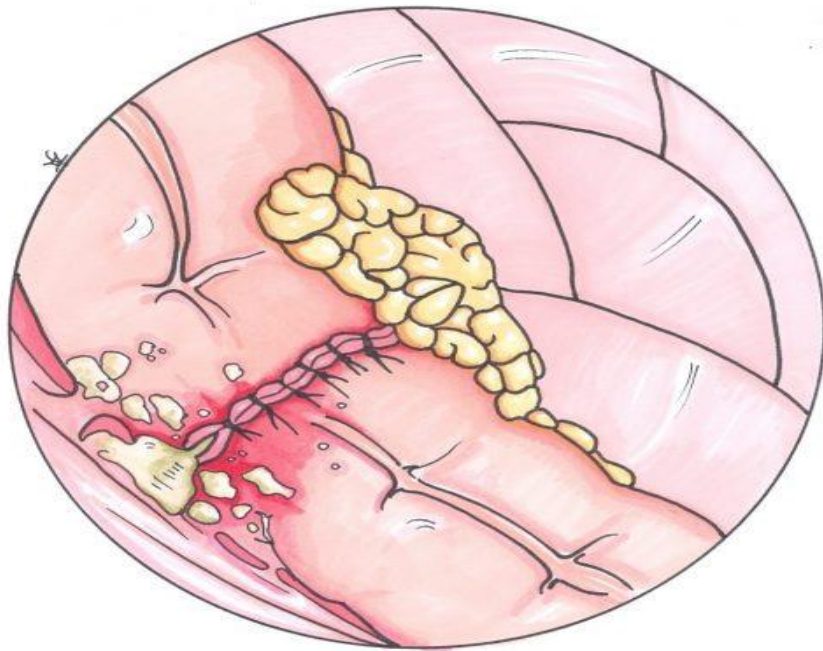


«Κλινικές και παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών»



ΜΑΝΕΣ ΚΩΝΣΤΑΝΤΙΝΟΣ

Γεν. Χειρουργός

Επιμελητής Α΄

Χειρουργική Κλινική

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«Κλινικές και παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών»

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Παρά:

- Πρόοδο αντιμετώπισης χειρουργικών λοιμώξεων,
- Χρήση νέων εργαλείων,
- Καλύτερη κατανόηση των παραγόντων κινδύνου Α.Δ.,
- Βελτίωση της περιεγχειρητικής φροντίδας,



Δυσκολία αναγνώρισης κι αντιμετώπισης Α.Δ.

Οι πιο σοβαρές επιπτώσεις της αναστομωτικής διαφυγής =
ΣΗΨΗ + ΘΝΗΤΟΤΗΤΑ



- > νοσηρότητα
- Poor QOL
- > κόστος
- > θνητότητα

AL (short term impact)

Kennedy. Ann R Coll Surg Engl 2008

Bertelsen . Colorect Dis 2010

ΟΓΚΟΛΟΓΙΚΟΣ ΑΝΤΙΚΤΥΠΟΣ

- > τοπική υποτροπή
 - < συνολική επιβίωση
- } **AL** < long term outcome

Kennedy. *Ann R Coll Surg Engl* 2008

Bertelsen . *Colorect Dis* 2010

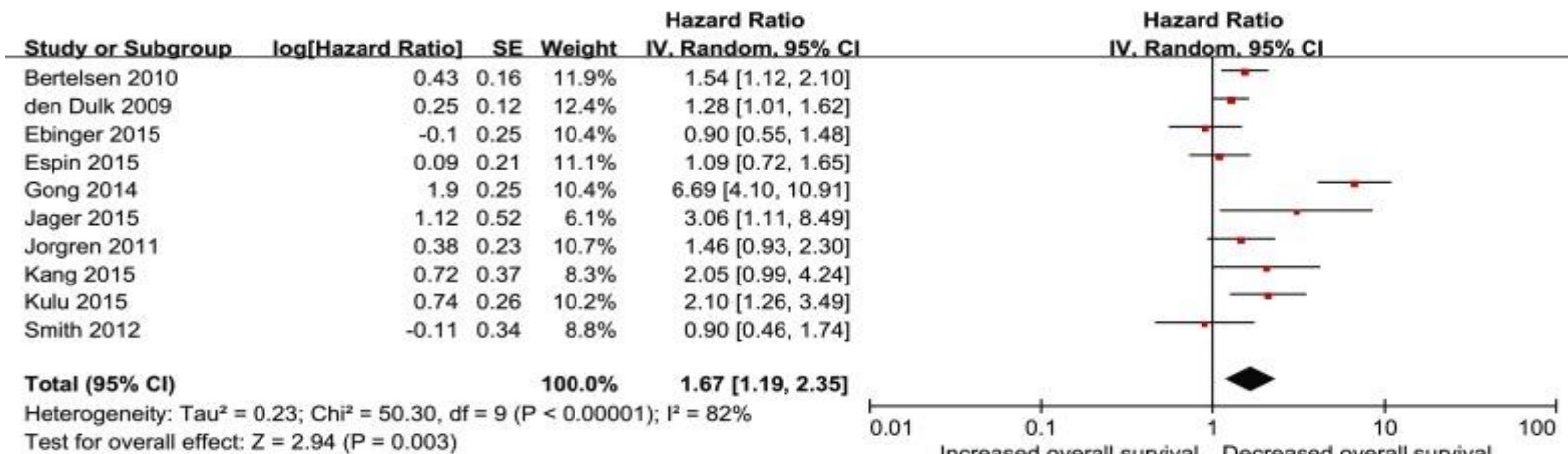
Reshef. *Dis Colon Rectum* 2012

SCIENTIFIC REVIEW

Adverse Effects of Anastomotic Leakage on Local Recurrence and Survival After Curative Anterior Resection for Rectal Cancer: A Systematic Review and Meta-analysis

Shuanhu Wang¹ · Jingjing Liu¹ · Shan Wang¹ · Hongyun Zhao¹ · Sitang Ge¹ · Wenbin Wang²

- 14 studies
- 11353 pts





- ***Delay*** in the recognition and intervention of a significant anastomotic failure has been demonstrated to contribute directly to > mortality.

Almeida. Inter J Surg 2012

- Delayed diagnosis (after POD 5) of AL is associated with a mortality rate of 18%, but minimal morbidity if diagnosed and treated before POD 5.

Alves. World J Surg 2012

κλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- Περισσότερα συμπτώματα κι ευρήματα
ΜΗ ΕΥΑΙΣΘΗΤΑ και ΜΗ ΕΙΔΙΚΑ.
- Επιπρόσθετα, πολύ Χαμηλές Πρόσθιες Εκτομές συνοδεύονται από **προφυλακτική ΕΙΛΕΟΣΤΟΜΙΑ ΕΚΤΡΟΠΗΣ.**

Thomas. *Clin Colon Rectal Surg* 2016

Rickert.

Colorectal Dis 2010

κλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- *Ταχυκαρδία,*
- *Υπερθερμία,*
- *Ταχύπνοια,*
- *Ολιγουρία,*
- *Διαταραχές επιπέδου συνείδησης*



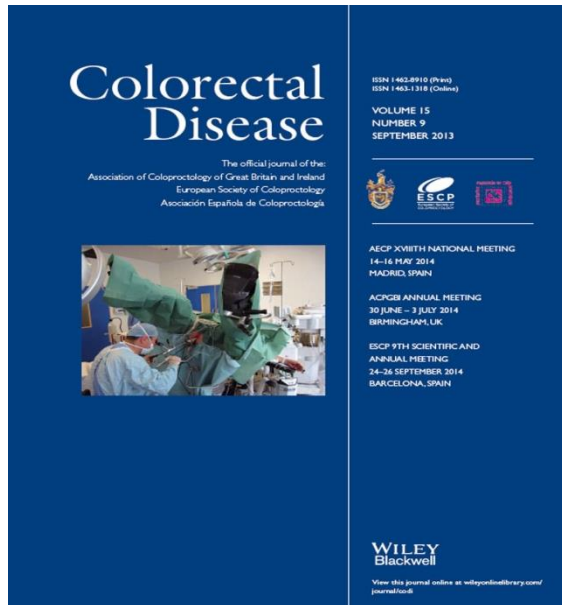
ΚΛΙΝΙΚΗ ΥΠΟΨΙΑ **AL**

ΣΥΝΗΘΩΣ ΜΕΤΑ την 4 μτχ.

Bellows . Tech Coloproctol 2009
Kingham . J Am Coll Surg 2009

Thomas. Clin Colon Rectal Surg 2016

κλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών



a useful clinical tool in the diagnosis of AL

modified DULK score:

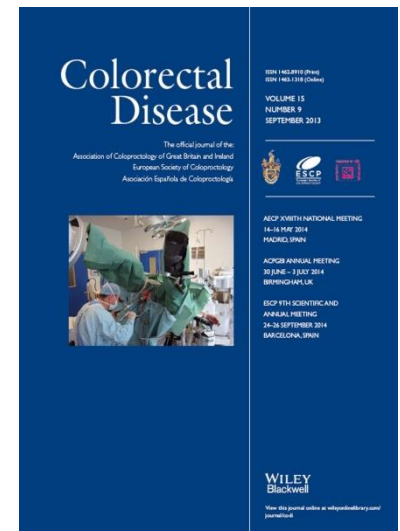
- clinical condition,
- *abdominal pain not localized at the wound,*
- CRP level
- respiratory rate.

The DULK (Dutch leakage) and modified DULK score compared: actively seek the leak
M. den Dulk. *August 2013*

The DULK (Dutch leakage) and modified DULK score

- 782 pts
- 5 Dutch centers
- between October 2007 and November 2009
- 10.4% clinical AL

M. den Dulk. *Colorect Dis* August 2013



The modified DULK score

- With at least one parameter present:
 - 1. overall sensitivity for AL = 97%,**
 2. overall specificity = 57%,
 3. PPV = 17% and
 - 4. NPV = 99.5%.**
- With at least 2 points PPV = 41% and with 3 points 57%.

Observational Study

Definition of colorectal anastomotic leakage: A consensus survey among Dutch and Chinese colorectal surgeons

Stefanus J van Rooijen, Audrey CHM Jongen, Zhou-Qiao Wu, Jia-Fu Ji, Gerrit D Slooter, Rudi MH Roumen, Nicole D Bouvy

Table 2 Sensitivity scores of clinical parameters for the suspicion of anastomotic leakage in the direct postoperative period in China and The Netherlands

Clinical parameter	China	The Netherlands	<i>P</i> -value
	Score \pm SD	Score \pm SD	
<u>Increased CRP</u>	4.35 \pm 2.466	7.45 \pm 1.871	< 0.001
Leukocytosis	5.96 \pm 2.596	6.53 \pm 1.824	0.095
<u>Tachycardia</u>	4.55 \pm 2.411	7.13 \pm 1.937	< 0.001
<u>Tachypnea</u>	4.46 \pm 2.244	7.13 \pm 1.937	< 0.001
Febrile temperature	6.23 \pm 2.281	5.86 \pm 1.963	0.207
Postoperative ileus	4.47 \pm 2.363	5.76 \pm 1.679	< 0.001
<u>Clinical deterioration</u>	6.67 \pm 2.033	7.83 \pm 1.205	< 0.001
<u>Abdominal pain</u>	6.61 \pm 2.247	6.74 \pm 1.835	0.659

CRP: C-reactive protein.

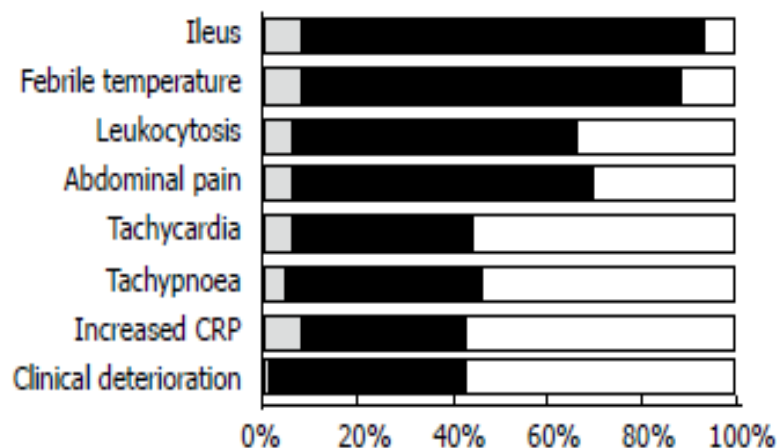
Observational Study

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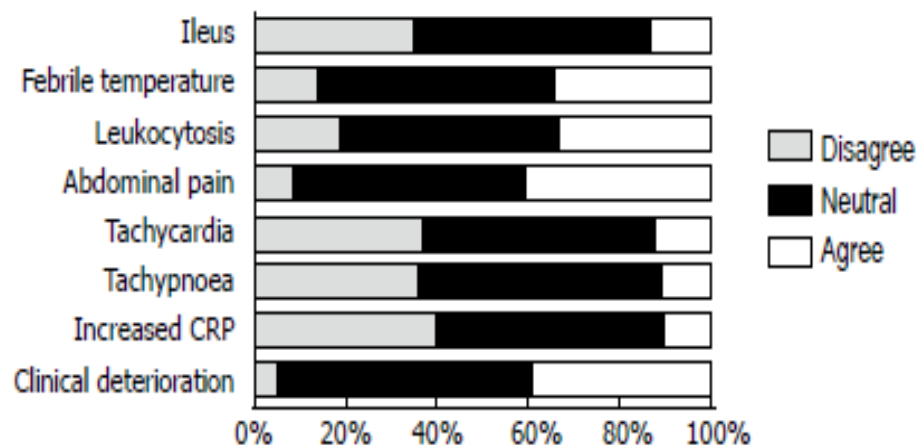
A

the Netherlands



B

China



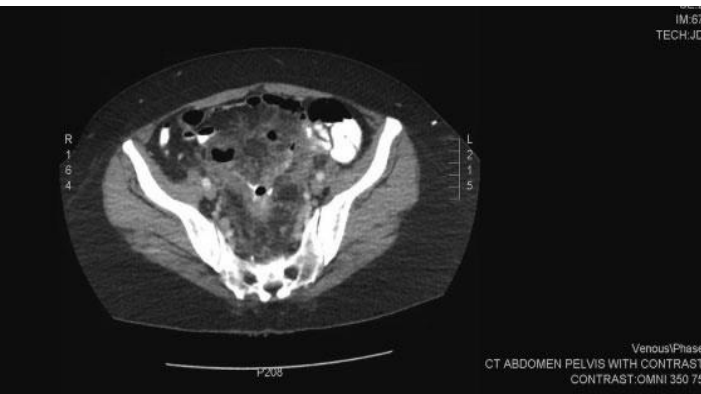
παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

Radiographic demonstration of:

1. large collection of free fluid,
2. extravasation of contrast material, or
3. perianastomotic fluid collection



indicative of AL



παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

{Early clinical and radiologic signs of AL are often nonspecific}

NEED for BIOMARKERS



```
graph TD; A([NEED for BIOMARKERS]) --> B[1. Systemic]; A --> C[2. from Drains];
```

1. Systemic

2. from Drains

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- **serum procalcitonin (PCT)**
 - **C-Reactive Protein (CRP)**
 - **Calprotectin**
 - **Interleukin-6**
- Inflammatory Markers**
- **Intestinal fatty acid binding protein**
 - **Ileal bile acid binding protein**
- Gut damage Markers**

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- C-reactive protein (CRP) —→ indicator of postoperative complications in abdominal surgery.
- CRP is a protein by the hepatocytes as part of the acute phase response
(stimulated by IL-6, α-TNF and IL-1b)
- Acts at the endothelial cells and on complement, thereby participating in the inflammatory cascade.

Its short half-life (19h) makes it a reliable marker of the SIRS secondary to complications

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- + clinical signs and other inflammatory markers, **CRP** has been evaluated as an **indicator of an unfavorable postoperative course**, including surgical and non-surgical complications.
- Is identified as an early predictor of septic complications after esophageal, pancreatic and **rectal resection**



Original research

Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery

A.B. Almeida ^{a,b,*}, G. Faria ^{a,b}, H. Moreira ^{a,b}, J. Pinto-de-Sousa ^{a,b}, P. Correia-da-Silva ^a, J. Costa Maia ^{a,b}

^a Department of General Surgery of Centro Hospitalar de São João, E.P.E., Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal

^b University of Porto Medical School, Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal

- 173 pts under colorectal resection
- Excluded ileostomies
- 24 pts with AL
- Daily measurement of CRP

Original research

Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery

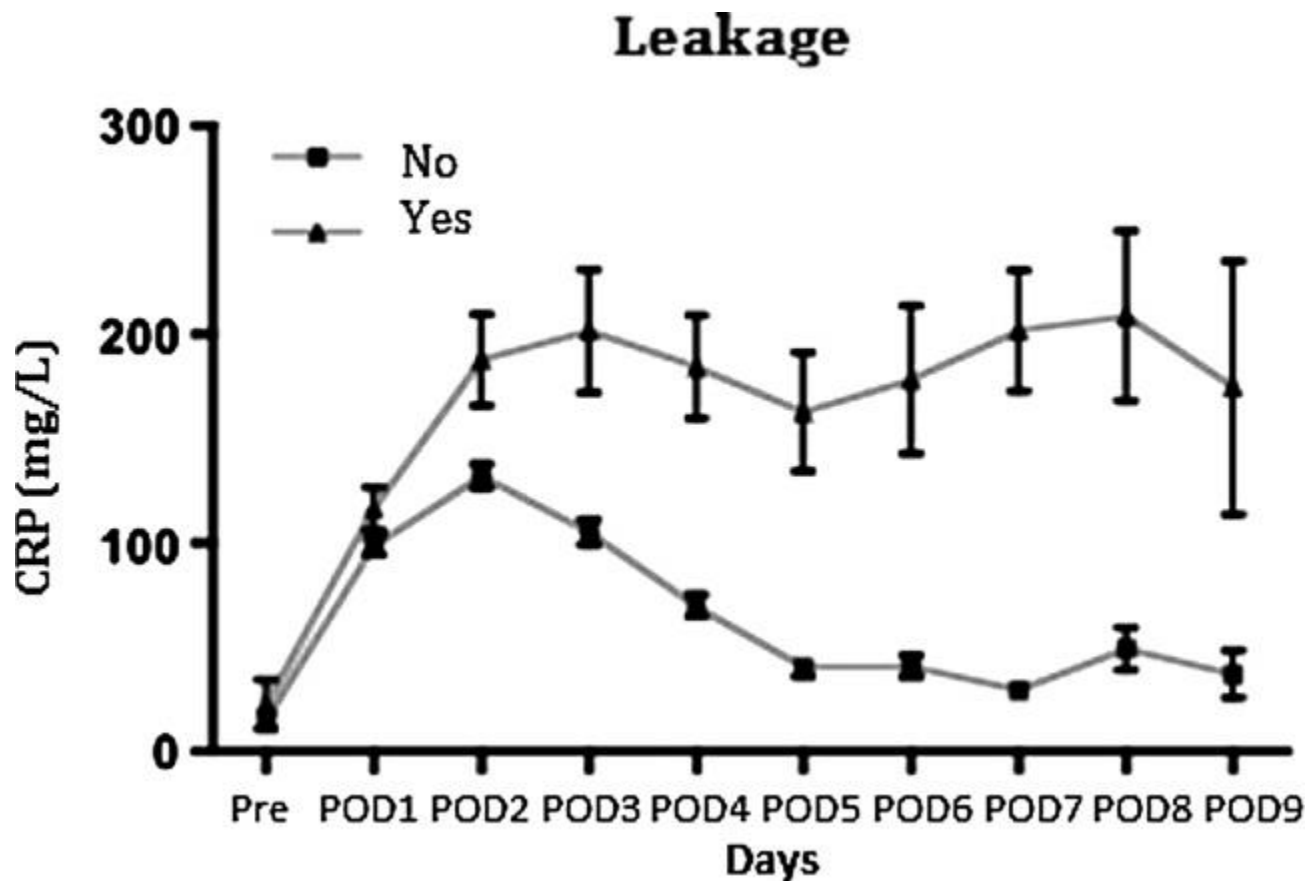
A.B. Almeida ^{a,b,*}, G. Faria ^{a,b}, H. Moreira ^{a,b}, J. Pinto-de-Sousa ^{a,b}, P. Correia-da-Silva ^a, J. Costa Maia ^{a,b}^a Department of General Surgery of Centro Hospitalar de São João, E.P.E., Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal^b University of Porto Medical School, Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal

Fig. Evolution of serum CRP in the pre- and postoperative period in patients with and without anastomotic leakage ($p < 0.003$).



Original research

Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery

A.B. Almeida ^{a,b,*}, G. Faria ^{a,b}, H. Moreira ^{a,b}, J. Pinto-de-Sousa ^{a,b}, P. Correia-da-Silva ^a, J. Costa Maia ^{a,b}^a Department of General Surgery of Centro Hospitalar de São João, E.P.E., Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal^b University of Porto Medical School, Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal**Table 3**

Sensitivity and specificity of serum CRP used as a cut-off in the identification of anastomotic leakage, calculated on postoperative days 2 and 3 (ROC analysis).

CRP (mg/L)	D2		D3	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
70	100	9	92	9
100	89	23	89	54
120	89	34	89	69
130	78	43	78	77
140	67	51	78	86
160	56	63	56	86

POD: postoperative day.

A cut-off value >140 mg/L on POD3 maximizes sensitivity and specificity

85.7%

90.5%



Original research

Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgeryA.B. Almeida ^{a,b,*}, G. Faria ^{a,b}, H. Moreira ^{a,b}, J. Pinto-de-Sousa ^{a,b}, P. Correia-da-Silva ^a, J. Costa Maia ^{a,b}^a Department of General Surgery of Centro Hospitalar de São João, E.P.E., Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal^b University of Porto Medical School, Alameda Professor Hernâni Monteiro, 4200 319 Porto, Portugal

Conclusion:

- According to these results, an early and persistent elevation of **CRP** after colorectal surgery with anastomosis, is a marker of anastomotic leakage.

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- 197 pts - 11 pts with clinical AL
- CRP, WCC and PCT = potential markers of AL in elective colorectal surgery (for the first 5 PODs)
- **CRP** trajectory is extremely accurate in diagnosing AL requiring intervention.

Biomarkers and anastomotic leakage in colorectal surgery: C-reactive protein trajectory is the gold standard. *Smith. Anz J Surg 2018*

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- 7 studies - 2483 pts
- Median AL: 9.6% - Median day of AL : POD 6 - POD 9
- Cut-off value : **172 mg/l on POD 3, 124 mg/l on POD 4 and 144 mg/l on POD 5**
- = negative predictive value of 97%
(low positive predictive value for AL, ~ 21 - 23 %)

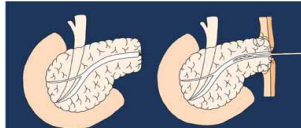
Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. *Singh 2014*

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April 2017, Volume 104, Number 5

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- Translational research in surgical oncology (this article is free online)
- Meta-analysis of biomarkers predicting risk of malignant progression in Barrett's oesophagus
- Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study)
- Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway
- Functional mucous layer and healing of proximal colonic anastomoses in an experimental model



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παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

CONCLUSION: **CRP** is a useful
negative predictive test for the
development of AL following
colorectal surgery

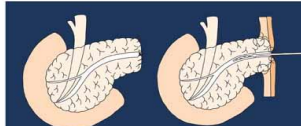
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παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- **Procalcitonin (PCT)** is a peptide precursor of the hormone calcitonin, involved with calcium homeostasis.
- The level of procalcitonin > in a response to a pro-inflammatory stimulus, especially **of bacterial origin**.
- It is therefore often classed as an acute phase reactant

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- 504 pts – 28 with clinical AL (5.6%)
- **PCT** and CRP demonstrated to have a good negative predictive value for AL, both in 3rd and in 5th POD.
(NPV = 96.9% in 3rd POD and 98.3% in 5th POD)

Procalcitonin Reveals Early Dehiscence in Colorectal Surgery: The PREDICS Study. Giagaglia. *Ann Surg* 2016

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- 6 studies
- 1629 pts

Procalcitonin is a biomarker used to monitor bacterial infections

- **PCT**: the highest diagnostic capability on POD 5 with diagnostic odds ratio of 32.9 (95% CI 15.01-69.88), **sensitivity** of 0.78 (95% CI 0.65-0.89), and **specificity** of 0.88 (95% CI 0.85-0.90).

Systematic review and meta-analysis of the use of serum procalcitonin levels to predict intra-abdominal infections after colorectal surgery.

Tan. *Int J Colorect Dis* 2018

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- **Calprotectin** = a heterodimeric peptide constitutes 60% of the cytosol proteins of neutrophils.
- 84 pts with colorectal resection – 8 ALs
- Highest diagnostic accuracy when CRP and calprotectin were combined at POD 3,
(sensitivity of 100%, *specificity of 89%*)



JACS

Journal of the
American College of Surgeons

Reisinger. 2014

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

BUT

- **Several Diseases**

(D.M., R.F., I.B.D., Asthma,
Autoimmune dis.)

- **DRUGS**

(Immunosuppressants, aspirin,
Statins, NSAIs)

affect Calprotectin levels



JACS

Journal of the
American College of Surgeons

Agili. 2015

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- From 1990 – 2016
- 36 studies
- 51 different biomarkers
- Both systemic and peritoneal

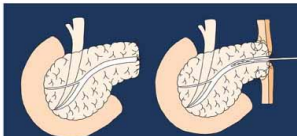
Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery **B. U. Su'a. March 2017**

April 2017 Volume 104 Number 5

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παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

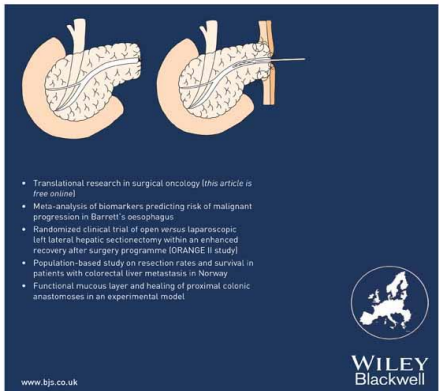
- **CRP, procalcitonin** and leucocytes _ the most commonly evaluated systemic biomarkers with significant negative and positive predictive values.
- The most commonly evaluated peritoneal drain fluid biomarkers were **interleukin (IL) 6, IL-10** and **TNF**
- > drain levels in the early postoperative period were reported to be associated with the development of AL.

Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery **B. U. Su'a. March 2017**


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παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών

- 134 pts under Lap Colorectal Surgery - (AL) in 6 pts (4.5%).
- Serum levels of **CRP and PCT** on POD 1, POD 2, and POD 3

significantly higher in pts with AL
- Using ROC analysis, the best AUC of CRP and PCT levels on **POD 3** (0.837 and 0.947, respectively).

“Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) program.” Munoz. *Surg Endosc* 2018

παρακλινικές παράμετροι στην έγκαιρη διάγνωση των αναστομωτικών διαφυγών


“Early diagnosis of anastomotic leakage after colorectal surgery by the Dutch leakage score, serum procalcitonin and serum C-reactive protein: study protocol of a prospective multicentre observational study by the **Italian ColoRectal Anastomotic Leakage.**”

Benedetti. *G Chir.* 2019 Jan-Feb;40(1):20-25.

AL and drains` measurement

- the (ERAS) program widely adopted last years, and recommends **no abdominal drainage** after surgery.
- In China, on the contrary, ERAS is less commonly implemented, and an intra-abdominal drain is often left **in situ**.

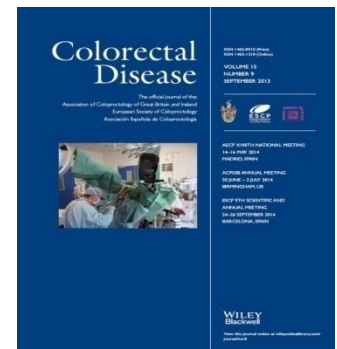
AL and drains` measurement

- 8 studies
- In most studies : > levels of **TNF- α** and **IL-6** in patients with AL during the first 3 postop days.
- IL-6 levels were significantly > from day 1 and TNF- α from day 2.
- MMP-9 was most often significantly  in patients with AL
- *“potential to diagnose colorectal AL at a preclinical stage, but is not yet ready for clinical use”.*

Systematic Review

Peritoneal fluid cytokines and matrix metalloproteinases as early markers of AL in colorectal anastomosis: a literature review and meta-analysis

Cini. *Colorectal Dis* 2013



AL and drains` measurement

- 172 pts
- July 2015 - January 2016
- **CRP** measurement from postop days (POD) 1 to 5
- AL group vs NAL group
- AL = 14% (24 pts)
- **CRP of AL group > continuously,**
while that of NAL group < with significant difference
[(65.3±38.9) g/L vs. (44.7±39.5) g/L, $t=-2.85$, **P=0.005**].

Diagnostic value of dynamic monitoring of C-reactive protein in
drain drainage to predict early AL after colorectal cancer surgery

LU. *Zhonghua Wei Chang Wai Ke Za Zhi.* 2017

AL and drains` measurement

- *The critical value* of CRP was **27.15 g/L**.
- When this value was used as the point of tangency to predict the occurrence of AL:
sensitivity = 87.5%,
specificity = 39.9%,
positive predictive value = 19.1%, and
negative predictive value = 95.2%.

Diagnostic value of dynamic monitoring of C-reactive protein in drain drainage to predict early AL after colorectal cancer surgery

LU. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2017

AL and drains` measurement

- “Continuous > of CRP level in abdominal drainage fluid from POD 1 to POD 5 *indicates* the occurrence of AL after colorectal cancer operation, **especially the detection of CRP level at POD 5 is important.**”

Diagnostic value of dynamic monitoring of C-reactive protein in drain drainage to predict early AL after colorectal cancer surgery

LU. *Zhonghua Wei Chang Wai Ke Za Zhi.* 2017

AL and drains` measurement

- 150 pts under colorectal resection
- **CRP drain** values on POD 1, 3, 5 and 7
- All patients with CRP values in drainage fluid above 108 mg/L on the POD 5 and above 93 mg/L on the POD 7 } **AL**

C-reactive protein in drainage fluid as a predictor of anastomotic leakage after elective colorectal resection.

Kostic . *Vojnosanit Pregl.* 2016

AL and drains` measurement

- lipopolysaccharide-binding protein (LBP)
- 243 pts
- AL= 8%
- CRP – **LBP** – PCT on drains measurement
(acute phase proteins)
- From 1-5 POD

The APPEAL study
Komen. *Am J Surg* 2014

AL and drains` measurement

- “Multivariate analysis showed ***LBP to be significantly related to AL.***
- An > in the average initial value at POD 1 with 1 standard deviation > the risk of AL by **1.6 times.**

CONCLUSION:

“Increased concentrations of LBP in drain fluid are significantly associated to a **higher chance of AL** and could contribute in a future prognostic model for AL.



**Take
home message*

- Delayed diagnosis (after POD 5) of AL is associated with a mortality rate of 18%, but minimal morbidity if diagnosed and treated before POD 5.

Alves. World J Surg 2012

- **AL** < long term outcome

Wang. World J Surg 2017



**Take
home message*

Open access

Original research

BMJ Open Surgeon perceived most important factors to achieve the best hospital performance on colorectal cancer surgery: a Dutch modified Delphi method

Julia Tessa van Groningen,^{1,2} Perla J Marang-van de Mheen,³ Daniel Henneman,¹ Geerard L Beets,⁴ Michel W J M Wouters^{2,4}

Conclusion Procedural hospital volume, specialisation of surgeons, screening for malnutrition, early recognition of complications followed by rapid action were perceived as most important factors to achieve good outcomes by gastrointestinal surgeons.

