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THE PREDICTIVE ROLE OF SELECTIVE LABORATORY PARAMETERS FOR THE OCCURANCE OF "UNWANTED EVENTS" IN ADULTS WITH LAPAROSCOPIC APPENDECTOMY

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Abstract

The aim of our study was to assess the potential predictive role of selected laboratory parameters in recognition of laparoscopic appendectomy (LA) associated with unwanted events defined as intraoperative difficulties, conversion to open approach and early postoperative complications.

A multicenter, prospective, clinical study was conducted. 75 randomly selected adults with acute appendicitis were selected as study participants. Twenty-five laboratory parameters were measured for all of them. In 69, LA was performed and in 6 of the patients, a conversion to open appendectomy had to be accomplished. For each patient, we registered the unwanted events in relation to the treatment.

Out of 75 participants with LA, 51 (68%) were without and 24 (32%) were with unwanted events. Binary analysis showed significantly higher levels of total bilirubin ($p = 0.0228$), sodium ($p = 0.0161$) and C – reactive protein ($p = 0.0005$) in the group with unwanted events. Multiple logistic regression analysis confirmed the total serum bilirubin as the only independent predictor – OR = 1.079 [$p = 0.041$, 95% CI = 1.003-1.162].

High levels of C – reactive protein, serum sodium and total serum bilirubin could be indicators of unwanted intraoperative or postoperative course in the patients treated with LA. In such cases it is wise to consider performing the laparoscopic exploration in the presence of an experienced surgeon.

Keywords: laparoscopic appendectomy, C- reactive protein, bilirubin, sodium.

Introduction

The open appendectomy (OA) that is performed through the so-called Mac Burney's incision [1] was the gold standard in the surgical treatment of acute appendicitis (AA) for over 100 years. Laparoscopic appendectomy (LA) as an alternative to OA was introduced in 1983 by Kurt Semm, a gynecologist who performed the first LA on a non-inflamed appendix [2].

Since then, a considerable number of studies as well as several meta-analyses [3] which analyze the advantages and disadvantages of LA in opposition to OA in patients with various characteristics and various local and generalized findings have been published.

The main conclusions state that LA and OA are at least equally safe in the cases with the uncomplicated AA, with several advantages of LA like: shorter length of hospital stay, lower postoperative

pain, fewer surgical site infections, better cosmetics, quicker return to the normal professional and everyday activities and lower overall cost.

The downsides of LA manly lie in the slight increase of the operating time, higher hospital cost and slightly higher incidence of postoperative intra-abdominal abscess. All the advantages of LA are especially highlighted in the obese patients with body mass index (BMI) >30m²/kg [4], women in the fertile period of age, elderly patients above 65 years and cases with complicated forms of AA were the usage of LA is strongly recommended [5,6].

The current recommendations from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) are mainly aimed towards the routine usage of LA, wherever there is a suitable equipment and trained personnel and there are no contraindications for laparoscopic approach. Additionally, they recommend that LA should be the preferred approach in cases with complicated forms of AA, in women of childbearing age, obese patients, pregnant women, and elderly patients [7].

The guidelines of the European Association for Endoscopic Surgery (EAES) are a product of a consensus meeting held at the Amsterdam congress in 2015, where the majority of 232 members of the EAES supported the overall 46 statements and recommendations regarding the current diagnosis and treatment of AA.

According to them, LA is a preferred procedure for the treatment of uncomplicated AA, perforated AA, for obese patients, elderly patients, pregnant women even in the third trimester, and for children with AA who need an appendectomy [8].

Finally, the World Society of Emergency Surgery (WSES) on its last consensus conference held in Nijmegen, Holland, in July 2019, once again stressed the superiority of LA over the OA and recommended LA as the preferred approach over OA, for both uncomplicated and complicated AA, wherever a laparoscopic equipment and expertise are available [9].

Although now LA is used as the preferred surgical approach in the treatment of AA in the developed countries [10], for many years the implementation was very slow [11, 12]. Partial usage of LA is still present in many less developed countries like ours [13].

There may be two main reasons for the slow implementation of LA. The first could be the fact that OA is already a perfect surgical procedure with over a century of experience, and there is very little space left for improvement. The second is the fact that appendectomy is an emergency operation that is mostly performed during night shifts, when the enthusiasm for the implementation of a novel procedure is low.

One of the opponents of the ambitious surgeon in that circumstance is the anesthesiologist, who is usually so satisfied with their perfect role in the routine procedure such as OA, that he/she feels that it is unnecessary to bother with a slightly more demandable guidance of a patient treated with laparoscopic procedure.

The other opponent may be the smaller enthusiasm of other members of the surgical staff, who will sometimes have to work twice as much in those late ours if the laparoscopic approach is used. In those conditions, the surgeon sometimes feels that he/she is promoting the new procedure all alone just to replace this already perfect procedure like OA.

It would be very helpful for that surgeon if all goes perfectly well without any kind of unwanted, intraoperative or postoperative course. In other words, it is important that there are not any stages of the operation where the surgeon is obviously struggling, that there are not any intraoperative complications such as vascular or visceral injuries, as well as no procedure related postoperative complications.

If the surgeon performs the first several laparoscopic appendectomies without any intraoperative or postoperative complications, it will open a clear path towards a routine usage of LA as a preferred approach in the surgical treatment of AA. For that reason, we decided to investigate whether we can somehow select the cases in whom LA would be performed straightforwardly, without any kind of unwanted outcome, especially regarding the intraoperative and the early postoperative course, i.e. only by evaluating some of the routine preoperative investigations.

Mainly for the purposes of providing a successful promotion of LA at the beginning of the implementation, we decided to find a way to improve the safety of the procedure by recognizing and

managing the situations where LA could lead to various kinds of "unwanted events" (UE) such as intraoperative or postoperative complications or conversion to an open approach.

The aim of our study was to assess the potential predictive role of selected laboratory parameters in recognition of laparoscopic appendectomy associated with "unwanted events" such as intraoperative difficulties, conversion or early postoperative complications.

Method

During the period between 2016 and 2018, we conducted a multicenter, prospective, clinical study at the Clinical hospital in Shtip and at the University clinic for digestive surgery, in Skopje, Republic of North Macedonia.

The research was approved by the Ethics Committee for Human Research of the Teaching Scientific Council of the Medical Faculty, at Ss. Cyril and Methodius University in Skopje. The implementation was also approved by the directors of the above mentioned institutions.

Each participant signed an informed consent.

According to certain defined inclusive and exclusive criteria, 75 adults with acute appendicitis were selected randomly as study participants.

Inclusion criteria were related to age, participants ranging from 15 to 60 years, then suspicion for AA that demands emergency operative treatment or in hospital observation, regardless of gender, religion, education grade, place of living, social status or other demographic characteristics.

The exclusion criteria were: age above 60 or below 15 years, contraindications for laparoscopic procedure, clinical finding consistent with diffuse peritonitis, appendiceal mass or abscess, and gravidity. All the patients that meet the mentioned criteria (N=98) were included in the study and in all of them the values of exactly 25 laboratory parameters were measured. In 13 of the patients, the symptoms subsided during the observation, and they were excluded from the study. In the remaining 85 patients, a laparoscopic exploration was performed.

The diagnosis of AA was confirmed or discarded intraoperatively on the preference of the surgeon according to the laparoscopic classification for AA and 10 of the patients in whom the appendix appeared normal were also excluded from the study. In 69 of the remaining patients, LA was performed, and in 6 of the patients a conversion to open appendectomy (OA) had to be performed.

The extracted appendixes of the 75 patients, who remained in the study, were sent to a histopathological examination and AA was confirmed in all of them.

LA was performed by using one 10 mm supraumbilical port and two 5 mm ports, one in the suprapubic region and one in the lower left abdominal quadrant.

Conversion to open approach when needed was performed by Mac Burney incision or infraumbilical median laparotomy. The mesoappendix with appendicular artery was cut and sealed with the ligasure device (figure 1 a).

The appendiceal base was ensured with endoloop (figure 1 b,c) and cut with ligasure (figure 1 d) and the appendix was removed from the abdominal cavity by using endobeg.

For each operation, the operative time was measured from the moment of the first skin incision until the last skin stitch placement.

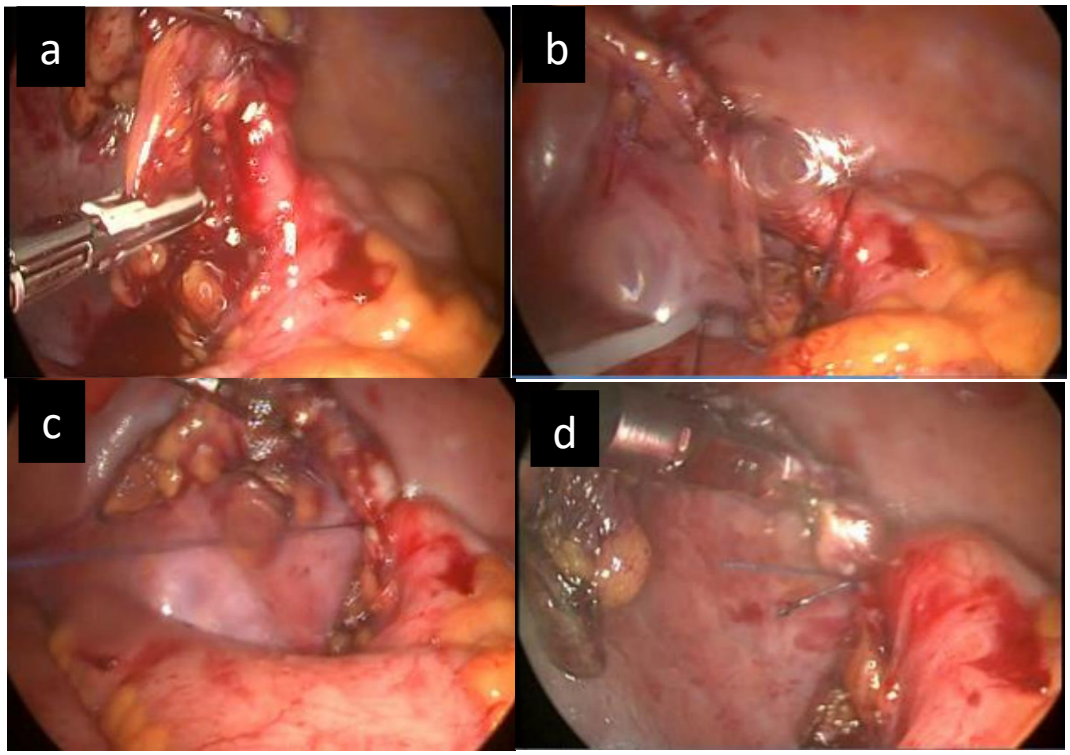

Figure 1. Laparoscopic appendectomy (a, b, c, d).

In each patient the intraoperative difficulties or complications were registered, as well as the reason for conversion, if present.

Postoperatively each patient was followed on the 7th and 30th postoperative day for the presence of any kind of abdominal or extra abdominal early postoperative complication. We divided the intraoperative difficulties while performing LA into difficulties during: a) establishing the pneumoperitoneum; b) introducing the trocars in the abdominal cavity; c) visualization and mobilization of the appendix; d) securing the appendicular artery; e) occluding the appendicular base, and f) extracting of the appendix.

The intraoperative complications were divided as complications from: a) pneumoperitoneum (disturbance of the normal venous return to the hart, hypercapnia with respiratory acidosis, pneumothorax, pneumomediastinum, etc.); b) entering the abdominal cavity, and c) surgical procedure (any visceral or vascular injury).

The early postoperative complications were classified as 1) abdominal (postoperative bowel obstruction, intestinal perforation, postoperative hemoperitoneum, intraabdominal abscess, perforation of the bladder, surgical site occurrences etc.) and 2) extra-abdominal (pulmonary atelectasis, pleural effusion, arrythmia, myocardial infarct, thromboembolism, thrombophlebitis, etc.).

They were closely defined and graded according to the Clavien-Dindo classification of the postoperative complication.

We defined the term “unwanted events” as any kind of intraoperative difficulties or complications, conversion or early postoperative complications.

Results

Out of 75 participants with LA, 51 (68%) were without and 24 (32%) were with "unwanted events". In the group without/with "unwanted events", 28 (54.9%) vs. 16 (66.7%) were male patients with no significant association between gender and the group to which the patient belonged (Pearson Chi square = 0.9315, df = 1, p = 0.3345).

The mean age of patients without "unwanted events" was 29±11.6 years, with a min/max age of 16/57 years and 50% of the patients younger than 25, for Median (IQR) = 25 (19-35). The mean age of the patients with "unwanted events" was 33±15.1 years, with a min/max of 15/60 years with 50% younger than 30 years for Median (IQR) = 30 (19.5-44.5).

There was no significant difference between the two groups regarding the age (Mann Whitney U Test: Z = -0.8404; p = 0 4006).

Intraoperative difficulties or intraoperative complications were registered in 22 (91.67%)/24 patients in the group with "unwanted events".

The struggling with the appendix mobilization was the most frequent difficulty present in 16 out of 22 (72.73%) patients (in six led to conversion). Difficulties with appendix extraction out the abdominal cavity were registered in 3 patients (13.64%).

In one patient (4.55%), there was a problem with securing the appendicular artery and in one (4.55%) there was an unexpected intraoperative finding of diffuse peritonitis that led to conversion. Only one (4.55%) intraoperative complication was registered in the form of serosal injury of the caecum and small bowel during the mobilization of the appendix.

Totally seven conversions were done with overall conversion rate of 9.3%. In five (20.83%) out of 24 patients with "unwanted events", there was a postoperative complication registered.

There were three cases with seroma from the operative wound (Clavien-Dindo grade I), one case with postoperative intra-abdominal hemorrhage that demand reoperation (Clavien-Dindo IIIb), and one case with infection of the supraumbilical incision (Clavien-Dindo II).

In the group with "unwanted events" compared to the one without, we found a significantly longer operative time (76.2±24.1 vs. 59.9±13.6 minutes) and length of hospitalization (4.7±1.5 vs. 3±1 days).

Binary analysis of the 25 laboratory parameters showed significant difference between the two groups for total bilirubin: 17.61±9.42 vs. 22.24±9.28 μmol/l (p = 0.0228), sodium: 133.47±18.92 vs. 138.2±3.08 mmol/l (p = 0.0161) and C – reactive protein (CRP): 45.35±58.61 vs. 97.81±83.26 mg/l, (p = 0.0005) with significantly higher levels in the group with "unwanted events" (Table 1a,b).

Additionally, multiple logistic regression analysis confirmed the total serum bilirubin as the only independent predictor - OR=1.079 [p = 0.041, 95% CI = 1.003-1.162] (Table 2).

Table 1.a Analysis of the laboratory parameters according to the groups.

Parameters	**Laboratory investigations**			**P**
	N	**X^2 ± SD**	**Median**	
Glycemia (mmol/l)				
without UE	50	5.56 ±0.86	5.76	t (72)=-1.6141; p=0.1109
with UE	24	5.91±0.89	5.87	
Serum Albumin (g/l)				
without UE	39	44.74±4.75	45.00	Z=-1.4568; p=0.1452
with UE	21	46.50±2.89	46.00	
Total serum protein (g/l)				
without UE	39	68.49±12.20	70.00	Z=-1.2089; p=0.2267
with UE	21	72.16±6.02	71.00	
Creatinine (µmol/l)				
without UE	49	71.51±13.25	69.60	Z=-0.1820; p=0.8556
with UE	24	71.10±9.76	69.85	
Serum urea(mmol/l)				
without UE	50	4.08±1.67	3.80	Z=-0.8545; p=0.3928
with UE	24	4.37±1.53	4.05	
Aspartate transaminase (u/l)				
without UE	50	18.56±8.03	17.00	Z=-0.5716; p=0.5676
with UE	24	17.91±3.85	17.50	
Alanine transaminase (u/l)				
without UE	50	22.40±13.61	16.50	Z=0.4907; p=0.6236
with UE	24	18.61±7.91	17.50	
Alkaline phosphatase (u/l)				
without UE	48	61.94±22.74	60.00	Z=0.5316; p=0.5950
with UE	24	62.21±29.27	53.00	
Lactate dehydrogenase (u/l)				
without UE	47	165.34±38.17	157.00	Z=-0.8562; p=0.3919
with UE	21	172.95±42.09	173.00	
Gamma glutamate transaminase(u/l)				
without UE	42	27.69±17.39	20.50	Z=-0.5061; p=0.6127
with UE	19	33.15±24.73	28.00	
Total serum bilirubin (µmol/l)				
without UE	45	17.61±9.42	14.60	Z=-2.2764; p=0.0228*
with UE	22	22.24±9.28	20.60	
Potassium (mmol/l)				
without UE	45	3.94±0.44	3.90	t (64)=-0.7234; p=0.4721
with UE	21	4.02±0.34	4.00	
Sodium (mmol/l)				
without UE	45	133.47±18.96	137.00	Z=-2.4092; p=0.0161*
with UE	21	138.2±3.08	138.00	
C – reactive protein (CRP) (mgl/l)				
without UE	51	45.35±58.61	23.80	Z=-3.4925; p=0.0005**
with UE	24	97.81±83.26	83.75	

[1]T-test for independent samples [2]Mann-Whitney U Test *significant for p<0.05
** significant for p<0.01

Table 1.b Analysis of the laboratory parameters according to the groups.

Parameters	**Laboratory investigations**			**P**
	N	**X^2 ± SD**	**Median**	
Leucocytes ($\times 10^9$/l)				
without UE	51	14.74±5.14	14.02	Z=-0.8745; p=0.3818
with UE	24	15.33±3.71	14.87	
Erythrocytes ($\times 10^{12}$/l)				
without UE	51	4.86±0.58	4.77	Z=1.2891; p=0.1974
with UE	24	4.72±0.36	4.72	
Hemoglobin (g/l)				
without UE	51	142.51±16.32	145.00	Z=0.3918; p=0.6952
with UE	24	141.54±13.99	142.50	
Hematocrit (%)				
without UE	51	41.41±4.78	41.00	t (73)=-0.2459; p=0.8062
with UE	24	41.69±4.31	42.92	
Thrombocytes ($\times 10^9$/l)				
without UE	51	249.63±71.55	236.00	Z=1.4992; p=1.4992
with UE	24	224.08±57.44	219.00	
Medium corpuscular volume (fl)				
without UE	50	85.13±6.74	86.25	Z=-1.6981; p=0.0894
with UE	23	88.49±5.94	88.50	
Medium corpuscular hemoglobin (pg)				
without UE	50	29.49±2.35	29.90	Z=-0.7101; p=0.4776
with UE	24	30.01±1.91	30.00	
Mean corpuscular hemoglobin concentration (g/dl)				
without UE	50	343.74±14.95	340.50	t-test (df=72)=0.8581; p=0.3937
with UE	24	340.37±17.44	341.00	
Neutrophils (%)				
without UE	51	83.54±9.29	85.30	Z=-0.8291; p=0.4071
with UE	24	85.91±4.99	85.30	
Lymphocytes (%)				
without UE	51	11.55±8.12	9.70	Z=0.9654; p=0.3343
with UE	24	9.22±4.37	8.50	
Monocytes (%)				
without UE	50	4.62±2.61	4.05	Z=-0.1212; p=0.9035
with UE	24	4.74±2.79	4.45	

[1]t-test for independent samples [2]Mann-Whitney U Test *significant for p<0.05
** significant for p<0.01

Discussion

Even though there is no prove of a significant role of the values of some laboratory parameters in establishing the diagnosis of AA, we tried to find a connection between those values and the emergence of complications and conversion during LA.

Our analysis showed that there is not such relation for the serum levels of: glucose, albumin, total protein, creatinine, urea, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, gamma glutamate transaminase and potassium.

The serum levels of all those parameters were in referent values. While reviewing related scientific literature, we found only one study (Goel at al.) in which the research presented was on the possible connection between the values of alanine transaminase (ALT) and aspartate transaminase (AST) in the serum with the so-called "hard LA".

The authors define "hard LA" as LA that was longer than 120 minutes, that end with conversion to open approach or LA in the cases with marked intra-abdominal adhesions.

There was no statistically significant connection between the levels of ALT and AST and "hard LA" [14].

Although most of the mentioned parameters have a role in assessing the overall functional status of the patient, we can say that they probably should not be a part of the routine laboratory investigations when assessing the patient for a safe LA without "unwanted" events.

There is scant literature about the possible usefulness of some parameters from the complete blood count both in diagnosing AA and in predicting the emergence of complications related to the laparoscopic approach in the treatment of a patient with AA.

Table 2. Multiple logistic regression analysis.

Variable	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Total serum bilirubin (μmol/l)								
Total serum bilirubin	**.076**	**.037**	**4.180**	**1**	**.041***	**1.079**	**1.003**	**1.162**
Sodium (mmol/l)								
Sodium	**.149**	**.129**	**1.336**	**1**	**.248**	**1.161**	**.902**	**1.494**
CRP (mgl/l)								
CRP	**.009**	**.006**	**2.320**	**1**	**.128**	**1.009**	**.997**	**1.021**

*** significant for p<0.0**

Our analysis showed that there is no significant difference between the groups with or without "unwanted" events regarding the values of: erythrocyte count, thrombocyte count, leucocyte count, hemoglobin concentration, hematocrit, medium corpuscular volume (MCV), medium corpuscular hemoglobin (MCH), medium corpuscular hemoglobin concentration (MCHC), and the percentage of lymphocytes or monocytes.

We can state again that most of those parameters are of greater importance in assessing the functional status of the patient.

As for the percentage of neutrophils, even though it is raised in accordance to the underlying disease, the fact that there is no statistical difference of the levels in the two groups disable its usefulness in predicting the outcome of LA.

Unlike the above, determining the serum level of CRP should be an essential part of the laboratory investigation pallet in the patients with suspicion for AA.

In many studies there is a clear relation between high levels of CRP and emergence of intraoperative and postoperative complications as well as conversion to open approach during LA in patients with AA.

Shelton et al. [15] analyzed exactly 517 appendectomies in patients with histopathological confirmation of AA postoperatively. In 429 (83%) of those patients LA was performed, and in 88 (17%) there was a conversion to open approach. They calculated significantly higher levels of CRP (162mg/l vs. 71mg/l) in the group of patients with conversion.

In an additional analysis the authors concluded that the levels of CRP >150mg/l were in significant relation with the emergence of postoperative complications.

At the end of the study, they asked whether it was better to perform an OA in the cases where the CRP level was above 150mg/l to avoid the strong possibility for conversion or emergence of complications related to the laparoscopic approach.

Abe et al. [16] registered that the level of CRP was significantly higher (103mg/l vs. 41mg/l) in the group with conversion.

They also concluded that CRP level >100mg/l was an independent predictor for conversion in patients treated by LA. Andert et al. [17] conducted a study on 2136 patients with AA with nearly half of them treated with LA and the others with OA.

They concluded that besides the emergence of conversion and age above 70 years, the high level of CRP was also an independent predictor of postoperative complications. Hellberg et al. (2001) [18] concluded that the high level of CRP was in a statistically significant relation to emergence of conversion although it was not an independent predictor.

Giesen et al. [19] registered significantly higher levels of CRP in the group with surgical site infections in 637 appendectomies, 79% of which were performed laparoscopically. Overall, the literature is full of evidence of a strong connection between high levels of CRP and emergence of complication and conversion during LA.

In the studies where such connection is not confirmed, this parameter was not investigated at all. In our study, the high level of CRP is a strong predictor for "unwanted events" related to LA that among others suggest that determining the serum level of CRP should be an essential part of the laboratory investigation in the selection of the patients for LA.

Unlike CRP, we could not find a single study that relates hypernatremia to complications or conversion during LA; therefore, we can just say that this parameter probably deserves more future investigations and should be taken into consideration when diagnosing AA as well as choosing the right operative approach.

Hyperbilirubinemia was first reported as a relevant parameter for establishing the diagnosis of AA, especially for complicated forms of AA, by Estrada et al. [20] in 2007.

Later, several studies gave the same results regarding the relation of hyperbilirubinemia with advanced grades of AA [21-23], but on the other hand, only a few found a relation with the emergence of complications and conversion during LA and were without statistical significance [24]. Hyperbilirubinemia in the patients with AA is mostly contributed to the disturbance of the normal bile flow by the Escherichia coli endotoxin.

In our study, the high value of this parameter is the only independent predictor of intraoperative difficulties, complications or conversion during LA.

Conclusion

Extremely high levels of CRP, high levels of serum sodium and most importantly, high levels of total serum bilirubin could be indicators of unwanted intraoperative or postoperative course in the patients treated with laparoscopic appendectomy. In such cases it is wise to consider performing laparoscopic exploration in the presence of an experienced surgeon.

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