THE RELATIONSHIP BETWEEN NONSPECIFIC INFLAMMATION MARKERS AND COMPUTERIZED TOMOGRAPHY IMAGING IN NON-TRAUMATIC ACUTE ABDOMEN

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ABSTRACT

***Aims**: The purpose of the study was to establish whether the patients presenting with abdominal pain should undergo to contrast enhanced CT (Computed tomography). For this purpose, we have investigated the possible relationship between CRP (C-reactive protein), WBC (White blood cell), neutrophil levels and the presence of pathological findings determined on abdominal pelvic CT images.*

***Materials and methods**: Patients who were admitted to Emergency Department between 01.01.2012 - 31.12.2012 with abdominal pain and underwent intravenous contrast-enhanced abdominal-pelvic CT scan were enrolled in this retrospective study.*

***Results**: Totally 130 patients were included in the study. A statistically significant correlation was found between the presence of pathological findings determined on abdominal-pelvic CT images and CRP, WBC and neutrophil levels. Pathological findings were found to be positive on CT images of patients with CRP > 0.8 mg / dl (78.33% sensitivity and 98% specificity), WBC > 12.91 x103/uL (sensitivity 48.3%, specificity 86%), neutrophils > 8.78 x103/uL (sensitivity 56.67%, specificity 86%).*

***Conclusion**: Abdominal-pelvic CT is a very useful diagnostic tool for determining the differential diagnosis of abdominal pain. CRP, WBC and neutrophil levels could be used for the determination of the need to contrast enhanced CT in patients with abdominal pain.*

***Key words**: Acute abdomen, abdominal-pelvic CT, CRP, WBC, neutrophil.*

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Introduction

Non-traumatic acute abdominal pain is a common symptom of 4 to 5 percent of patients who admitted to the emergency room. It is important to reach the correct diagnosis and start treatment as soon as possible in patients with acute abdominal pain. The diagnosis of abdominal pain starts with a complete history and careful physical examination. Patient's history may vary depending on patient's telling ability and physical findings may vary depending on physician's clinical experience. Serological and haematological markers such as C-reactive protein (CRP), white blood cell count (WBC), neutrophil count, haemoglobin, amylase, lipase, urea and creatinine usually helps narrow the differential diagnosis and guide further analysis, including imaging methods[1-3].

Computerized tomography (CT) significantly increases the rate of correct diagnosis with clinical information in acute abdomen. In previous studies, CT in patients with acute abdominal pain is reported to change initial diagnosis and earlier planned treatment, reduce the rate of hospitalization and length of stay, gain extra time before surgery, lead to alternative diagnoses by excluding potential diagnoses and reduce negative laparotomy rates[4-6]. Therefore, the use of CT has increased considerably in recent times by physicians for patients with abdominal pain. For example, in the United States, the number of CT examinations performed for this indication increased 141% between 1996 and 2005. However, not being

able to be used in pregnant women and reasons such as excessive exposure to ionizing radiation, complications due to use of intravenous contrast material restricts the use of CT[3]. For this reason, it is very important to determine in which patients abdominal-pelvic CT would be useful under emergency conditions, and whether there is need for laparotomy or not in the management of non-traumatic acute abdomen.

CRP, a non-specific marker of inflammation and an acute phase reactant acting through the classical complement pathway, rises rapidly in parallel with the severity of pathological efficiency in infection or inflammation environment and falls rapidly in post-infectious or post-inflammatory phase because of 4-9 hours of elimination half-life. This rapid rise and fall of CRP levels are quite useful in monitoring an acute inflammatory disease processes[7,8]. In previous studies, levels of CRP and WBC were shown to increase in diseases that cause acute inflammation in the abdomen and it was reported that CRP is a measurable variable in the diagnosis of acute abdominal pain and can be used to identify the serious situations such as hospitalization[9-15].

The purpose of the study was to establish whether the patients presenting with abdominal pain should undergo to contrast enhanced CT. For this purpose, we have investigated the possible relationship between CRP, WBC, neutrophil levels and the presence of pathological findings determined on abdominal pelvic CT images.

Material and methods

Patients who were admitted to Adana Numune Training and Research Hospital Emergency Department between 01.01.2012-31.12.2012 with abdominal pain and underwent intravenous contrast-enhanced abdominal-pelvic CT scan were enrolled in this retrospective study. Patients whose necessary patient record data, lab results and CT images cannot be obtained, who have a history of recent trauma, (three months) surgical operations, known malignancy, or inflammatory bowel disease or who were admitted to emergency department with any other complaint and underwent CT without contrast material were excluded from the study. CRP, WBC and neutrophil counts were recorded on standard data entry form.

CRP measurement was done by Cobas Integra 800 instrument (Roche Diagnostics, Hyogo, Japan) with Beckman Coulter Latex Enhanced Turbidometric method. The normal value of CRP was set as 0-0.5 mg/dl. For statistical analysis, increases in CRP level were graded (Grade 0: 0-0.8 mg/dl, Grade 1: 0.9-1-6 mg/dl, Grade 2: 1.7-3.2 mg/dl, Grade 3: 3.3-6.4 mg/dl, Grade 4: 6.5 mg/dL and above). WBC and neutrophil counts of patients were done with Sysmex XT 2000 instrument (Roche Sysmex, Kobe, Japan) that automatically does haematological analysis procedures. The normal value of WBC and neutrophil count were taken as 4.4-11.3 103/uL and 1.5-7 103/uL.

Siemens Somatom Single Slice CT scanner (Siemens Medical Solutions, Erlangen, Germany) was used for abdominal-pelvic CT scans in the emergency department. Abdominal-pelvic CT images of all patients in the study were obtained from Picture Archiving and Communication System (Keogh Radiology Information Systems, version 2.7) of our hospital. Images were evaluated by two experienced radiologists from our radiology department. After images were evaluated as positive or negative according to presence of pathological findings, positive images were classified according to the severity of inflammation symptoms. The classification was made according to the fat volume and severity kept in visceral adipose tissue. Severity of involvement was graded from 0 to 4 (Stage 0: No inflammatory involvement; Stage 1: There is difficult seen thin oil involvement; Stage 2: There is a visible oil involvement, but oil density is still clean in the involved area; Stage 3: There is severe involvement of oil, but almost no oil density in the involved area; Stage 4: There is very severe involvement of oil, but no selectable oil density in the involved area).

Adipose tissue involvement was classified as none, organ-localized, or 1 to 4 abdominal quadrant involvements. Amount of free liquid in abdomen is also evaluated. The amount of free fluid was classified as none, minimal, moderate, and severe and diffuse in all abdomen.

Statistical Package for the Social Sciences (SPSS) 17.0 statistical software was used for statistical analysis of this study. Chi-square test statistic was used to compare categorical measurements between the two groups. T test was used in case of proved assumptions and Mann-Whitney U test was used in case of unproved assumptions for numerical comparison of the measurements between the two groups for independent samples. Kruskal-Wallis test was used for general comparison of quantitative measurements of abnormal distribution between more than two groups. Pearson correlation was used in case of

proved assumptions and Spearman correlation was used in case of unproved assumptions for examination of interaction between quantitative measurements. Statistical significance level of p was taken as < 0.05 for all tests.

Results

Of 130 patients included in the study, 63 were male and 67 were female. The mean age was 44.11 ± 5.18 (18.00-85.00) years. Mean age was 42.4 ± 16.6 years for men and 45.8 ± 19.3 years for women. There was no statistically significant difference between the mean age (p= 0.285).

Of the patients, while there was no pathological findings on CT in 56 (43.1%), 74 (56.9%) had pathological findings. Diagnoses of patients with pathological findings on abdominal-pelvic CT are shown in Table 1.

Diagnosis (n=)	Stage 1	Stage 2	Stage 3	Stage 4	Total
Acute appendicitis	4	6	3	2	15
Acute pancreatitis	6	5		2	13
Acute cholecystitis	3	3	3		9
Ileus	7	1		1	9
Perforation	3	1	1	0	5
Pancreatic abscess			3		3
Pneomobilia				3	3
Ovarian cyst rupture	3				3
Plastron appendicitis			1	1	2
Volvulus	2				2
Colitis		1	1		2
Perforated appendicitis				1	1
Strangulation				1	1
Intussusception			1		1
Incarcerated hernia			1		1
Acute cholangitis	1				1
Crohn's disease			1		1
Ileitis		1			1
Diverticulitis			1		1
Total	29	18	16	11	74

Table 1: Patient's diagnosis according to the CT stages.
CT = computed tomography; n = number of patients.

Pathologic findings were present on CT's of all patients who were included in the study and had a CRP > 0.8 mg / dl. The sensitivity and specificity values corresponding to the critical value were 78.33% and 98.00% (78.2 to 96.7) respectively, and positive likelihood ratio (+LR) and negative likelihood ratio (-LR) were 39.17 and 0.22, respectively. It may be proposed that patients who admitted to emergency department with abdominal pain and suspected acute abdomen with CRP > 0.8 mg / dl should undergo CT examination (Areas under the curve, AUC = 0.932, p < 0.0001) (Table 2). In our study, only 20 of the 76 patients (26.3%) with CRP levels of 0.0-0.8 mg/dl had positive findings on the CT.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥0	100,00	94.0 - 100,0	0,00	0,0 - 7,1	1,00	
>0	98,33	91.1 - 100,0	18,00	8,6 - 31,4	1,20	0,093
>0,1	93,33	83.8 - 98,2	44,00	30,0 - 58,7	1,67	0,15
>0,2	93,33	83.8 - 98,2	58,00	43,2 - 71,8	2,22	0,11
>0,3	91,67	81.6 - 97,2	68,00	53,3 - 80,5	2,86	0,12
>0,5	91,67	81.6 - 97,2	90,00	78,2 - 96,7	9.17	0.093
>0,6	86,67	75.4 - 94,1	92,00	80,8 - 97,8	10,83	0,14
>0,7	78,33	65.8 - 87,9	94,00	83,5 - 98,7	13,06	0.23
>0,8	78,33	65.8 - 87,9	98,00	89,4 - 99,9	39,17	0,22
>1,2	71,67	58,6 - 82,5	98,00	89,4 - 99,9	35,83	0.29
>1,3	70,00	56.8 - 81,2	100,00	92,9 - 100,0		0.30
>32,4	0,00	0.0 - 6,0	100,00	92,9 - 100,0		1.00

Table 2: The sensitivity, specificity, + LR and- LR values of the CRP levels (mg/dl) in determining the presence of positive CT findings
+ LR = positive likelihood ratio; - LR = negative likelihood ratio; CRP = C-reactive protein; CT = computed tomography; CI = level of confidence.

WBC > 12.91 x103/uL value can be used as a critical value for differentiation of the existence of pathological findings on the CT. Value of sensitivity corresponding to the critical value is 48.3% and specificity is 86%, + LR is 3.45, and -LR is 0.60. It may be recommended that patients who admitted to emergency department with abdominal pain and WBC > 12.91 x 103/uL should undergo CT examination (AUC = 0.710, p < 0.0001) (Table 3).

Neutrophils > 8.78 x 103/uL value can be used as a critical value for differentiation of the existence of pathological findings on the CT. Value of sensitivity corresponding to the critical value is 56.67% and

specificity is 86%, + LR is 4.05, and -LR is 0.50. It may be recommended that patients who admitted to emergency department with abdominal pain and neutrophils > 8.78 x 103/uL should undergo CT examination (AUC = 0.761, p < 0.0001) (Table 4).

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>10.13	61,67	48,2 - 73,9	60,00	45,2 - 73,6	1,54	0,64
>10.61	61,67	48,2 - 73,9	66,00	51,2 - 78,8	1,81	0,58
>11.13	56,67	43,2 - 69,4	66,00	51,2 - 78,8	1,67	0,66
>11.45	56,67	43,2 - 69,4	72,00	57,5 - 83,8	2,02	0,60
>11.47	55,00	41,6 - 67,9	72,00	57,5 - 83,8	1,96	0,62
>11.61	55,00	41,6 - 67,9	74,00	59,7 - 85,4	2,12	0,61
>11.95	51,67	38,4 - 64,8	76,00	61,8 - 86,9	2,15	0,64
>12.06	50,00	36,8 - 63,2	76,00	61,8 - 86,9	2,08	0,66
>12.77	50,00	36,8 - 63,2	84,00	70,9 - 92,8	3,12	0,60
>12.8	48,33	35,2 - 61,6	84,00	70,9 - 92,8	3,02	0,62
>12.91	48,33	35,2 - 61,6	86,00	73,3 - 94,2	3,45	0,60
>13.27	45,00	32,1 - 58,4	86,00	73,3 - 94,2	3,21	0,64
>13.4	45,00	32,1 - 58,4	88,00	75,7 - 95,5	3,75	0,62
>13.72	41,67	29,1 - 55,1	88,00	75,7 - 95,5	3,47	0,66
>13.81	41,67	29,1 - 55,1	92,00	80,8 - 97,8	5,21	0,63
>14.11	40,00	27,6 - 53,5	92,00	80,8 - 97,8	5,00	0,65

Table 3: The sensitivity, specificity, +LR and-LR values of the WBC levels (x103/uL) in determining the presence of positive CT findings.
+ LR = positive likelihood ratio; -LR = negative likelihood ratio; WBC = white blood cell; CT = computed tomography; CI = level of confidence.

It was detected that as the degree of CRP of patients increase, severity of inflammation on CT images increases in parallel (p < 0.05). A significant correlation was found between CT stages and CRP (p = 0.001, r = 0.800**), WBC (p = 0.001, r = 0.444**) and neutrophils (p = 0.001, r = 0.478**). As inflammation and severity of adipose tissue involvement on CT images increase, CRP, WBC and neutrophil levels had increased.

Of the patients, 80 (61.5%) were hospitalized and 50 (38.5%) were discharged from the Emergency Department. Of inpatients, 52 (40%) were operated. No statistically significant correlation was found between rate of surgery and levels of CRP (p = 0.74, r = 0.156).

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	LR
>7,16	68,33	55,0 - 79,7	70,00	55,4 - 82,1	2,28	0,45
>7,21	68,33	55,0 - 79,7	72,00	57,5 - 83,8	2,44	0,44
>7,25	66,67	53,3 - 78,3	72,00	57,5 - 83,8	2,38	0,46
>7,39	65,00	51,6 - 76,9	74,00	59,7 - 85,4	2,50	0,47
>7,51	63,33	49,9 - 75,4	74,00	59,7 - 85,4	2,44	0,50
>7,52	63,33	49,9 - 75,4	78,00	64,0 - 88,5	2,88	0,47
>7,98	58,33	44,9 - 70,9	78,00	64,0 - 88,5	2,65	0,53
>8,12	58,33	44,9 - 70,9	82,00	68,6 - 91,4	3,24	0,51
>8,2	56,67	43,2 - 69,4	82,00	68,6 - 91,4	3,15	0,53
>8,78	56,67	43,2 - 69,4	86,00	73,3 - 94,2	4,05	0,50
>9,77	48,33	35,2 - 61,6	86,00	73,3 - 94,2	3,45	0,60
>9,8	48,33	35,2 - 61,6	88,00	75,7 - 95,5	4,03	0,59
>10,17	43,33	30,6 - 56,8	88,00	75,7 - 95,5	3,61	0,64
>10,7	43,33	30,6 - 56,8	92,00	80,8 - 97,8	5,42	0,62
>11,07	41,67	29,1 - 55,1	92,00	80,8 - 97,8	5,21	0,63

Table 4: The sensitivity, specificity, +LR and -LR values of the neutrophil levels (x103/uL) in determining the presence of positive CT findings.
+LR = positive likelihood ratio; -LR = negative likelihood ratio; CT = computed tomography; CI = level of confidence.

CT Stage	CRP (mg/dl) mean ± sd (min-max)	WBC (x103/uL) mean ± sd (min-max)	Nötrofil (x103/uL) mean ± sd (min-max)	Length of hospital stay (day) mean ± sd (min-max)
0	0.2±0.2	8.8±3.7	5.6±3.6	0±0.9
	(0-0.8)	(4,14-23,37)	(2,38-20.93)	(0-4)
1	0.7±0.4	10.3±4.6	7.9±4.6	3±2
	(0.2-1.8)	(5.54-18.84)	(2.57-15.97)	(2-8)
2	2±1.2	12.5±4.72	10±4.2	4.5±2.5
	(1.2-5.7)	(3.7-21.15)	(2-18)	(1-8)
3	5.1±3	13±4.5	9.9±4.6	5±3
	(3.9-12)	(8.25-26.44)	(5,34-24,6)	(3-15)
4	18.3±6.7	15.9±5.2	13.96±3.96	10±4.4
	(6-32.4)	(7.5-26.42)	(5.00-20.87)	(3-14)

Table 5: Comparison of CT stages, and CRP, WBC, neutrophil levels, length of hospital stay.
CT = computed tomography; CRP = C-reactive protein; WBC = white blood cell; min = minimum; max = maximum; sd = standard deviation.

There was a statistically significant correlation between length of stay of inpatients and CT phases ($p > 0001$ r = 0.725**) and C-RP ($p > 0001$ r = 0.520**). It was found that as grade is increased on CT images, duration of hospitalization is also increased (Table 5).

Discussion

Acute abdomen is described as severe abdominal pain occurring within a few hours. It is important to diagnose these patients accurately and quickly to reduce morbidity and mortality. But it is difficult to assess clinical status of these patients and conventional X-rays and laboratory studies are often not specific. Being accurate and reliable, the use of imaging methods, especially CT, by physicians in determining the diagnosis of acute abdomen, has greatly increased. However, radiation and possible complications due to contrast medium during CT limits its use[3]. For this reason, it is very important to determine in which patients abdominal-pelvic CT would be useful under emergency conditions.

CRP, an acute phase reactant, is synthesized in the liver by the stimulation of cytokines such as interleukin (IL)-1-beta, IL-6 and tumor necrosis factor (TNF) alpha during acute inflammation and starts to rise within 4-6 hours and reaches peak levels within 2-3 days. Under proinflammatory conditions, CRP is synthesized by extrahepatic tissues and adipocytes in intra-abdominal fat tissue. Depending on the severity of inflammation, it rises 1000 times or more. This increase is much faster than erythrocyte sedimentation rate (ESR) and returns to normal more quickly than this last one with improvement of clinical condition and flogosis disappearance. Inflammation and tissue damage occur in the abdomen during acute appendicitis, diverticulitis, cholecystitis, pancreatitis, colitis and similar conditions causing acute abdomen. In several studies, it was shown that levels of CRP and WBC are increased in these cases that cause acute inflammation in the abdomen[7-15]. Also CRP levels are shown to increase as severity of inflammation increases in acute abdomen. For example, CRP levels were shown to be higher in acute necrotizing pancreatitis than acute interstitial pancreatitis[9,16]. In another study comparing simple ileus and strangulated ileus, statistically significant difference between the levels of CRP and WBC was found[15]. In another study conducted in patients with acute appendicitis, CRP values were found very high in perforated appendicitis[17].

Inflammation and tissue damage in abdomen causing acute abdomen are reflected to CT images. Severity of findings on CT images increases in parallel with an increase in the levels of CRP which is an inflammation marker. For example, in a study conducted in patients with acute appendicitis, CT findings graded as 0,1,2,3,4 according to the severity of inflammation were found to be associated with increased CRP and WBC. Also in this study, a significant correlation was found between CT severity score and CRP and WBC[18]. In another study regarding pancreatitis cases, it was found that CRP level and CT severity index are significantly lower in living patients, organ failure develops in patients with two or more liquid collection on CT and with high levels of CRP, and CT-CRP are important markers in predicting death in patients with acute pancreatitis[19]. CRP levels of patients with acute necrotizing pancreatitis were higher compared to patients with only edema on CT images[10].

In a study of patients with acute abdominal pain, positive pathologic findings were detected on CT images of patients with CRP > 5 mg/L (sensitivity 82.9, specificity: 47.0), WBC > 11.3 x 103/uL (sensitivity 57.7, specificity: 71.2),and neutrophils >6.6 x103/uL (sensitivity 59.4, specificity 65.2). In the same study, the specificity of detecting positive pathologic findings on CT imaging was found to be 91% when CRP is over 130 mg/L[8].

In our study, of all 130 patients, pathological findings were found in abdominal-pelvic CT images of 74 (56.9%) patients. A significant correlation was detected between positive pathologic findings on abdominal-pelvic CT images and CRP, WBC, neutrophil levels. Positive pathologic findings were detected on CT images of patients with CRP > 0.8 mg/dL (78.33% sensitivity and 98%specificity), WBC > 12.91 x 103/uL (sensitivity 48.3%, specificity86%), and neutrophils > 8.78 x 103/uL (sensitivity 56.67%, specificity 86%). These results make us think that abdominal-pelvic CT imaging would be more useful in making a diagnosis in patients with CRP > 0.8 mg/dl, WBC > 12.91 x 103/uL, neutrophils > 8.78 x 103/uL. In our study, inflammation findings on CT images were staged according to severity. A significant correlation was found between CT phases and CRP ($p < 0.001$, r = 0.800**), WBC ($p < 0.001$, r = 0.444**) and neutrophils ($p < 0.001$, r = 0.478**). These findings show that CRP, WBC and neutrophil levels increase parallel to the increase in inflammation in the abdomen and that this situation is reflected to CT images. Besides, significant

correlation was found between CT stage and duration of hospitalization. The duration of the hospital stay especially in patients who were assessed as grade 3 and 4 on CT images were found to be longer. In our study, positive findings on CT images were detected in 20 of 76 patients (26.3%) with a CRP level of 0.0-0.8 mg/dl (Table 3). CT findings of these patients were interpreted as stage 1. The severity of inflammation was classified as very light for stage 1. The reason why CRP levels of that patients is low may be due to early admitting to emergency department before signs of inflammation occur fully. In addition, as possible uses of steroids, nonsteroidal anti-inflammatory drugs or antibiotics depress inflammation, CRP may not increase due to this. In this retrospective study, only missing aspect of this study is that we do not know drug use of patients and start time of pain.

Conclusion

We have found a statistically significant correlation between the presence of pathological findings determined on abdominal-pelvic CT images and CRP, WBC, neutrophil levels. Abdominal-pelvic computed tomography (CT) is a very useful diagnostic tool for determining the differential diagnosis of abdominal pain. CRP, WBC and neutrophil levels could be used for the determination of the need to contrast enhanced CT in patients with abdominal pain. Furthermore, CRP, WBC and neutrophil levels may be helpful in determining the need for laparotomy in non-traumatic acute abdomen in some conditions such as, when it is inappropriate to use CT (pregnancy, contraindications due to intravenous contrast material, allergy, renal failure, etc.), and in the difficulty of access to CT imaging especially in rural hospitals.

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