în grupul fără fistule a fost de 1.57 puncte (DS=1.61 puncte).

Concluzii: Riscul de fistulă de anastomoză trebuie apreciat și

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cuantificat cu un sistem multivariabil de scor. "FISTULA SCORE" poate identifica, cu o semnificație statistică bună, pacienții la risc pentru fistule de anastomoză, modificând managementul cazului, diminuând durata de spitalizare, costurile, mortalitate și impactul psihologic asupra pacientului și personalului medical.

Cuvinte cheie: anastomoză, fistulă, factori de risc, scor

Abstract

Introduction: A patent digestive anastomosis is not only the result of the surgery team experience, but also dependent on the patient's factors. Accepting the possible dramatic effects of an anastomotic leak, identification of risk factors remains a priority in case management.

Material and methods: Multifactorial assessment scores permit risk quantification, increase grade of suspicion and early management implementation. The correlation between diverse potential risk factors and anastomotic leak (AL) was studied. The identified risk factors were included in a predictive score system. FISTULA SCORE represents a feasible instrument based on 12 clinical, paraclinical and therapeutic variables, with good statistical significance (Se = 79.5%, Sp = 90.2%).

Results: Anastomotic leaks (AL) were observed in 39 cases (7.68%) out of 508 patients analysed, appearing in days 2 – 10 after surgery, with a mean value of 6 days. FISTULA SCORE was based on attributed risks found in our study group for each factor and has the purpose to identify patients at risk for AL and, in some cases, to change the therapeutic or surgical strategy. In AL patients' group, the mean score was 5.06 ± 1.95 points, and in AL-free patients' group – 1.57 ± 1.61 points.

Conclusions: The risk for AL must be appreciated and quantified with a multivariable scoring system. FISTULA SCORE can identify, with a good statistical significance, patient at risk for AL, changing the management of case, reducing length of stay, costs, morbidities, mortality and psychological effects on patient and medical staff.

Key words: anastomosis, anastomotic leak, risk factors, FISTULA SCORE

Introduction

An anastomosis in good conditions represents the best way to finish a resection in digestive surgery, for non-oncological, malignant or borderline pathologies, in children or adult patients (1,2). Studied for a long time, a lot of techniques of anastomosis were proposed, but not all of them can certainly eliminate the risk of leakage (AL) - the most severe complication of an anastomosis (3). The reported incidence in national and international studies can vary by author, differences based on surgery team experience, center profile, site of anastomosis (4,5). We have to accept that AL is a reality and all patients with this complication are at risk for prolonged length of hospital stay,

morbidities, poor long-term outcome and death (6,7). The most frequent risk factors cited in literature are male sex, obesity, diabetes, advanced malignant disease, ASA score, perioperative blood loss or perioperative transfusion, long operation time, emergency operation and altered nutritional status (8,9).

Identification of patients at increased risk for anastomotic dehiscence is imperative for surgical approach choice and early diagnosis of AL. AL result from an interrelation of a multitude of risk factors and multiple risk assessment scores were proposed (The REAL Score – Rectal Anastomotic Leak Score, mCLS – modified Colon Leakage Score, DIACOLE) (10-12). Unfortunately, none of these can identify or predict all cases of AL and other

scoring systems with improved predictive power are needed.

Materials and Methods

A retrospective analysis of the medical records of a consecutive 508 patients who underwent surgical bowel resection for different pathologies, between January 2015 and December 2020, at 1st Department of General Surgery of the University Emergency Hospital, Bucharest, was carried out. This study was approved by Ethics Committee of the Emergency University Hospital of Bucharest (Romania). Written informed consent was obtained from the patients prior to publication.

The inclusion criteria were: [1] both sexes, [2] age ≥ 18 years, [3] benign or malignant pathologies, and [4] surgical procedure with at least one intestinal anastomosis. Conversely, the exclusion criteria were: [1] age < 18 years, [2] surgical procedure without anastomosis (with end stoma only).

For each patient, data such as sex, age, place of origin, hospitalization regime, type of pathology, type and technique of the performed anastomosis, length of stay, associated pathologies, occurrence of AL and complications and various laboratory data (hemoglobin, protein status, serum calcium) were extracted from the records.

The diagnosis of AL was established by clinical examination, radiological examination, endoscopy or reoperation.

The characteristics of study group are described in *Table 1*.

The correlation between diverse potential risk factors (sex, age, nature of pathology, preoperative hemoglobin, necessity of blood transfusion, total proteins, albumin, blood calcium, obesity, cardiac arrhythmias, congestive heart failure, atherosclerosis, diabetes, liver pathologies, renal failure, presence of peritonitis, gut obstruction, presence of metastasis, hemodynamic instability, type of admission, anastomosis technics) and AL was studied. The identified risk factors were included in a predictive score system.

Table 1. Description of study group

Characteristics		n	%	IC (95%)
Sex	Male	281	55.31	50.97 – 59.58
	Female	227	44.69	40.42 – 49.03
Place of origin	Urban	325	63.98	59.71 – 68.03
	Rural	183	36.02	31.97 – 40.29
Age group (years)	18 – 25	6	1.18	0.54 – 2.55
	25 – 34	13	2.56	1.50 – 4.33
	35 – 44	23	4.53	3.04 – 6.70
	45 – 54	46	9.06	6.86 – 11.87
	55 – 64	129	25.39	21.80 – 29.35
	65 – 74	159	31.30	27.42 – 35.46
	75 – 84	115	22.64	19.21 – 26.47
Admission	> 85	17	3.35	2.10 – 5.29
	Emergency	130	25.59	21.99 – 29.56
Type of pathology	Scheduled	378	74.41	70.44 – 78.01
	Benign	114	22.44	19.03 – 26.27
Anastomotic leak	Malignant	394	77.56	73.73 – 80.97
	Yes	39	7.68	5.67 – 10.32
Death	No	469	92.32	89.68 – 94.33
	Yes	21	4.13	2.72 – 6.24
	No	489	95.87	93.76 – 97.28

Statistical Analysis

Collected data were processed using statistical analysis programs Microsoft Excel 2016 and Epi Info™ 3.5.3 (<https://www.cdc.gov/epiinfo/index.html>; Centers for Disease Control and Prevention; CDC). Continuous data (as age, hemoglobin level) were calculated as mean and standard deviation (SD). Data were compared between groups using two-tailed Student's t-test. Categorical data (as gender, necessity of blood transfusion) were analyzed using a chi-square test or Fisher's exact probability test. Differences were considered statistically significant at a probability value of $P < 0.05$. To determine whether a studied condition is a risk factor and to compare the magnitude of those factors for AL the odds ratio (OR) was used.

Results

Out of 508 patients, 281 were male (55.3%) and 227 were female (44.7%), with a mean age 65.5 ± 12.9 years.

The majority of anastomosis was made manually (423 anastomosis, 83.27%), in a single plane (365 anastomosis, 87.11%), with polypropylene (366 anastomosis, 87.35%), 3-0

USP (241 anastomosis, 57.66%).

ALs were observed in 39 cases (7.68%), appearing in days 2 – 10 after surgery, with a mean value of 6 days. Almost a half of patients with AL were reoperated (18 cases, 46.15%).

General mortality in studied group was 4.13% (21 cases), greater in AL group (7 cases, 17.95%), versus non-AL group (14 cases, 2.99%).

Malignant pathologies were the most common type (394 cases, 77.6%), including malignant GISTs. Identified differences of occurrence of ALs were statistically insignificant between men (25 cases, 8.90%) and women (14 cases, 6.17%) ($P=0.25$), between patients with benign (114 patients, 5.3%) and malignant nature of pathology (394 patients, 8.3%) ($P=0.27$), protein or albumin status ($P=0.35$ and $P=0.33$). Emergency surgery was affected by 11.54% of AL incidence (95% CI: 6.60-18.32), scheduled – by 6.35% incidence (95% CI: 4.30-9.27) ($P=0.05$). There were no significant differences between hand sewn or mechanical anastomosis and AL incidence ($P=0.51$).

Mean hemoglobin (Hb) level was 11.57 ± 2.15 g/dL, smaller in AL group (10.18 ± 2.05 g/dL) compared with non-AL group (11.69 ± 2.12 g/dL) ($P=0.001$).

Preoperative serum calcium level (Ca) was analyzed in 169 patients. The mean value was 8.67 ± 0.91 mg/dL, with 8.15 ± 1.03 mg/dL in AL group and 8.75 ± 0.92 mg/dL in non-AL group. In 67 of 169 patients (37.43%) we found that Ca level was below 8.5 mg/dL, including them in hypocalcemia group. Hypocalcemia was observed in 11 of 18 patients with AL (61.11%) and in 56 of 161 patients without postoperative anastomotic dehiscence (34.78%). In normal serum calcium level group AL occurred in 6.25% of cases (7 patients) and in 16.42% (11 cases) of cases in patients with hypocalcemia ($P<0.001$).

AL incidence in patients with advanced oncologic pathologies with presence of distant metastasis was 20.51% (8 cases), significantly greater than in patients without metastasis ($P=0.002$).

Studying the medical histories, we observed that presence of atherosclerotic disease, arrhythmias, diabetes, liver diseases, obesity, chronic kidney disease or acute renal injury favor appearance of AL (*Table 2*).

Atherosclerosis was found in 136 patients (26.77%), with no significant difference between sexes ($P=0.21$). AL was present in 28 patients of them (20.59%). The incidence of AL in non-atherosclerotic patients was 2.96% (11 cases). We conclude that atherosclerosis can be included in risk factors' list considered as a risk factor for AL ($P<0.001$).

Sixty-eight patients were known or diagnosed de novo with diabetes (13.39%), without significant differences between men and women ($P=0.34$). In this group ALs occurred in 17.65% of patients (12 cases), more frequent than in non-diabetic group of patients (6.14%), differences being significant ($P=0.003$).

Atrial fibrillation (AF) was the preponderant heart arrhythmia identified in this group (9.45%). AL incidence in patients with AF was 20.83% and 6.30% in non-arrhythmic patients ($P<0.001$).

Presence of acute or chronic liver diseases negatively affect AL incidence (17.07%, vs. 6.85%) ($P=0.02$).

The same effect was observed in patients with congestive heart failure. AL incidence was 19.44% vs 6.78% ($P=0.006$).

Anastomosis was made in 92 of patients with acute or subacute intestinal obstruction, more than a half of those for tumoral pathologies (57.61%). AL was observed in 13 patients (14.13%, 95% CI: 7.74-22.95). Data analysis show that a patient with bowel obstruction is more exposed to AL, comparing with patients without intestinal obstruction ($P=0.01$).

Presence of peritonitis was noted in 45 patients (8.86%). Postoperative period was marked by ALs in 7 of them (15.56%). The AL incidence in non-peritonitis patients was 6.91% (32 patients). Comparing this data we conclude that peritonitis favor appearance of AL and can be included in the list of risk factors ($P=0.037$).

Hemodynamic instability (objected especially by hypotension, arrhythmias) was

Table 2. Risk factors, associated incidence of AL and statistical significance

Risk factor		AL+		AL-		P*
		n	%	n	%	
Atherosclerosis	Yes	28	20.59	108	79.41	<0.001
	No	11	2.96	361	97.04	
Diabetes	Yes	13	18.84	56	81.16	0.002
	No	26	5.92	413	94.08	
Atrial fibrillation	Yes	10	20.83	38	79.17	<0.001
	No	29	6.30	431	93.70	
Liver disease	Yes	7	17.07	34	82.93	0.018
	No	32	6.85	435	93.15	
Obesity	Yes	11	21.57	40	78.43	<0.001
	No	28	6.13	429	93.87	
Kidney disease	Yes	9	32.14%	19	67.86%	<0.01
	No	30	6.25%	450	93.75%	
Metastasis	Yes	8	20.51%	31	79.49%	0.002
	No	31	6.61%	438	93.39%	
Hb < 10 g/dL	Yes	15	14.02%	92	85.98%	0.006
	No	24	5.99%	377	94.01%	
Hypocalcemia	Yes	11	16.42%	56	83.58%	0.028
	No	7	6.25%	105	93.75%	
CHF**	Yes	7	19.44%	29	80.56%	0.006
	No	32	6.78%	440	93.22%	
Peritonitis	Yes	7	15.56%	38	84.44%	0.037
	No	32	6.91%	431	93.09%	
Intestinal obstruction	Yes	13	14.13%	79	85.87%	0.010
	No	26	6.25%	390	93.75%	
Haemodynamic instability	Yes	9	20.45%	35	79.55%	<0.001
	No	30	6.47%	434	93.53%	

*determined using chi-square test; **chronic heart failure; presence of anastomotic leak (AL+); absence of anastomotic leak (AL-)

observed and treated in 44 patients (8.66%), and was the main indication for vasopressors or inotropes use. We found that patients with this type of pre-, intra- and post-operative treatment develop AL more often, compared with hemodynamically stable patients (20.45% vs 6.47%) ($P<0.001$).

AL occurred in 21.57% of patient with obesity (11 cases) versus 6.13% in patients without obesity (28 cases) ($P<0.001$).

Acute or chronic kidney diseases was found in 28 cases (5.51%), without significant difference between sexes ($P=0.55$). In 9 of 39 cases of AL, patients were diagnosed with kidney insufficiency (23.08%). AL occurred in 32.14% (9 cases) of patients with renal diseases and in 6.25% of patients without this type of pathology (30 cases) ($P<0.001$).

These data, presented above, were summarized in *Table 2*.

Identifying those factors we propose a risk evaluation score, based on 12 of them: eight

associated pathologies or personal pathological histories, two clinical and imagistic variables (intestinal obstruction, peritonitis) and two therapeutical variables (necessity of blood transfusion and/ or vasopressors).

To temper the effect of OR and to make measures symmetrically, the weight of every risk factor was calculated as natural logarithm of OR, - noted with "k" (*Table 3*).

The total score was calculated as sum of "k" coefficient for every present risk factor:

The minimal possible score is 0 points (if there are no risk factors) and the maximum possible is 16.22 points.

The mean score in our study group was 1.84 ± 1.89 points, with 0 points minimal and 11.12 points maximum values. In AL patients' group, the mean score was 5.06 ± 1.95 points, and in AL-free patients' group – 1.57 ± 1.61 points.

The optimal cut-off value was determined using the Younden's index and accuracy. For a cut-off value of 4 points, the sensibility of the

Table 3. Risk factors included in FISTULA SCORE and value of weight (k) used for risk quantification

Variables	OR	k	Variables	OR	k
Presence of obesity	4.21	1.44	Presence of spreaded cancer	3.64	1.29
Presence of heart arrhythmia	3.91	1.36	Presence of congestive heart failure	3.32	1.20
Presence of diabetes	3.28	1.19	Blood transfusion need	4.43	1.49
Presence of liver pathologies	2.80	1.03	Vasopressors need	3.72	1.31
Presence of renal disease	7.11	1.96	Presence peritonitis	2.48	0.91
Presence of atherosclerosis	8.51	2.14	Presence of intestinal obstruction	2.47	0.90

score is 79.5% and the specificity is 90.2%, with a predictive positive value of 40.26%, predictive negative value of 98.14%, and accuracy of 89.4%. ROC curve based on risk points can be found in *Graphic 1*.

We named this preoperative risk quantification system “FISTULA SCORE”, acronym result from: Fat (obesity), Irregular heartbeat (arrhythmias), Sugar (diabetes), Transfusion need, Untouchable abdomen (peritonitis), Liver pathologies, Atherosclerosis, Spreaded cancer (presence of distant metastasis), Congestive heart failure, intestinal Obstruction, Renal failure, Epinephrine need (hemodynamic instability).

Discussion

AL remain a serious complication in digestive surgery, increasing the length of stay and associated costs, affecting the overall survival rate, delaying the start of adjuvant treatment, involving sometimes different complex thera-

peutic strategies and emotionally affecting not only the patient, but also the surgeon and all medical staff (13-16).

Identifying risk factors in every patient is mandatory, but not enough to assess the risk of AL, especially in those with more than one. The presence of multiple associated conditions favorable for AL return a final risk, different from the simple sum of risks, even if it is necessary to apply a complex formula.

There are a lot of other negative factors identified in this study or in others (17,18), not included in this proposed score. We demonstrated the impact of hypocalcemia on AL in a smaller group of patients, even if the complete pathophysiological mechanism is unclear and the causes of hypocalcaemia can be various.

Anemia and other disorders linked to renal diseases can't be separate from other causes (18-21) and were studied as independent risk factors, as well as pathologies affecting renal function (22). The differences between eGFR, hemodialyzed and non-hemodialyzed subgroups wasn't been studied, even if it was known that first group of patients are pre-disposed to chronic inflammation (23) and transmissible diseases (24) and can have a poorer outcome.

Our score (FISTULA SCORE) was based on attributed risks found in our study group for each factor and has the purpose to identify patients at risk for AL and, in some cases, to change the therapeutic or surgical strategy (diverting stoma). Using FISTULA SCORE preoperatively, even an unexperienced surgeon can choose between a surgical strategy implying an anastomosis or a Hartmann's procedure (5).

This score has a good sensibility, specificity

Graphic 1. ROC curve for FISTULA SCORE

and predictive negative value, but a low predictive positive value. By applying this score, it is important to consider risk-benefit assessment.

For practical benefits, larger studies are required and other identified risk factors can be included.

Conclusions

AL have multifactorial aethiology and not all the factors are known yet. The risk for AL must be appreciated and quantified with a multivariable scoring system.

FISTULA SCORE can identify, with a good statistical significance, patients at risk for AL, changing the case management, reducing length of stay, costs, morbidities, mortality and psychological effects on patient and medical stuff.

Authors' Contribution

CB, DS, DG designed the study, performed the literature search and selected the included studies, performed statistical analysis and interpretation of the results. CB wrote the paper. IA, DV critically revised the manuscript. All authors read and approved the final version of the manuscript.

Availability of Data and Materials

The used and/or analyzed data sets during the present study are available from the author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval and Consent to Participate

This study was approved by Ethics Committee of the Emergency University Hospital of Bucharest (Romania) (approval no. 50706/08.10.2020). Written informed consent was obtained from the patients prior to publication.

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