ORIGINAL ARTICLE

ASSOCIATION OF SCREENING MARKERS OF COAGULATION WITH THE SHORT-TERM OUTCOME IN THE SMALL BOWEL OBSTRUCTION IN ADULTS: A RETROSPECTIVE STUDY

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ABSTRACT

The aim: To evaluate the possibility of using screening markers of coagulation to the assessment of severity and predict short-term outcomes in patients with small bowel obstruction.

Materials and methods: The study was based on the results of treatment of 71 patients 18-60 years old in 2019-2021. Patients were divided into two groups: in the 1st included those with a positive outcome (90.1%), and in the 2nd those with adverse outcome: (9.9%).

Results: Only the laparoscopy approach has been in 12.5%, the laparotomy in 78.9%, andthe hybrid in 9.9% of patients. There were no significant differences in screening tests of coagulation function indicators, including D-dimer, fibrinogen, Activated Partial Thromboplastin, International Normalised Ratio levels, and the International Society on Thrombosis and Hemostasis Criteria (ISTHC) score in two groups of patients before surgery. The predictive value of preoperative Sequential Organ Failure Assessment (SOFA) data (AUC = 0.844), serum lactate (AUC = 0.805), and systolic blood pressure (SPB) data (AUC = 0.808) before surgery were significant. The SOFA (AUC = 0.844) and APACHE II scores (AUC = 0.802), serum lactate (AUC = 0.884), D-dimer (AUC = 0.812), Antithrombin (AUC = 0.815), and CRP (AUC = 0.856) levels, SPB (0.856) wthin the first 72 hours after surgery were also good predictors of short-term outcomes (P = 0.000).

Conclusions: It was confirmed that three parameters were predictors of early mortality before surgery, none of them included parameters of coagulation and seven parameters via 72 hours after surgery, which had included some parameters of coagulation.

KEY WORDS: small bowel obstruction, parameters of coagulation, severity, prognosis, surgery, mortality

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INTRODUCTION

Surgical treatment small bowel obstruction (SBO) remains one of the most challenging problems of emergency abdominal surgery nowadays, most studies have shown that one is a heterogeneous syndrome caused by an imbalanced host response to obturation and ischemia/necrosis of the small intestine. In all of these cases, the pathological processes may lead to ischemia, necrosis, intestinal perforation, peritonitis, sepsis [1, 2]. It has been reported that SBO accounts for 12% to 16% of surgical hospitalizations, about 40% of cases are associated due with strangulation of the small intestine, at least 300,000 surgical procedures are performed annually in the United States [3]. Nonviable asphyxiation of the small intestine accounts for 16% of SBO, which four times increase the risk of death in comparison with the rates in patients with viable asphyxiation [4], and in patients with strangulation, SBO had a mortality rate of 2 to 10 times higher than patients with non-strangulation [5]. It was noted that the violation of macro-and microcirculation in the early stages before and after surgery in patients with SBO contributes to significant shifts in homeostasis and plays a major role in the development of multiple organ disorders due to frequent disseminated and often uncontrolled activation of coagulation. Lots of pathological conditions can also cause disseminated intravascular coagulation, with sepsis, organs destruction (e.g., severe pancreatitis, necrosis of the large intestine, reperfusion syndrome, cancer, trauma, etc.) that being among the most common triggering factors [6,7]. The prevalence of these disorders depends on the conditions of hospitalization, timing onset of diseases and is higher in critically ill patients admitted to intensive care units [8-12]. The International Society for Thrombosis and Hemostasis has defined DIC syndrome is an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from various causes [13]. The data on the possibility of using screening coagulation parameters for the assessment and predicting early mortality in patients with simple and strangulated SBO are contradictory nowadays.

THE AIM

The study aimed to evaluate the possibility of using screening markers of coagulation to the assessment of severity and predict short-term outcomes in patients with small bowel obstruction.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

A two-center retrospective study at the Kharkiv National Medical University, Ukraine, included 71 patients over 18 and less than 60 years of age who was admitted to the ICU during the immediate postoperative phase. The study was conducted a bit more than two years, from September 1, 2019, to November 30, 2021, and with the approval of the University Ethics Committee (the protocol of Ethics Committee No. 5-21 (0116u00499) from October 25, 2021).

Inclusion criteria: the study included men and women who were admitted to the hospital with SBO.

Exclusion criteria: patients with mechanical large bowel obstruction; inguinal hernia; early postoperative SBO occurring less than 30 days after the abdominal operation; patients with a known history of ascites; comorbidity with acute myocardial infarction and stroke; post-resuscitation illness due to stopping effective blood circulation and a refractory shock; pregnancy; cancer in anamnesis.

PATIENTS AND COLLECTED VARIABLES

All of these patients were undergoing surgery. The primary outcome measure was death and it was defined as all-cause in-hospital mortality 30 days after surgery. Patients were divided into two groups: in the 1st included those with a positive outcome (survivors, n = 64), and in the 2nd those with adverse outcomes (non-survivors, n=7). The following data were collected: age, gender, body mass index (BMI), laboratory data with the determination of coagulation status in the volume of screening coagulogram; the severity was calculated for each patient: Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA) and the International Society on Thrombosis and Hemostasis (ISTH) Criteria for Disseminated Intravascular Coagulation (DIC) scores (ISTH for DIC), and the nature of complications and results (short-term mortality up to 3 days and during 30 days). There were two clinical observations and assessments during surgery: patients with reversible small bowel ischemia and patients with irreversible small bowel ischemia. Complications after surgery were graded according to the Clavien-Dindo classification [14].

STATISTICAL ANALYSIS

Comparison of demographic and clinical data of the patients (survivors and non-survivors) was accomplished by employing Mann–Whitney test and $\chi 2$ test for quantitative variables (1st step). Continuous data were presented as Me (Q1; Q3), where Me is the median, Q1 and Q3 is the interquartile range (IQR). Zero hypotheses (H0) in statistical tests were rejected at a significance level of $p \geq .05$. The capability of each prognostic index and biological markers to predict mortality was analyzed by the receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) and the respective confidence interval (CI) was used as a measure of the overall index accuracy by the selection of parameters in the 1st step. The areas under the ROC curve were determined for each score and each biomarker, and the significance of the differences between them was assessed and taken into account its 95% confidence interval. The prognostic efficacy of the models was assessed by discrimination based on the AUC index: the efficacy of the model was considered limited at AUC $\geq$ 0.70; was considered a good model at AUC $\geq$ 0.80, and excellent at AUC $\geq$ 0.90. Statistical analyses were performed using the software STATISTICA 13.3 EN.

RESULTS

PATIENTS, OPERATING DATA AND POSTOPERATIVE COMPLICATIONS

During the study period, 71 patients underwent emergency surgery for SBO. Of these, 7 patients (9.9%) died in the hospital postoperatively (Figure 1). From 28 (39.4%) patients with strangulated small bowel obstruction (SSBO), the adhesive disease was the primary etiology in patients (71.4%), and the volvulus was the second (28.6%).

Patient characteristics are shown in Table I. The groups that were studied did not have significant differences in gender. In survivors of patients were of onset of surgery more likely than in non-survivors, and in patients who survived were of onset of resuscitation and its duration before surgery also more early. Only the laparoscopy approach has been in 12.5%, only the laparotomy in 78.9%, and the hybrid in 9.9% of patients.

LABORATORY STUDIES

BASELINE CHARACTERISTICS

The results of the distribution of patients by the changes of laboratory data and severity depending on the outcome are presented in Table II. There was no significant correlation between the individual parameters of the integration tests and the indicators of the screening coagulogram before surgery in two groups of patients.

The data of patients with increased levels of D-dimer, CRP, and lactate in patients before surgery in a comparative aspect is presented in Figure 2. As it was shown, only the level of blood lactate significantly differed in patients with non-SSBO and SSBO before surgery (P = 0.012).

ROC CURVES ANALYSIS OF BIOMARKERS FOR PREDICTING EARLY MORTALITY

The indicators were selected that were credible and belonged to the category of good and excellent models before and after surgery as shown in Table III. The AUC of lactate before surgery was 0.805 (P = 0.000), and AUC of SBP was 0.808 (P = 0.000). At the same time, the APACHE II and SOFA scores were reliable for assessing the severity of patients, however, the SOFA score turned out to be more

Table I. Patients, operating data and postoperative complications

Indicators	Outcomes		P value
	Survivors (n = 64)	Non-survivors (n = 7)	
Ages, Me [IQR]	54 [18-58]	56 [43-60]	.132
Sex:			
- male	28 (43.8%)	2 (28.6%)	.078
- female	36 (56.2%)	5 (71.4%)	
BMI, kg/m2, Me [IQR]	24 [22-29]	31 [24-35]	.000
Hypotension at diagnosis (SBP < 90 mm Hg), (%) **			
IV fluid administration before surgery, (%) **	7 (10.9%)	5 (71.4%)	.014
Vasopressor before surgery, (%) **	64 (100%)	7 (100%)	.778
Onset to surgery, (min) *	5 (7.8%)	7 (100%)	.000
Me [IQR]	80 [60–150]	90 [60-125]	.449
Surgical approach, (%) **:			
Laparoscopy only	8 (12.5%)	–	.014
Laparotomy only	50 (78.1%)	6 (85.7%)	
Laparoscopy + Laparotomy	6 (9.4%)	1 (14.3%)	
Type of surgery, (%) **:			
Adhesiolysis, drainage	42 (65.6%)	1 (14.3%)	.000
Resection of the small intestine, anastomosis	19 (29.7%)	5 (71.4%)	
Resection of the small intestine, stoma formation	3 (4.7%)	1 (14.3%)	
Time of surgery (min), Me [IQR]	148 [40-170]	184 [110-190]	.016
Intraoperative fluid administration, (%) **	64 (100%)	7 (100%)	.078
Amcunt of fluid during surgery, (L) Me [IQR]	2.4 [1.8–2.8]	3.0 [1.5-3.2]	.011
Intra-abdominal complications, (%)**	12 (18.8%)	2 (28.6%)	.987
Re-laparotomy, (%)**	1 (1.6%)	2 (28.6%)	.041
Hospital length of stay (days), Me [IQR]	11 [9–23]	3 [1-5]	.000
Clavien-Dindo classification:		NA	
I		31 (43.7%)	
II		15 (21.1%)	
IIIa		7 (9.9%)	
IIIb		3 (4.2%)	
IVa		4 (5.6%)	
IVb		3 (4.2%)	

Note: * The time of surgery was defined as the time of starting surgery; ** Statistically significant difference as determined by χ2–criteria; P - Mann-Whitney test; NA - not applicable; BMI - body mass index.

significant before surgery: the AUC of its was 0.855 (P = 0.000).

At 72 hours after surgery, the predictive value of D-dimer, antithrombin, lactate levels, CRP, SBP, APACHE II and SOFA was also assessed using the ROC method (Table III). The area under the ROC curve (AUC) of D-dimer was 0.812 (P = 0.000); AUC of antithrombin was 0.815 (P = 0.000); AUC of lactate was 0.884 (P = 0.000); AUC of CRP was 0.833 (P = 0.000); AUC of SBP was 0.856 (P = 0.000). As it was shown by this research data, the APACHE II (AUC = 0.802) and SOFA (AUC = 0.844) scores were also reliable for assessing the severity of patients after surgery (P = 0.000).

Despite the small number of observations, the predictive value of ROC curves significantly differed and was more significant for the SOFA and APACHE II scores before surgery (Figure 3) compared to the level of D - dimer (AUC = 0.673) and the ISTH Criteria for DIC score

Table II. Laboratory data and scores of severity in patients depending on the outcome

Indicators	Before surgery		P	Via 72 hours		P value
	Survivors (n = 64)	Non-survivors (n = 7)		Survivors (n=64)	Non-survivors (n=7)	
Platelet (10^9/L), Me [IQR]	277 [210-401]	253 [203-309]	.055	267 [223-311]	211 [178-215]	.000
D-dimer (ng/mL), Me [IQR]	214 [112–324]	241 [213–378]	.268	212 [111-267]	265 [221-412]	.000
Fibrinogen (g/L), Me [IQR]	4 [3.1-5.4]	4.5 [3.8-6.8]	.141	4.7 [4.0-6.2]	5.8 [4.6-6.8]	.006
APTT (sec), Me [IQR]	31.5 [25-43]	33.5 [21-46]	.315	32 [22-44]	36.5 [24-48]	.350
INR (%), Me [IQR]	89 [65-99]	77 [64-82]	.176	85 [72-104]	73 [56-82]	.032
Antithrombin, (%)	80 [65-95]	68 [42-78]	.058	74 [62-91]	56 [40-74]	.003
Lactate (mmol/l), Me [IQR]	2.1 [1.8-2.8]	3.2 [2.6-5.1]	.000	2.2 [1.9-3.6]	4.8 [3.2-8.3]	.000
CRP (mg/l), Me [IQR]	86 [76-153]	183 [141-211]	.000	92 [82-162]	201 [160-213]	.000
SBP (mm Hg), Me [IQR]	115 [100-160]	80 [70-100]	.000	130 [90-155]	65 [60-100]	.000
APACHE II score (points), Me [IQR]	11 [9-16]	21 [15-28]	.000	14 [6-15]	26 [12-32]	.000
SOFA score (points), Me [IQR]	4 [3-9]	8 [5-11]	.000	9 [3-9]	14 [5-12]	.000
ISTH Criteria for DIC (points), Me [IQR]	0 [0-2]	1 [0-3]	.169	1 [0-2]	2 [1-4]	.006

Note: P - Mann-Whitney test; NA - not applicable; CRP - C reactive protein; APTT - Activated Partial Thromboplastin Time; INR - International Normalised Ratio; SBP – systolic blood pressure; APACHE II - Acute Physiology And Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment; ISTH for DIC – International Society on Thrombosis and Hemostasis Criteria for Disseminated Intravascular Coagulation.

(AUC = 0.503). At 72 hours after surgery, such markers as SOFA and APACHE II scores, and also D-dimer studied had a good predictive ability (Figure 4).

DISCUSSION

As usual, the non-neoplastic mechan includes two forms like a simple (non-SSBO) and a strangulated obstruction (SSBO) with the following causes: adhesions (80 - 91%), volvulus (4-6%), intussusception (3-5%), bezoar (1.2-4%), gallstones (0.5-6%), Crohn's disease (0, 7-3%), foreign bodies (0.2-1%), others (0.5-3%). The development of SBO triggers a whole cascade of diverse pathological processes affecting all organs and systems. However, the central link in the development of obstruction is directly itself the small intestine, representing the primary and main source of endogenous intoxication and MODS [15].

It is known that SBO with/without small bowel entrapment, sepsis and other critical disorders in abdominal surgery are associated with coagulopathy ranging from hypercoagulability to acute disseminated intravascular coagulation (DIC) [16]. It was shown that the hemostasis-related parameters as a predictor of poor outcomes in ICU patients [17]. Wherein, D-dimer, protein C, protein S, von Willebrand factor and antithrombin indicators were most often mentioned in this context [18, 19].

In our study was shown that independent use standard (screening) of coagulogram parameters, such as fibrinogen, APTT, INR, D-dimer and ISTH Criteria for DIC in patients with SBO was not associated with the adverse short-term prognosis. Several studies have been published on the diagnostic significance of D-dimer in acute lesions of the small intestine [20], as it is well have known that damage to the vascular wall triggers a cascade of physiological reactions in the body leading to activation of endothelium with the formation of a blood clot. It consists of blood cells and fibrin protein but as a result of working of the fibrinolytic system, fibrin is split into smaller fragments, and a variety of fibrin degradation products of various molecular weights are formed, including D-dimers. For these reasons, the clot does not spread from the site of the vessel damage throughout the entire

Table III. Diagnostic value of D-dimer, Platelet, Antithrombin, Lactate, CRP, SBP, APP, APACHE II, and SOFA scores for in-hospital mortality

Variable	AUC	Optimal cutoff value	SE	95% CI	Sensitivity	Specificity
D-dimer, (ng/mL):						
Before surgery	0.673	215.5	0.0512	0.565-0.771	0.542	0.853
Via 72 hours	0.812	243.5	0.0846	0.773-0.854	0.864	0.857
Platelet, (10^9/L):	0.730	310	0.0587	0.622-0.754	0.500	1.0
Before surgery						
Via 72 hours	0.765	245	0.0723	0.632-0.789	0.612	0.876
Antithrombin, (%):	0.786	82.0	0.0762	0.689-0.832	0.560	0.789
Before surgery						
Via 72 hours	0.815	70.0	0.0876	0.694-0.843	0.621	0.794
Lactate, (mmol/L):	0.805	2.15	0.0643	0.711-0.854	0.600	0.821
Before surgery						
Via 72 hours	0.884	2.65	0.0721	0.743-0.934	0.782	0.911
CRP, (mg/l):	0.625	136.5	0.0512	0.511-0.721	0.486	0.877
Before surgery						
Via 72 hours	0.833	210.0	0.0867	0.754-0.897	0.667	0.905
SBP, (mm Hg):	0.808	112.0	0.0667	0.693-0.861	0.791	0.818
Before surgery						
Via 72 hours	0.856	135.0	0.0932	0.724-0.922	0.689	0.976
APACHE II score:						
Before surgery	0.785	13.0	0.0543	0.667-0.821	0.897	0.542
Via 72 hours	0.802	14.5	0.0789	0.676-0.864	0.95	0.857
SOFA score:						
Before surgery	0.855	5.5	0.0734	0.699-0.872	0.758	0.8
Via 72 hours	0.844	9.5	0.0812	0.682-0.883	0.840	0.966
ISTH Criteria for DIC:						
Before surgery	0.503	2.5	0.0512	0.412-0.546	0.45	0.071
Via 72 hours	0.762	1.5	0.0614	0.765-0.808	0.875	0.7

Note: CRP – C-reactive protein; SBP – systolic blood pressure; APACHE II - Acute Physiology And Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment; ISTH DIC - International Society on Thrombosis and Hemostasis Criteria for Disseminated Intravascular Coagulation.

vascular bed. The presence of fibrin degradation products reflects the simultaneous activation of both coagulation and fibrinolysis. The high D-dimer level is observed in different conditions such as ageing, inflammation, cancer, renal failure, etc. [21-23]. As it was shown by our study that an increase in the level of D-dimer level was observed in 11 (39.3%) of patients with SSBO before surgery, but it data was not reliable in comparison to patients with non-SSBO. Naturally, the issues may arise about the objectives of the study using these markers of coagulation in patients, especially since the laboratory diagnostic data do not play a significant role in establishing the fact of obstruction and strangulation of the small intestine? Since the biomarkers of coagulability such as fibrinogen, APTT, INR, D-dimer and ISTH Criteria for DIC, were not shown as specific enough for the diagnosis of obstruction and strangulation of the small intestine before surgery in our study, and they had been also useless for determining the need for surgery in any particular cases, these markers had used to determine the presence and severity of metabolic disorders in all of the patients.

In addition, for these purposes, we used commonly measured markers such as C-reactive protein (CRP), lactate level, systolic blood pressure, scores of SOFA and APACHE II [24, 25]. It should be pointed out that, even in the case of intestinal ischemia, many studies did not find significant differences in these indicators between patients requiring conservative treatment and those requiring surgery, making these markers a little informative for distinguishing between these categories of patients before surgery. Nevertheless, attempts to use indicators that are sensitive for diagnostics continue and one of these sensitive indicators is L-lactate which is the end product of anaerobic glycolysis, in that time while D-lactate is mainly produced by the intestinal bacteria. Since cells of people contain only an isomer lactate dehydrogenase that is synthesized in humans, the content of L-lactate is increasing during tissue hypoperfusion and cell hypoxia [26]. In 2020, M. Şahin

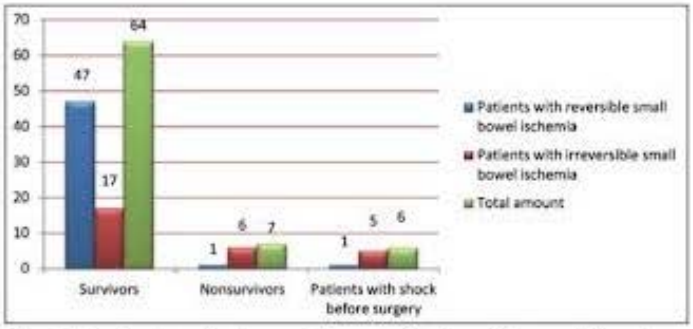

Fig. 1. Distribution of patients with strangulation of the small intestine.

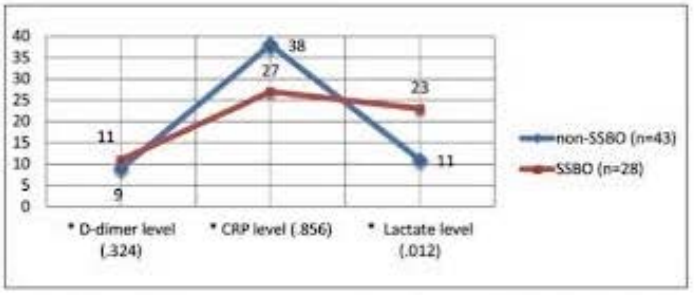

Fig. 2. Elevated preoperative D-dimer, CRP, and lactate levels in patients with non-SSBO and SSBO (* – the comparison was according to the χ2 test).

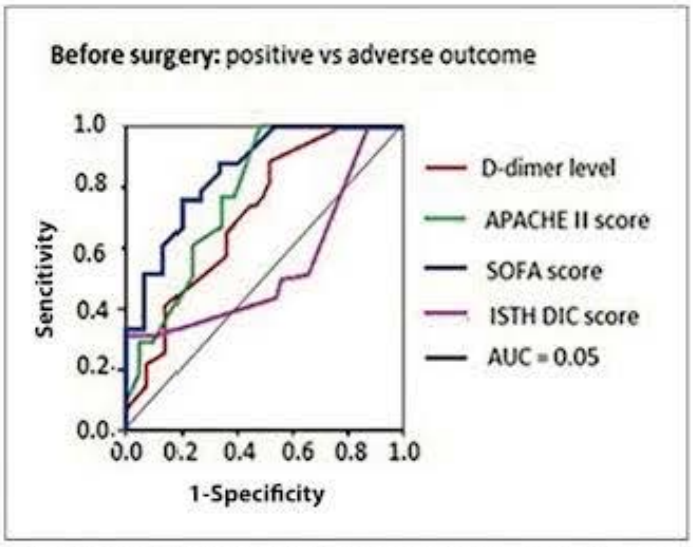

Fig. 3. Performance of prediction models as assessed by the AUC for death before surgery.

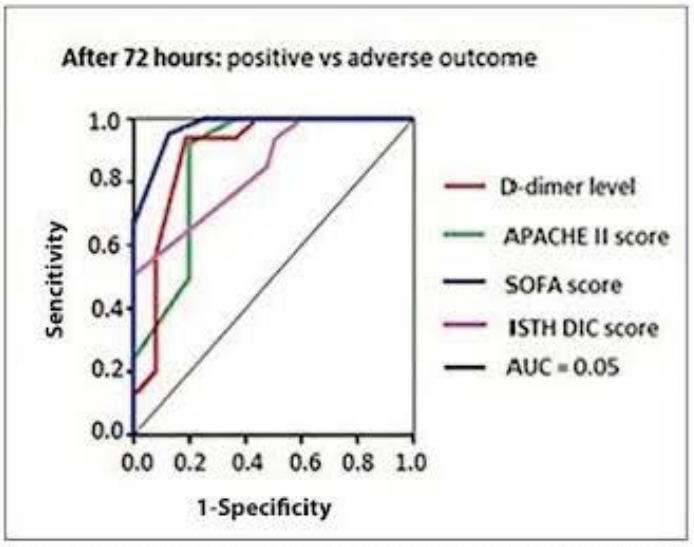

Fig. 4. Performance of prediction models as assessed by the AUC for death via 72 hours of surgery.

et al. noted that the presence of an intestinal obstruction in hernias and high serum lactate levels might indicate a poor prognosis and the need for resection of the small intestine in patients with strangulation during the preoperative assessment [27]. In our study, serum lactate before surgery (optimal cutoff value was 2.15 mmol/L) had a good predictive value (AUC = 0.805) with low sensitivity (60%) and high specificity (82.1%) (P = 0.000) as an indicator of prognosis for short-term mortality before surgery. This indicator also significantly differed in patients with SSBO and non-SSBO before surgery (P = 0.012).

To be sum up, the careful monitoring of hypotension and biochemical changes associated with metabolic disturbances in patients with SBO can contribute to the early prevention of complications that might occur after emergency surgery in these patients.

Our research has several limitations. First of all, this was a retrospective study, our data was based on the medical records of patients who were treated in only two hospitals, and we could not completely avoid some bias in the selection of data. Secondly, due to the relatively small clinical sample, the results obtained require further verification, which will make it possible to more clearly establish the set of preoperative data on the presence of infringement of the small intestine before the operation and the timing and type of surgical interventions in our opinion.

CONCLUSIONS

The study confirmed that three clinical and laboratory parameters are factors associated with short-term outcomes in SBO before surgery (lactate level, systolic blood pressure, and SOFA score) and seven parameters during 72 hours after surgery (D-dimer, antithrombin, lactate, CRP levels, systolic blood pressure, APACHE II, and SOFA scores). Screening tests of coagulation did not affect prognosis before emergency surgery in adults, and although in patients with SBO some of the fibrin degradation products were sensitive markers for short-time mortality due 72 hours after surgery, monitoring of indicators of coagulogram can be used as an estimate the potential risk of developing DIC and monitor an initiated conservative therapy. Taking into account the complexity and ambiguity of the results obtained, and the inconsistency of other data, it is necessary to continue studying the potential factors affecting the risk of bowel strangulation in SBO and the prognosis of mortality in different age groups.

ABBREVIATIONS

APACHE II: Acute Physiology and Chronic Health Evaluation; APTT: activated partial thromboplastin time; AUC: area under the ROC curve; BMI: body mass index; CRP: C-reactive protein; CT: computed tomography; DIC: dis-

seminated intravascular coagulation; ICU: intensive care units; IQR: interquartile range; ISTH: International Society on Thrombosis and Hemostasis; IV: intravenous; MODS: multiple organ failure syndrome; non-SSBO: non-strangulated small bowel obstruction; INR: International Normalised Ratio; SBO: small bowel obstruction; SBP: systolic blood pressure; SOFA: Sepsis-related Organ Failure Assessment; SSBO: strangulated small bowel obstruction.

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