Inflammatory Biomarkers and Clinical Judgment in the Emergency Diagnosis of Urgent Abdominal Pain

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Running Title: Biomarker in acute abdominal pain

Word count: 3389

Key words: Acute abdominal pain, Interleukin-6, Emergency Department, diagnostic accuracy, sensitivity, specificity

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List of Abbreviations (in order cited)

UAP - urgent abdominal pain

ED - emergency department

VAS - visual-analog-scale

ROC - Receiver-operating-characteristic

AUC - area under the curve

IDI - integrated discrimination improvement

IBS - irritable bowel syndrome

ERCP - endoscopic retrograde cholangiopancreatography

Abstract (word count: 250)

Background: The early diagnosis of urgent abdominal pain (UAP) is challenging. Most causes of UAP are associated with extensive inflammation. We therefore hypothesized that quantifying inflammation using interleukin-6 and/or procalcitonin would provide incremental value in the emergency diagnosis of UAP.

Methods: This was an investigator-initiated prospective, multicenter diagnostic study enrolling patients presenting to the Emergency Department (ED) with acute abdominal pain. Clinical judgment of the treating physician regarding the presence of UAP was quantified using a visual-analog-scale after initial clinical and physician-directed laboratory assessment, and again after imaging. Two independent specialists adjudicated the final diagnosis and the classification as UAP (life threatening, needing urgent surgery and/or hospitalization for acute medical reasons) using all information including histology and follow-up. Interleukin-6 and procalcitonin were measured blinded in a central laboratory.

Results: UAP was adjudicated in 376/1038 (36%) patients. Diagnostic accuracy for UAP was higher for interleukin-6 (ROC AUC 0.80, 95%CI 0.77-0.82) versus procalcitonin (AUC 0.65; 95%CI 0.62-0.68) and clinical judgment (AUC 0.69; 95%CI 0.65-0.72, both $P<0.001$). Combined assessment of interleukin-6 and clinical judgment increased the AUC at presentation to 0.83 (95%CI 0.80-0.85) and after imaging to 0.87 (95%CI 0.84-0.89) and improved the correct identification of patients with and without UAP (net improvement in mean predicted probability: presentation +19%; after imaging +15%, $P<0.001$). Decision-curve-analysis documented incremental value across the full range of pretest probabilities. A clinical judgment/interleukin-6 algorithm ruled-out UAP with a sensitivity of 97% and ruled-in UAP with a specificity of 93%.

Conclusion: Interleukin-6 significantly improves the early diagnosis of UAP in the ED.

Introduction

Acute abdominal pain is the most common presenting symptom in emergency department (ED) patients*(1-3)*. Its differential diagnosis is extensive and challenging*(4, 5)*. While 20-25% of patients require hospital admission and 10% of all episodes are life threatening or require urgent surgery, most episodes of acute abdominal pain are self-limiting and benign*(3, 4, 6)*. Hence, rapid and accurate diagnosis of urgent causes of abdominal pain (UAP) is essential for the early initiation of effective therapy and efficient patient flow.

Clinical assessment including patient history, detailed physical examination and routine laboratory testing remains the cornerstone of initial patient care*(7, 8)*. However, in isolation this strategy has poor diagnostic accuracy*(9, 10)*. Imaging techniques, particularly CT-scans*(10, 11)*, are of enormous value*(12)* but the appropriate selection of patients benefiting from imaging remains an unmet clinical need. Routine CT-scans in all patients with acute abdominal pain would inappropriately increase the incidence of rare, but potentially fatal adverse events such as allergic reactions to intravenous contrast agents, long-term hazards related to radiation exposure, as well as inherent costs*(13, 14)*. On the other hand, an overly restrictive use of CT-scans would delay the detection and treatment of UAP and thereby potentially increase morbidity and mortality.

The incremental value of biomarkers in the early diagnosis of UAP still is uncertain. Based on the enormous medical and economic value provided by biomarkers in patients presenting to the ED with acute chest pain and acute dyspnea*(15-21)*, which are supported by a Class I recommendations in current clinical practice guidelines*(22, 23)*, we hypothesized that biomarkers may also be able to provide incremental value in patients presenting with acute abdominal pain.

As most causes of UAP are associated with inflammation, this study aimed to evaluate the incremental value of two biomarkers quantifying inflammation -interleukin-6*(24-26)* and procalcitonin*(27, 28)*- in a large multicenter diagnostic study.

Methods

Trial design and oversight

Basel Abdominal Symptoms Evaluation Study (Basel VII) was an investigator-initiated prospective, international, multicenter diagnostic study enrolling unselected patients in six hospitals in three countries (Switzerland, Spain, Italy). The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered, analyzed and report the data according to the STARD guidelines for studies of diagnostic accuracy (see **Table S1** in the online Supplemental file).

Patients

To ensure the inclusion of the full spectrum of patients with acute abdominal pain, unselected adult patients presenting to the ED with acute non-traumatic abdominal pain as their main complaint were enrolled after written informed consent was obtained, irrespective of prior counseling by a general practitioner and triage severity*(29)*. Importantly, the study investigators were not directly involved in patient care/treatment or the selection of imaging procedures, nor did they have any influence on the decision to admit or discharge patients. Patients were evaluated in the ED by at least two physicians not involved in the study: a resident in emergency medicine/surgery and a board-certified emergency medicine specialist and/or a board-certified surgeon. All patients underwent an initial clinical evaluation including history taking, detailed physical examination, standard physician-directed blood measurements and in women of childbearing age, a urine pregnancy test. All imaging including CT-scans, plain abdominal radiographs, ultrasound and magnetic resonance imaging was performed as clinically indicated. Clinical judgment of the treating physician regarding the urgency of acute abdominal pain was quantified using a visual-analog-scale (VAS) from 0

(benign, non-urgent abdominal pain) to 10 (UAP, life threatening, needing urgent (<72h) surgery and/or hospitalization for acute medical reasons) after initial clinical and physician-directed laboratory assessment and again after physician-directed imaging and serial clinical assessment when the patient was considered ready for admission/discharge. The treating physicians were blinded to the interleukin-6 and procalcitonin concentrations.

Follow-up

Patients were contacted by telephone 1 and 6 months after the initial ED presentation. Referring physicians and/or administrative databases were contacted in case of any remaining uncertainties regarding health status, further hospitalizations or surgeries.

Adjudicated Final Diagnosis

The final diagnosis and classification as UAP was centrally adjudicated by two independent internists/surgeons who reviewed all available medical records —clinical history, findings on physical examination, results of laboratory tests, radiologic studies, surgical interventions, histopathology reports, and follow-up data. The independent specialists were blinded to the interleukin-6 and procalcitonin concentrations. When there was disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third specialist. The final diagnosis was adjudicated in two domains: First, urgent versus non-urgent causes of abdominal pain; second the specific diagnosis causing abdominal pain. UAP was defined as life threatening, needing urgent (<72h) surgery and/or hospitalization for acute medical reasons (e.g. i.v. antibiotic therapy). Surgery and/or hospitalization *per se* did not define UAP. Non-urgent causes of abdominal pain were defined as disorders not meeting these criteria.

Blood sampling and laboratory methods

Blood samples for the determination of interleukin-6 and procalcitonin were collected in tubes containing potassium EDTA at the time of the patient`s ED presentation. Additional samples were obtained 3h after presentation. After centrifugation, samples were frozen at −80°C until assayed in a blinded fashion in a dedicated core laboratory. For the primary analysis, interleukin-6 and procalcitonin were measured using highly sensitive immunoassays based on the concept that high analytical sensitivity is critical for a rule-out strategy. Interleukin-6 was measured with the Erenna® immunoassay system (Singulex, Inc., singulex.com), which uses a micro-particle immunoassay and single-molecule counting in a capillary flow system. The assay's limit of detection is 0.01ng/L with lower and upper limits of quantification at 0.08ng/L and 50ng/L, respectively. Intraassay and interassay coefficents of variation were 6% and 13%, respectively. Procalcitonin was quantified with an automated sandwich immunoassay using a time-resolved amplified cryptate emission (TRACE) technology assay (PCT Kryptor®, B.R.A.H.M.S. GmbH, brahms.de) with a detection limit of 0.02µg/L and a functional assay sensitivity of 0.06µg/L according to the manufacturer. The interassay coefficient of variation for concentrations >0.3µg/L is <6%. Secondary analyses were performed to validate the robustness of this approach for routine clinical care using assays that run on a widely available laboratory analyzer. Detailed characteristics of the secondary immunoassays are described in the online Supplemental file.

Statistical analysis

Diagnostic uncertainty for UAP was defined as clinical judgment of 3/10 to 7/10 for an urgent cause. Receiver-operating-characteristic (ROC) curves were constructed to assess sensitivity, specificity and 95% confidence intervals of interleukin-6 and procalcitonin. Mean predicted probabilities for clinical judgment VAS, log-transformed interleukin-6 (because of non-normal distribution) and the combination of both were

calculated using multivariable binary logistic regression models. The comparison of areas under ROC curves (AUC) was performed as recommended by DeLong*(30)*. To assess the incremental yield of interleukin-6 for the early diagnosis of UAP on top of clinical judgment, reclassification tables for net reclassification improvement (NRI) were used*(31)*. Results were verified using integrated discrimination improvement (IDI) analysis, which is not dependent on risk groups because probability differences are used*(31)*. Clinical usefulness and net benefit of interleukin-6 were estimated with decision-curve-analysis*(32)*.

Secondary analyses included a direct comparison of the diagnostic accuracy of the open-label routine laboratory tests WBC and CRP (e.g. available to the clinical team and the adjudicating experts, thereby contributing to clinical judgment and final diagnosis and prone to inclusion bias) with the blinded, investigational interleukin-6 and procalcitonin concentrations. All hypothesis testing was two-tailed, *P*-values <0.05 were considered to indicate statistical significance. Cutoff values were determined using predefined sensitivities and specificities (70%, 80%, 90% and >95%) for UAP using ROC analysis. The impact of interleukin-6 groups on 30-day and 180-day mortality was assessed by Kaplan-Meier curves and compared by log-rank test. Statistical analyses were performed using SPSS for Windows 22.0 (IBM), MedCalc 11.2.1.0. (MedCalc Software) and the R statistics package (R Foundation for Statistical Computing).

Results

Patient characteristics

Patient flow is shown in **Figure S1** in the online Supplemental file. From October 2009 to January 2012, 1150 patients were recruited and 1038 patients were available for the primary analysis (**Table 1**). Diagnostic uncertainty of the treating physician regarding

UAP was present in 58% of patients after initial clinical and laboratory assessment and in 49% after imaging, when the patient was considered ready for admission/discharge (**Figure S2**). Overall, 1343 imaging studies were performed in 887 patients (**Table 2**). The need for imaging was higher in UAP patients than in patients with non-urgent causes of abdominal pain (94% vs 81%, p<0.001). In UAP patients abdominal ultrasound (173, 46%) and abdominal CT (150, 40%) were the most frequently performed imaging procedures. The median time interval from ED presentation until patients were considered ready for admission/discharge was 329 minutes.

Adjudicated final diagnosis

The adjudicated final diagnosis was UAP in 376 (36%) patients; urgent surgery was necessary in 217 (58%), hospitalization in 128 (34%) and a non-surgical urgent intervention in 31 (8%) UAP patients. The specific diagnoses causing acute abdominal pain are described in the online Supplemental results (**Table S2**).

Diagnostic accuracy of interleukin-6 and procalcitonin at presentation

Interleukin-6 and procalcitonin plasma concentrations were significantly higher in patients with UAP compared to patients with non-urgent causes (interleukin-6: median 23.3ng/L [IQR: 8.7-77.7] vs. 4.4ng/L [2.1-10.9], *P*<0.001; procalcitonin: 0.10µg/L [0.07-0.27] vs. 0.07µg/L [0.05-0.10], p<0.001). (**Table 2**; **Figure S3**). The frequency of findings on clinical examination and their respective diagnostic accuracies are described in the supplemental results (**Table S3**).

Diagnostic accuracy for UAP, as quantified by the AUC was significantly higher for interleukin-6 (0.80; 95%CI 0.77-0.82) compared to procalcitonin (0.65, 95%CI 0.62-0.68, *P*<0.001; **Figure S4**) and initial clinical judgment (0.69; 95%CI 0.66-0.73, *P*<0.001)**.** In IDI analysis, interleukin-6 adequately decreased the mean predicted probability of UAP in patients with non-urgent pain by 6% and increased the mean

predicted probability by 10% in patients with UAP compared to clinical judgment alone (net improvement in mean predicted probability +16%, *P*<0.001).

The AUC for interleukin-6 significantly also exceeded the AUCs for open-label WBC (0.74; 95%CI 0.71-0.77, *P*=0.001) and CRP (0.73, 95%CI 0.70-0.77, *P*<0.001; **Figure S5**).

Early incremental value

Combined assessment of interleukin-6 at presentation and initial clinical judgment (AUC 0.83, 95%CI 0.80-0.85) significantly improved the diagnostic accuracy over initial clinical judgment alone (AUC 0.69, 95%CI 0.66-0.73; *P*<0.001, **Figure 1**). The NRI of the additional use of interleukin-6 compared to initial clinical judgment alone (**Table 3**) amounted to 27.3% (*P*<0.001). In patients with non-urgent abdominal pain, 111 patients (16.7%) correctly moved downward and 23 (3.5%) incorrectly moved upward in the classification. In patients with urgent abdominal pain, 85 patients (22.6%) correctly moved upwards and 32 (8.5%) incorrectly moved downward in the classification. The combined use of interleukin-6 and initial clinical judgment, improved the correct identification of patients with and without UAP in IDI analysis (net improvement in mean predicted probability +19%, *P*<0.001) compared to clinical judgment alone. Interleukin-6 provided incremental clinical usefulness in addition to clinical judgment over the full range of probability thresholds (i.e. increased number of true positives predictions without increasing the number of false positive predictions, **Figure 2**). Exemplified, in a patient clinically judged to have a low probability of urgent abdominal pain (VAS2/10), using the combined model identified 169 more true positives per 1000 patients without an increase in false positive predictions compared to the VAS alone. In a patient clinically judged to have a medium to high risk of urgent

abdominal pain (VAS8/10) the combined model identified 56 more true positives per 1000 patients without increase in false positive predictions compared to the VAS alone.

Late incremental value

The combined assessment of interleukin-6 at presentation and final clinical judgment after imaging when the patient was considered ready for admission/discharge (AUC 0.87, 95%CI 0.84-0.89) continued to significantly improved the diagnostic accuracy over final clinical judgment alone (*P*<0.001, **Figure S6**). The NRI of the additional use of interleukin-6 compared to final clinical judgment alone amounted to 28.0% (*P*<0.001).

Similarly, the combined use of interleukin-6 and final clinical judgment improved the correct identification of patients with and without UAP in IDI analysis (net improvement in mean predicted probability +15%, *P*<0.001) compared to final clinical judgment. Again, interleukin-6 provided incremental clinical usefulness in addition to clinical judgment over the full range of probability thresholds (**Figure S7**).

Combined triage algorithm

Figure 3 displays an early triage algorithm combining clinical assessment and interleukin-6 concentrations. In short, interleukin-6 concentrations below 2.4ng/L ruled-out 197 patients (20%) with a sensitivity of 97% and a negative likelihood ratio of 0.11 for UAP. The diagnostic characteristics of interleukin-6 at pre-specified sensitivity and specificity target levels (**Table S4**) are described in the online Supplemental file. Eight patients (8/376 UAP patients; 2%) were incorrectly classified by the combined triage algorithm are summarized in **Table S5**.

Serial sampling

A second interleukin-6 measurement after 3 hours did not improve the diagnostic accuracy provided by interleukin-6 at presentation (AUC for combination 0.79, 95%CI 0.76-0.82, *P*=0.47).

Subgroups

Results from pre-specified subgroup analyses are described in the Supplemental results.

Prognostic performance of interleukin-6

There were 4 deaths during the initial hospitalization and 27 deaths in the whole cohort within 180 days. Survival at 30 days (*P*=0.002) and 180 days (*P*=0.031) was significantly associated with interleukin-6 concentrations (**Figure S8**). Cumulative survival rates were 100%, 99.5% and 97.4% at 30 days and 98.6%, 96.1 and 91.4% at 180 days, respectively. The hazard ratio for the risk of death within 180 days was 4.2 (95%CI 1.1-15.9, *P*=0.034) for patients in the rule-in group as compared with patients in the rule-out group. Similarly, 30-day survival was 100% in patients triaged towards rule-out by the combined clinical/interleukin-6 algorithm. The cause of death was cancer in 15 patients (8 primarily extraabdominal, 7 primarily intrabdominal), cardiovascular in 3 patients, UAP in 2 patients and unknown in 7 patients dying at home. Of the four patients dying during the initial hospitalization 2 patients died of UAP and 2 patients died of primarily extraabdominal cancers.

Secondary analysis

Measurements of interleukin-6 and procalcitonin on a large automated analyzer revealed similar findings compared to the primary analysis (online Supplemental file).

Discussion

This prospective, multicenter diagnostic study examined interleukin-6 and procalcitonin plasma concentrations for the early diagnosis of UAP. We report seven major findings: First, the diagnostic accuracy of the initial clinical assessment of acute abdominal pain was only modest and significantly inferior to the diagnostic accuracy of initial clinical assessment for the two other common presenting symptoms to the ED: acute dyspnea and acute chest pain*(33, 34)*. Diagnostic uncertainty of the treating physician regarding an urgent cause of abdominal pain was present in 58% of patients after initial clinical and laboratory assessment and in 49% after imaging, when the patient was considered ready for admission/discharge. Second, the diagnostic accuracy of interleukin-6 was significantly superior to initial clinical judgment, procalcitonin and the open-label routine blood parameters WBC and CRP. Third, interleukin-6, but not procalcitonin, provided incremental diagnostic value to both initial and final clinical judgment and significantly increased the diagnostic accuracy. The additional use of interleukin-6 significantly improved the adequate detection of patients with non-urgent abdominal pain (rule-out) as well as the identification of UAP patients (rule-in). Decision-curve-analysis documented incremental value and clinical usefulness across the full range of pretest probabilities. Fourth, the combined use of clinical judgment and interleukin-6 concentrations allowed the development of a rapid triage algorithm to assign patients towards rule-out or rule-in of UAP. In 197 (20%) patients with a low to intermediate clinical probability for an urgent cause of acute abdominal pain (e.g. VAS<8/10) interleukin-6 concentrations below 2.4ng/L ruled-out UAP with a sensitivity of 97%, similar to the sensitivity of CT-angiography in the rule-out of pulmonary embolism*(35)*. The immediate consequence of triage towards rule-out will be considering early discharge from the ED and outpatient management. A high clinical probability for an urgent cause of acute abdominal pain (e.g. VAS>8/10) or interleukin-6 concentrations

above 63.5ng/L ruled-in UAP in 176 patients (17%) with a specificity of 93%. The high specificity for an urgent cause of acute abdominal pain in the rule-in group justifies early CT-imaging and/or surgical consultation as the immediate consequence of triage towards rule-in. Fifth, 30-day survival was 100% in patients triaged towards rule-out, highlighting the suitability of many of these patients for early discharge and outpatient management. Sixth, the diagnostic accuracy of interleukin-6 was consistent in various pre-specified subgroups. Seventh, secondary analyses using measurements of interleukin-6 and procalcitonin performed on a widely available automated large analyzer showed similar results and thereby provided internal validation of our findings. In addition, it documents the immediate availability of this novel strategy in clinical practice.

These findings extend and corroborate previous research on the clinical use of biomarkers in acute abdominal pain*(24-27)*. Small single-center pilot studies recruiting selected patients with right iliac fossa pain suggested that interleukin-6 and procalcitonin concentrations might act as disease severity markers with higher levels being associated with a need for surgery*(24-27)*.

Importantly, although interleukin-6 does substantially improve the emergency diagnosis of UAP, its concentrations should always be interpreted in conjunction with all other clinically available information. This is highlighted by the combined interpretation of clinical assessment and interleukin-6 concentrations achieving the best diagnostic accuracy at every diagnostic step in the present study. In addition, the release of interleukin-6 seems to be time-dependent. Accordingly, repeat measurements may be considered in interleukin-6 negative early patients presenting very early after the onset of acute abdominal pain, although our data could not show a significant difference.

The most important non-urgent disease entity to consider in interleukin-6 positive patients is irritable bowel syndrome (IBS). A recent small pilot study highlighted increased interleukin-6 serum concentrations in patients with IBS as diagnosed by the Rome III criteria*(36)*. Similarly, 10 of the 29 patients with a non-urgent cause of abdominal pain and interleukin-6 concentrations >63.50ng/L suffered from non-specific abdominal pain, which is strongly associated with the IBS*(37)*.

The most important urgent entity to be considered in patients incorrectly ruled-out by the combined triage algorithm appears to be persistent biliary colic. In fact, 2 of the 4 patients with persistent biliary colic were clinically judged to have a low to intermediate clinical probability for an urgent cause of acute abdominal pain and presented with interleukin-6 concentrations below 2.4ng/L. The need for endoscopic retrograde cholangiopancreatography (ERCP) in the setting of choledocholithiasis is dictated by persistent biliary pain, obstructive jaundice, cholangitis, pancreatitis, or any combination thereof. While the interleukin-6 positive patient presented with clinically apparent jaundice, the ERCP indication was based on persistent pain in all triage algorithm negative patients, which in itself does not seem to induce an acute phase response. Also, 3 of 91 (3%) patients suffering from acute appendicitis were incorrectly ruled-out by the combined triage algorithm.

Acute abdominal pain may also occasionally be caused by acute life-threatening extra-abdominal disorders, such as acute myocardial infarction. Accordingly, these disorders were classified as urgent in this study. However, our findings should not be misinterpreted as suggesting the use of interleukin-6 plasma concentrations in the work-up of patients, in whom, e.g., acute myocardial infarction is suspected. If an acute life-threatening extra-abdominal disorder is suspected, established standard operating procedures for its safe rule-out*(23)* should be strictly adhered to irrespective of interleukin-6 concentrations.

Current guidelines for the assessment of acute abdominal pain*(7, 8)* call for an early blood draw in all patients with potentially urgent abdominal pain. Our data suggest that interleukin-6 should be considered for inclusion in this laboratory panel. Used in conjunction with all clinically available information, interleukin-6 could simplify the allocation of patients to imaging and/or surgical evaluation (rule-in pathway), additional medical work-up of differential diagnoses and early clinical reappraisal (observe), or rapid discharge and outpatient management (rule-out pathway).

The current study has several limitations. First, while the multicenter design should blunt local differences in referral patterns, diagnostic work-ups, and health care systems, and thereby allows the generalization of these findings to EDs, the generalizability of our findings to other settings, e.g. primary care, remains unknown. Second, as this was not an intervention study, we cannot assess the effect of interleukin-6 guided triage on clinical management, patient outcome and its cost-effectiveness. While an open-label randomized controlled management trial will surely provide important additional information, a diagnostic study with blinded measurements and central adjudication of the final diagnosis provides more precise estimates of the incremental value of novel diagnostic tests*(16, 19)*. It is likely that more rapid and more accurate rule-out using interleukin-6 will reduce time to discharge and treatment costs in the ED*(15, 20)*.

In conclusion, interleukin-6 concentrations significantly improve the early diagnosis of patients presenting with acute abdominal pain to the ED. Use of an Interleukin-6-based early triage algorithm has the potential to provide substantial medical and economic value.

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FUNDING SOURCES

This study was supported by research grants from the Swiss National Science Foundation, the University of Basel, the University Hospital Basel, the Cardiovascular Research Foundation Basel, BRAHMS, Roche, and Singulex. Interleukin-6 and procalcitonin assays were donated by the manufacturers.

ACKNOWLEDGEMENTS

We thank the patients who participated in the study, the staff of the EDs, the research coordinators, and the laboratory technicians (particularly Esther Garrido, Irina Klimmeck, Kathrin Meissner, Claudia Stelzig, Christine Kruse, Kristin Podkowik and Fausta Chiaverio) for their most valuable efforts.

DISCLOSURES

Dr. Breidthardt has received research grants from the Swiss National Science Foundation (PASMP3-134362), University Hospital Basel, Abbott and Roche as well as speakers honoraria from Roche. Dr. Brunner-Schaub has received a research grant from the University of Basel. Dr. John Todd is Chief Scientific Officer and Employee at Singulex. Professor Mueller has received research grants from the Swiss National Science Foundation and the Swiss Heart Foundation, the European Union, the Cardiovascular Research Foundation Basel, the University of Basel, 8sense, Abbott, ALERE, Astra Zeneca, Beckman Coulter, Biomerieux, BRAHMS, Critical Diagnostics, Nanosphere, Roche, Siemens, Singulex, and the University Hospital Basel, as well as

speaker or consulting honoraria from Abbott, ALERE, Astra Zeneca, BG Medicine, Biomerieux, BMS, Boehringer Ingelheim, BRAHMS, Cardiorentis, Daiichi Sankyo, Novartis, Roche, Sanofi, Singulex, and Siemens. The other authors report no conflicts.

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Table 1. Baseline characteristics	**Final adjudicated diagnosis**						
	Overall (N=1038)		Non-urgent pain (N=662)		Urgent pain (N=376)		*P*-Value*
Age, yrs.	49	±19	47	±19	53	±19	<.001
Sex, male	531	(51)	320	(48)	211	(56)	.030
Symptoms							
Duration of Pain , h	18	[7-58]	20	[6-69]	17	[7-48]	.176
Acute onset of pain (within minutes) n pat (%)	457	(44)	287	(43)	170	(45)	.106
Worsening pain, n (%)	460	(44)	271	(41)	189	(50)	.010
Co-morbidities							
BMI, kg/m^2	24.9	[22.0-28.4]	24.8	[21.8-28.4]	25.2	[22.5-28.1]	.202
Diabetes	78	(8)	46	(7)	32	(9)	.394
Hypertension	233	(22)	129	(20)	104	(28)	.004
Cardiac Disease	98	(9)	44	(7)	54	(14)	<.001
Hepatic disease	64	(6)	39	(6)	25	(7)	.689
Diverticulosis	56	(5)	24	(4)	32	(9)	.001
Neoplastic disease	61	(6)	34	(5)	27	(7)	.218
Clinical examination at presentation							
Distended abdomen	70	(7)	41	(6)	29	(8)	.170
Localized tenderness	829	(80)	512	(77)	317	(84)	.024
Localized rebound tenderness	232	(22)	103	(16)	129	(34)	<.001
Localized guarding	180	(17)	71	(11)	109	(29)	<.001
Vital signs							
Systolic blood pressure, mmHg	135	[120-148]	135	[120-149]	134	[121-148]	.682
Diastolic blood pressure, mmHg	79	[70-87]	79	[70-88]	78	[69-86]	.148
Heart rate, bpm	80	[70-93]	79	[69-89]	84	[72-99]	<.001
Body Temperature, °C	36.7	[36.2-37.2]	36.6	[36.2-37.1]	36.9	[36.3-37.4]	<.001

Routine Laboratory Parameters							
Hemoglobin, g/l	142	[131-153]	142	[131-152]	142	[130-154]	.647
White blood count, G/l	9.4	[7.1-12.6]	8.3	[6.5-10.5]	12.0	[9.2-15.4]	<.001
Creatinine, umol/l	68	[57-82]	68	[57-81]	70	[59-85]	.038
AST, U/l[#]	25	[20-32]	24	[20-31]	25	[20-33]	.033
Alkaline phosphatase, U/l	69	[57-87]	68	[56-83]	71	[57-94]	.005
Pancreatic amylase, U/l	28	[20-44]	29	[21-44]	27	[18-45]	.052
C-reactive protein, mg/l	6.1	[2.2-37.7]	4.9	[1.6-14.9]	27.5	[4.9-93.2]	<.001

Values are mean ± SD, number (percentage) and median [interquartile range]. **P*-Value for differences between groups. [#] AST, aspartate aminotransferase

Table 2. Clinical judgment, imaging and Biomarker results	Overall (N = 1038)		Non-urgent pain (N=662)		Urgent pain (N=376)		*P*-Value*
Clinical judgement							
ED Clinical VAS (x/10)	4.0	[2.0-6.0]	3.0	[2.0-5.0]	6.0	[3.0-7.0]	<.001
ED Conclusion VAS (x/10)	4.0	[2.4-6.5]	3.0	[1.8-5.0]	6.5	[4.2-8.0]	<.001
ED Resources							
Need for imaging, n pat (%)	887	(86)	533	(81)	354	(94)	<.001
Plain abdominal X-ray, n pat (%)	355	(34)	234	(35)	121	(32)	0.315
Abdominal ultrasound, n pat (%)	386	(37)	213	(32)	173	(46)	<.001
Abdominal CT, n pat (%)	283	(27)	131	(20)	152	(40)	<.001
Chest/upper abdomen CT, n pat (%)	15	(1)	7	(1)	8	(2)	0.182
Abdominal MRI, n pat (%)	9	(1)	3	(1)	6	(2)	0.079
Plain Chest X-ray, n pat (%)	295	(28)	169	(25)	126	(33)	0.006
Number of imaging modalities	1.41	±0.87	1.41	±0.88	1.67	±1.07	<.001
Treatment time in ED, min	329	[209-581]	276	[190-458]	460	[276-758]	<.001
Biomarker							
Erenna Interleukin-6, ng/L	7.4	[2.9-4.6]	4.4	[2.1-10.9]	23.3	[8.7-77.7]	<.001
Elecsys Interleukin-6, ng/L	5.7	[1.5-21.8]	2.2	[1.5-9.9]	20.7	[7.1-72.3]	<.001
Kryptor Procalcitonin, µg/L	0.08	[0.05-0.13]	0.07	[0.05-0.10]	0.10	[0.07-0.27]	<.001
Elecsys Procalcitonin, µg/L	0.02	[0.02-0.05]	0.02	[0.02-0.03]	0.03	[0.02-.0.11]	<.001

Values are mean ± SD, number (percentage) and median [interquartile range]. ED denotes Emergency Department; **P*-Value for differences between groups.

Table 3 **Reclassification of patients with and without urgent abdominal pain by Erenna Interleukin-6**

Patients with non-urgent abdominal pain

ED Initial Clinical Judgment	Clinical Judgment & Interleukin-6			Total
	Low probability	Observe	High probability	
Low probability (VAS < 3/10)	266	1	6	273
Uncertainty (VAS 3/10-7/10)	91	243	16	350
High probability (VAS >7/10)	6	14	19	39
Total	363	258	41	662

Patients with urgent abdominal pain

ED Initial Clinical Judgment	Clinical Judgment & Interleukin-6			Total
	Low probability	Observe	High probability	
Low probability (VAS < 3/10)	57	1	13	71
Uncertainty (VAS 3/10-7/10)	9	158	71	237
High probability (VAS >7/10)	3	20	45	68
Total	68	179	129	376

Figure Legends:

Figure 1: Receiver-operating-characteristic (ROC) curves showing the diagnostic accuracies of initial clinical judgment after patient history, clinical examination and routine laboratory tests and its combination with interleukin-6 for the diagnosis of urgent abdominal pain.

Figure 2: Decision curve analysis of combined use of blinded interleukin-6 and initial ED clinical judgment versus clinical judgment alone for the diagnosis of urgent abdominal pain. Assume all without urgent abdominal pain - all patients have a predicted probability of 0.0. Assume all with urgent abdominal pain - all patients have a predicted probability of 1.0. ED Clinical VAS - patients have a predicted probability based on initial clinical judgment after patient history, clinical examination and routine laboratory tests. Combination Interleukin-6/ED Clinical VAS - patients have a predicted probability based initial clinical judgement and its combination with interleukin-6

Figure 3: Algorithm for the early diagnosis of urgent abdominal pain combining initial clinical judgment and interleukin-6 concentrations in patients presenting with acute abdominal pain. 0h indicates Interleukin-6 at presentation to the ED