

Received: 2019.01.29

Accepted: 2019.04.12

Published: 2019.08.23

Predictors of 30-Day In-Hospital Mortality in Patients Undergoing Urgent Abdominal Surgery Due to Acute Peritonitis Complicated with Sepsis

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Source of support: The Research Council of Lithuania – MIP-051/2015

Background: Sepsis is a life-threatening condition with high morbidity and mortality rate. Identifying early prediction factors of critical situations in intra-abdominal sepsis patients can help reduce mortality rates. This prospective study was carried out to evaluate the association of technically available factors with 30-day in-hospital mortality.





Material/Methods: There were 67 intra-abdominal sepsis patients included in the study; patients were observed for 30 days post-operatively. The data was processed using SPSS24.0 statistical analysis package. All tests that had a significance level of 0.05 were selected.

Results: Septic shock in association with increase in age per year showed increase the odds of mortality and prognosed 30-days in hospital mortality correctly in 79% of cases. The observed OR was 12.24 ($P < 0.001$). Multiple logistic regression model 2 for the 30-day mortality identified a combination of septic shock, age (≥ 70 years), time from peritonitis symptoms to surgery prognose mortality with accuracy of 82%. The most accurate model to prognose 30-day in-hospital mortality included the presents of septic shock, age, time from peritonitis symptoms to surgery, drop of MAP < 65 mmHg post-induction, the odds of mortality 8.86 ($P = 0.001$). Severe hypotension post-induction was more frequent in patients who were not diagnosed with sepsis ($P = 0.035$).

Conclusions: The present study revealed a simple indicator for the risk for death under diffuse peritonitis patients complicated with sepsis. Septic shock, increase in age per year, peritonitis symptoms lasting more than 30 hours, and severe hypotension post-induction had a negative prognostic value for mortality in patients with intra-abdominal sepsis, and might be a high risk for 30-day mortality.

MeSH Keywords: **Mortality • Peritonitis • Sepsis • Shock, Septic**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/915435>

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Background

Sepsis is a systemic inflammatory response caused by infection and is a life-threatening condition with a high morbidity and mortality rate [1–3]. The overall mortality rate of sepsis varies between 28% and 50% [4,5]. Sepsis is a common syndrome in Intensive Care Units (ICUs) with the incidence of approximately 11–15% [5]. Intra-abdominal sepsis is the second most prevalent sepsis after pulmonary sepsis [6]. In spite of major advances in diagnostics and surgical and antimicrobial treatment, it remains the leading cause of death in ICUs and has a huge healthcare cost [7,8]. Treating intra-abdominal sepsis involves a complex set of decisions. Appropriate oxygenation, antibiotic therapy, cardiovascular support to maintain organ perfusion, and surgical intervention are required specific treatments for underlying disease. Even though sepsis and septic shock are medical emergencies which require immediate treatment [9], they remain undiagnosed in about 41% of cases prior to admission to the ICU [7]. Early identification and treatment of sepsis has already been shown to improve survival [5]. Timely undiagnosed sepsis is a huge problem which leads to delayed treatment, lost “golden hour” and dramatically decreases the survival rate. There is an urgent need to identify intra-abdominal sepsis patients as soon as possible to start adequate treatment. More knowledge is required regarding the factors that increase the risk of death from intra-abdominal sepsis.

There is a number of peri-operative risk scoring tools which can be used to calculate the risk of mortality and morbidity accurately [10–12]. Perioperative risk assessment has a significant influence on patient outcomes by improving multi-disciplinary decision-making, allocation of critical care resources, and communication with patients [12]. However, it is important to note that urgent laparotomy is associated with increased risk of mortality, which is approximately 15% [13,14] in combination with sepsis mortality rate increases [15].

Revealing early prediction factors of critical situations in intra-abdominal sepsis patients could reduce the currently observed high mortality rate. The aims of this prospective observational study were to evaluate the predict factors associated with 30-day in-hospital mortality in intra-abdominal sepsis patients and to assess the incidence of unrecognized sepsis in patients undergoing urgent abdominal surgery due to acute peritonitis.

Material and Methods

This prospective observational study was carried out in the Anesthesiology Department of Lithuanian University of Health Sciences (LUHS) from April 1, 2016 to December 1, 2017. The ethical approval for this study was provided by the LUHS

Kaunas Region Biomedical Research Ethics Committee according to the protocol No. BE-2-4 (session protocol no. BE-10-4).

The inclusion criteria were as follows: new arrivals, age ≥ 18 years, signed written consent to participate in the study, urgent abdominal surgery due to acute peritonitis, and SOFA (sequential [sepsis-related] organ failure assessment) score 2 points or above. The exclusion criteria were as follows: known pregnancy, acute mesenteric ischemia or thrombosis, intra-abdominal trauma, and re-laparotomy.

The initial standard assessment of the patients was determined by the doctor in charge. Assessment of the patient's pain location, character, onset, intensity, radiation, duration and progression, provocative and palliating factors, and associated symptoms were performed. Past medical and surgical history, current medications, and social history were taken. Physical examination was performed and vital signs (mental status, body temperature, heart rate, not invasive arterial blood pressure, tachypnoea, saturation, etc.) were evaluated. Blood samples (full blood count, urea, creatinine and electrolytes, liver function tests and serum amylase, prothrombin time, activated partial thromboplastin time, international normalized ratio, lactate, and arterial blood gas) were taken. The following imaging test were performed: chest x-rays, abdomen ultrasound examination and/or computed tomography. Following their initial assessment, focused screening for sepsis by calculating the SOFA score was performed by study investigators during the first hour after admission to general surgery department. Sepsis was diagnosed if the SOFA score was 2 points or above. Patients who had SOFA score of 2 or above and had not documented diagnosis of sepsis at the time of focused screening were considered as not identified as septic by a doctor in charge. SOFA score was chosen because the predictive validity for in-hospital mortality is higher for full SOFA score (AUROC 0.74) compared with qSOFA (AUROC 0.66) [16].

Patients who were 70 years old or older were considered to be old age patients [17]. Body temperature in the first 24 hours of admission was used for calculations. Patients were divided into 3 groups according to body temperature: I group – temperature $< 36^{\circ}\text{C}$ [18,19], II group temperature $36\text{--}38^{\circ}\text{C}$, and III group temperature $> 38^{\circ}\text{C}$ [9]. The first 6 hours from inclusion to the study urine output was monitored.

Coagulation impairment was considered if international normalized ratio (INR) ≥ 1.2 [20,21].

Hypotension on admission was defined as systolic blood pressure < 90 mmHg. Severe post-induction hypotension was defined as a drop in MAP below 65 mmHg during the first 5 minutes after induction of anesthesia. Septic shock was confirmed

if norepinephrine was required to maintain mean arterial pressure (MAP) above 65 mmHg despite fluid resuscitation [9].

Demographic and clinical characteristics of the study population were collected.

The primary endpoints included 30-day in-hospital mortality and assessment of mortality predictors in intra-abdominal sepsis patients. Secondary endpoint was to evaluate the incidence of undiagnosed sepsis during the preoperative period.

Statistics

Data was processed using the SPSS 24.0 statistical analysis package. Kruskal and Wallis test was used for comparison of data distributions. Nonparametric χ^2 test was applied for analysis of nominal qualitative data. Mann-Whitney U test helped to compare distributions of 2 samples. Receiver operating characteristic (ROC) curve was used to determine the threshold value for the prognostic ability of a binary classifier. We considered prognostic ability as clinically relevant when the area under the curve (AUC) was more than 0.7. Kaplan-Meier estimator was used for survival statistics. Binary logistic regression was carried out to identify the risk factors associated with mortality of patients. Significance level of 0.05 was used for all tests. Minimal sample size of at least 60 patients to detect significant difference in mortality in regarding to associated factors was determined assuming significance level alpha 0.05 and power of the test 0.8.

Results

During the study period, we recruited 196 patients admitted to LUHSH Kaunas Clinics due to acute intra-abdominal disease. Sixteen of them were excluded due to mesenteric thrombosis, and 10 had terminal phase of malignant disease. Peritonitis with SOFA score less than 2 points was diagnosed in 103 patients. Sixty-seven patients, 36 males and 31 females, who had had signs of intra-abdominal sepsis (SOFA score 2 points or above) were involved in further analysis. Patient inclusion and follow-up are shown in Figure 1 and demographic data of the patients is shown in Table 1.

Surgical pathologies included the sites of stomach 23 (34%), duodenum 14 (21%), biliary tract 3 (5%), small bowel 11 (16%), large bowel, and appendix 16 (24%). Detailed causes of peritonitis and type of surgery are shown in Tables 2 and 3. *Escherichia coli* and *Enterococcus faecium* were the bacteria most commonly identified in these cases.

Sepsis was not suspected or documented in 21 cases (31%) prior to the focused screening by SOFA score. Hypotension

Table 1. Demographic patient data.

	Intra-abdominal sepsis (n=67)	
30-day mortality (n,%)	27	(40)
Sepsis, 30-day mortality (n,%)	3	(9)
Septic shock, 30-day mortality (n,%)	24	(69)
Age (y), mean (CI)	62 (57.6–66.4)	
Sex		
Female (n,%)	31	(46)
Male (n,%)	36	(54)
ASA status (n,%):		
III	28	(42)
IV	29	(43)
V	10	(15)
BMI, mean (CI)	25	(23–26)
In-hospital stay (d), mean (SD)		
Overall	13	(±13)
ICU	8	(±10)
Septic shock	32	(52)
Vasopressor administration (h)	95	(±112)
SOFA score (min–max)	5	(2–12)
APACHE II score (min–max)	13	(5–32)
Time from first peritonitis symptoms to surgery (h, SD)	37	(±20)
First dose of antibiotics (h: min, SD)	2: 20	(±00:30)
Time from diagnosis to surgery (h: min, SD)	3: 45	(±02:58)

SD – standard deviation; CI – confidence interval; y – years; d – days; h – hours; min – minutes; BMI – body mass index; ICU – Intensive Care Unit; SOFA – The Sequential Organ Failure Assessment; APACHE II – a severity-of-disease classification system.

(systolic blood pressure <90 mmHg) on admission was the core symptom which induced surgeon to suspect sepsis (OR 1.89; $P=0.022$, confidence interval [CI] 0.466–7.682). Also, acute peritonitis patients were identified as septic more likely if hypothermia was diagnosed (OR 1.82; $P=0.047$; CI 0.38–3.69). We did not find age ($P=0.16$), gender ($P=0.746$), tachycardia ($P=0.86$), hyperthermia ($P=0.452$), C-reactive protein ($P=0.485$), co-morbidities ($P=0.746$), or peritonitis symptom duration ($P=0.347$) to be significantly associated with sepsis suspicion on admission to General Surgery Department. There were no differences in

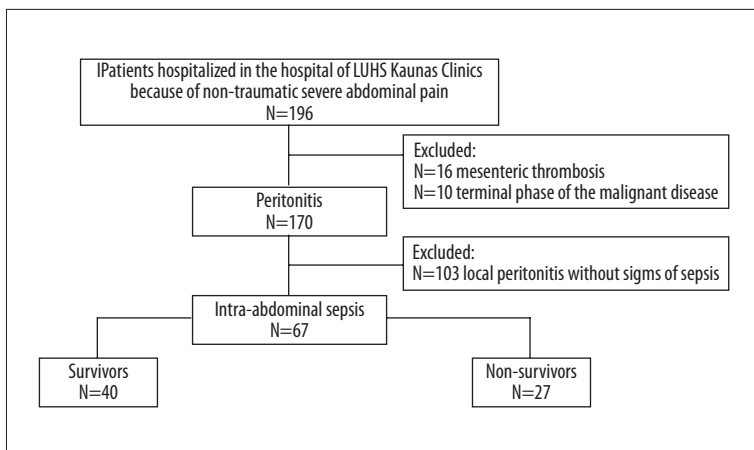


Figure 1. Flow chart of patient inclusion: follow-up and analysis.

Table 2. Etiology of intra-abdominal sepsis.

Cause of intra-abdominal sepsis	Overall (n, %)	Non-survivors (n, %)	P
Stomach peptic ulcer perforation	23 (34)	6 (26)	0.048
Duodenum peptic ulcer perforation	14 (21)	7 (50)	
Gall bladder perforation	3 (4)	1 (33)	
Small bowel perforation	11 (16)	6 (55)	>0.05
Diverticulum perforation	5 (8)	2 (40)	
Colon perforation	5 (8)	3 (60)	
Ruptured appendix	6 (9)	2 (33)	

Table 3. Type of surgery.

Type of surgery	Overall (n)
Laparotomy. Gastrorrhaphy suture of perforated gastric ulcer. Lavage and drainage of peritoneal cavity	23
Laparotomy. Suture of perforated duodenal ulcer. Lavage and drainage of peritoneal cavity	14
Cholecystectomy. Lavage and drainage of peritoneal cavity	3
Suture of small intestine (enterorrhaphy) for perforated ulcer or diverticulum. Lavage and drainage of peritoneal cavity	6
Resection of small intestine with or without ileostomy. Lavage and drainage of peritoneal cavity	5
Resection of colon. Lavage drainage peritoneal cavity	6
Colectomy, partial. Colostomy. Lavage drainage peritoneal cavity	4
Appendectomy. Lavage drainage peritoneal cavity	6

30-day and the first perioperative day mortality rate comparing patients who were diagnosed with sepsis on admission to those who were not ($P=0.28$ and $P=0.382$ respectively). Septic shock was more common among the patients who were diagnosed with sepsis (56% compared to 43%, respectively), however, the difference was not significant ($P=0.303$). Severe hypotension post-induction was more frequent in patients who were not diagnosed with sepsis and was registered in 67% compared to 46% of patients with sepsis diagnosis ($P=0.035$). The first 6-hour urine output was lower in patients not diagnosed with sepsis on admission compared to those diagnosed with sepsis on admission (0.34 mL/kg/hour compared to 0.55 mL/kg/hour ($P=0.039$)). For more details see Table 4.

The overall 30-day in-hospital mortality rate was 40%. Septic shock was documented in 35 patients (52%). The observed 30-day in-hospital mortality rate was significantly higher in patients with septic shock (24 patients, 69%, $P=0.001$). The factors found to significantly affect the mortality rate are shown in Table 5.

Age

The mean age of patients was 62 years (CI: 58–66 years), it ranged from 18 to 92 years. For survivors, the mean age was

Table 4. Comparison between patients who were diagnosed with sepsis on admission to undiagnosed sepsis patients.

	Before SOFA scoring				P value
	Diagnosed sepsis n=46		Not diagnosed sepsis n=21		
30-day in-hospital mortality (n, %)	17	(38)	10	(48)	0.28
Died within 24 hours post hospitalization (n, %)	3	(7)	3	(14)	0.382
Septic shock (n, %)	26	(56)	9	(43)	0.303
MAP on arrival (mmHg, SD)	77	(±13)	86	(±11)	0.012
HR (beats/min, SD)	103	(±18)	95	(±19)	0.147
Severe hypotension post-induction (n, %)	20	(46)	15	(67)	0.035
Urine output (mL/kg/h, SD)	0.55	(±0.35)	0.34	(0.37)	0.039
Hypothermia (n,%)	17	(37)	2	(10)	0.022
Capillary refill time >2 s (n, %)	39	(85)	16	(76)	0.376
CRP (mg/L, SD)	234	(±96)	213	(±115)	0.8
Symptoms duration till surgery (h, min, SD)	36: 30	(±30)	27: 26	(±18)	0.215
APACHE II score	14	(5-30)	10	(5-24)	0.046

MAP – mean arterial blood pressure; min, minute; SD – standard deviation; HR – heart rate; h – hour; hypothermia – temperature <36°C registered within the first 24-hour post inclusion to the study; s – seconds; CRP – C reactive protein.

Table 5. Variables significantly associated with 30-day in-hospital mortality.

Variables	OR	95% CI	P value
Septic shock	20.2	5.27–84	<0.001
Age (per 1 year)	1.08	1.032–1.121	0.001
ASA status	8.58	2.919–25.2	<0.001
SOFA score	1.87	1.414–2.48	<0.001
APACHE II score	1.17	1.081–1.281	0.001
Hypothermia	5.26	1.67–16.62	0.005
Severe hypotension post-induction	3.56	1.23–10.1	0.017
Coagulation impairment	9.5	1.85–48	0.007
Peritonitis symptoms lasting more than 30 hours until surgery	3.56	1.26–10.1	0.02

Severe hypotension post-induction drop of MAP < 65 mmHg immediately post-induction; hypothermia: core temperature <36°C; coagulation impairment INR >1.2; OR – odds ratio; CI – confidence interval.

55 years (CI: 49–61 years) compared to non-survivors (72 years (67–76 years, $P=0.001$). The increase in age per year increased the odds of 30-day in-hospital mortality (OR 1.08, $P=0.001$).

ASA physical status and APACHE II score

Twenty-eight patients (42%) were ASA physical status III, 29 patients (43%) were ASA IV and 10 patients (15%) were physical status V. There were 3 non-survivors (11%) who were

ASA physical status III ($P=0.001$), 15 non-survivors (52%) who were ASA IV ($P>0.05$), and 9 non-survivors (90%) who were ASA V ($P<0.001$). Severity of disease classification system (APACHE II) score was 13 points (5–32 points). For survivors APACHE II score was 10 points (7–28 points) compared to non-survivors 18 points (7–30 points) ($P<0.001$). Both higher ASA status and increased APACHE II score were associated to increased odds of 30-day in-hospital mortality respectively OR 8.58, $P<0.001$ and OR 1.17, $P=0.001$.

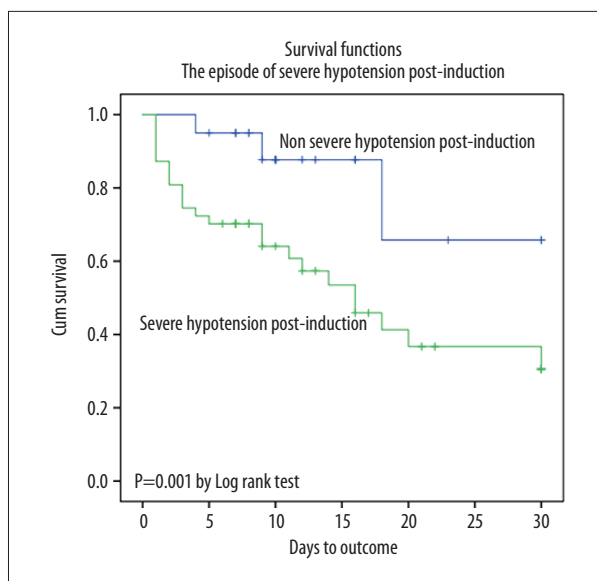


Figure 2. Survival curves for Kaplan-Meier: 30-day in-hospital survival by severe post-induction drop in MAP in patients with sepsis caused by diffuse peritonitis. * Reduced survival rate was significantly associated with severe hypotension after anesthesia induction ($P<0.001$ by log-rank test). MAP – mean arterial pressure.

Temperature

The observed mean temperature was 37.6°C (CI: $37.3\text{--}37.9^{\circ}\text{C}$). We found only hypothermia less than 36°C to be associated with an increase in odds of mortality – OR 5.26, $P=0.005$. Hyperthermia showed opposite results and was associated to better survival as odds of 30-day in hospital mortality was less than 1 (OR 0.68, $P=0.11$).

Coagulation

Coagulation impairment was observed in 34 patients (51%). In survivors, the observed INR was 1.13 ± 0.2 compared to non-survivors, which was 1.7 ± 1.5 ($P=0.015$). Coagulation impairment increased odds of mortality (OR 9.5, $P=0.007$).

Severe hypotension post-induction and septic shock

Out of 52 patients (78%) who were non-hypotensive preoperatively, severe hypotension (MAP <65 mmHg) occurred in 27 cases (52%) post-induction. In 19 cases (70%), it resulted in hemodynamic instability and manifestation of septic shock intra- and post-operatively ($P=0.001$). There was no difference in incidence of perioperative septic shock between the patients who had been hypotensive prior to surgery compared with non-hypotensive patients ($P>0.05$). Post-induction hypotension (MAP <65 mmHg) was related to higher in-hospital

mortality: among the 27 non-survivor cases, and of these, severe post-induction hypotension had been documented in 23 cases (85%) despite their stable hemodynamic state prior to surgery ($P=0.006$). The 10-day possibility of surviving intra-abdominal sepsis for patients who had an episode of severe post-induction hypotension was less than 60%, compared to 85% for those who had not ($P=0.001$). Analysis of the Kaplan-Meier survival function is shown in Figure 2. The presence of severe hypotension post-induction MAP <65 mmHg despite fluid resuscitation increased odds of mortality (OR 3.56, $P=0.017$).

Overall, there were 32 cases of septic shock (52%). Manifestation of septic shock increased the odds of 30-day in-hospital mortality (OR 20.2, $P<0.001$).

Symptoms duration

There was no difference in length of time intervals (hospitalization to diagnosis, diagnosis to surgery) noted between survivors and non-survivors ($P>0.05$). Longer duration from first peritonitis symptoms to surgery was associated with a higher mortality rate: symptoms that had lasted approximately 28 ± 17 hours in survivors compared to 50 ± 34 hours in non-survivors ($P=0.002$). Delayed arrival to hospital was established to be an independent mortality risk factor (AUC 0.74 (95% CI 0.612–0.868, $P=0.001$)). Symptoms that had lasted for more than 30 hours were predictive of bad outcomes with sensitivity of 74% and specificity of 60%. Peritonitis symptoms lasting for more than 30 hours until surgery increase the odds of 30-day in-hospital mortality (OR 3.56, $P=0.02$).

Binary logistic models

The evaluation of collinearity was carried out for variables using the ROC curve. The following parameter were considered as eligible to prognose 30-day in hospital mortality: age AUC 0.773 (CI 0.661–0.884, $P<0.001$), ASA status AUC 0.81 (CI 0.704–0.915, $P<0.001$), APACHE II score AUC 0.816 (CI 0.713–0.918, $P<0.001$), symptoms duration AUC 0.74 (CI 0.612–0.868, $P=0.001$). Although, hypotension on admission did not prognose 30-day in hospital mortality AUC 0.619 (CI 0.485–0.73, $P=0.1$) severe post-induction hypotension had a prognostic value AUC 0.787 (CI 0.669–0.904, $P<0.001$). Hypothermia prognosed mortality AUC 0.72 (CI 0.726–0.84, $P=0.008$) with the best cut off value of $T<36^{\circ}\text{C}$. Hyperthermia was not associated to increased mortality risk AUC 0.68 (CI 0.035–0.526, $P=0.06$). Laboratory variables urea AUC 0.713, CI 0.7590–846 $P=0.006$, INR ROC 0.777, CI 0.657–0.97, $P<0.001$, lactate value AUC 0.768, CI 0.637–0.9, $P=0.001$ were associated to 30-day in hospital mortality. A multiple logistic regression model was applied to the overall 30-day mortality, considering variables which were statistically significant. Categorical variables the presents of septic shock, gender was also included. After conducting univariate analysis

Table 6. Predictors of mortality in intra-abdominal sepsis patients.

Model	Percentage correct (%)	OR	95% CI for EXP(B)	P value
1	79	12.24	2.86–52.29	0.001
2	82	9.44	1.9–45.54	0.005
3	84	8.86	3.8–87.5	0.001

Model 1 predictors : septic shock, age; Model 2 predictors: septic shock, age, time from first peritonitis symptoms to surgery; Model 3 predictors: septic shock, age, time from first peritonitis symptoms to surgery, reduced mean arterial blood pressure (MAP <65 mmHg) immediately post-induction despite fluid resuscitation. OR – odds ratio; CI – confidence interval.

for the logistic regression, age, septic shock, symptoms duration and severe post-induction hypotension were considered eligible for the model.

Septic shock in association with increase in age per year showed increase in the odds of mortality and prognosed 30-days in hospital mortality correctly 79% of cases. The observed OR was 12.24 ($P<0.001$). The second model showed the combination of septic shock, age, and time from first peritonitis symptoms to surgery prognosed mortality with an accuracy of 82%. The most accurate model to prognose 30-day in-hospital mortality in intra-abdominal sepsis patients included the presence of septic shock, age, time from first peritonitis symptoms to surgery, drop of MAP <65 mmHg) immediately post-induction, and showed the odds of mortality 8.86 ($P=0.001$) with an accuracy of 84%. For more details see Table 6.

Discussion

Urgent laparotomy is associated with significant increased risk of mortality and is reported to be approximately 15% [13,14]. However, this number might vary and depends on the indications, specific patient characteristics, and health system factors [13,22]. Acute peritonitis remains an important cause of morbidity and mortality in emergency abdominal surgery [23]. Mortality in intra-abdominal sepsis ranges from 28% to 47% [22,24,25]. Sepsis is a life-threatening complication [13,21] of peritonitis. Our study confirmed a worldwide problem of undiagnosed sepsis, which is common in all departments. The current situation in our hospital at the time of this study was that patients with abdominal sepsis are admitted to our surgery ward regardless of their specific condition. Due to this reason, we have a heterogeneity of severity of cases. Unfortunately, a shortage of ICU beds reduces the possibility of preoperative treatment even for a limited period in an appropriate and sophisticated setting. For this reason, it is important at our hospital to recognize sepsis, and later to evaluate the patient response to abdominal infection and possibility to improve preoperative condition. Due to the varying severity of sepsis cases and the underestimation on the

patient's part, the patients are often not in the best possible shape at the beginning of the surgery. For this reasons, it is important to change daily practice for these patient's management in our hospital, based on objective findings, such as this study. We found a 31% incidence of undiagnosed sepsis prior to the focused screening by SOFA score among the patients undergoing emergency abdominal surgery due to acute peritonitis at our hospital. Even though, according to the literature, the rate of undiagnosed sepsis can be up to 41–59% [7], we believe that our study showed a very high rate of the aforementioned problem as well. Mortality rate of diffuse peritonitis complicated with sepsis was unsatisfactory high. We did not find statistical differences according to 30-day in-hospital mortality between patients who were diagnosed with sepsis and those who were misdiagnosed before SOFA scoring. Early diagnosis of sepsis might not improve outcomes due to more severe patient condition such as shown by APACHE II scores that were significantly higher in patients with diagnosed sepsis on admission ($P=0.046$). Septic shock was more common among the patients who were diagnosed with sepsis; however, the difference was not significant ($P=0.303$). This finding was supported by the fact that patients diagnosed with sepsis had severe conditions on admission. In addition, there were 6 patients who died during the first 24 hours post-hospitalization: 3 patients (7%) in the diagnosed sepsis group and 3 patients (14%) in not diagnosed sepsis group. Even though the difference was not significant ($P=0.382$) it alerts us to the big problem of properly evaluating patient's condition on admission. This study reveals several key points where systemic changes could be made to improve patient outcomes. Even if peritonitis was diagnosed quickly and surgery was not delayed, concentrating attention on the surgical pathology can lead to failure to suspect sepsis and to failure to activate sepsis protocol. In most cases, sepsis was suspected when there were obvious signs of tissue hypoperfusion. When hypotension was diagnosed on admission, sepsis was suspected more often. Failure to recognize sepsis in early stages lead to a series of problems, like insufficient fluid resuscitation or delayed antibacterial treatment. Severe hypotension post-induction was more frequent in patients who were not diagnosed with sepsis, and it was registered in 67% of these patients compared to 46% of

patients without severe hypotension, which was a statistically significant difference. We interpreted such results as inadequate fluid resuscitation prior to the surgery due to misdiagnosed sepsis. The problems related to a sudden drop in MAP (<65 mmHg) immediately post-anesthesia induction is important to discuss. Source control and antibiotic therapy remain the main principals in treatment of critically ill patients with abdominal sepsis [26]. On average, the first dose of antibiotics was administered in less than 2.5 hours from emergency department triage if sepsis was diagnosed. Patients without signs of sepsis that underwent urgent laparotomy due to peritonitis usually received their antibiotics after induction of anesthesia and before surgery. On average, it takes approximately 4 hours from diagnosis to surgery, so the antibiotics are delayed if sepsis is not identified. One study demonstrated no difference in outcomes of peritonitis patients having received antibiotic therapy in between 1 to 3 hours [1]. Still, the recommendation of sepsis treatment states that antibiotics should be started within 1 hour from diagnosis [8,9] as it has been shown that mortality is lower when appropriate antibiotic therapy is commenced early [22]. Patients without suspected sepsis demonstrated significantly frequent rates of severe post-induction hypotension and lower urine output, and hypothermia was more common in these patients.

The present study showed that it is possible to obtain a simple indicator of the risk for death under conditions of diffuse peritonitis complicated with sepsis. Our results demonstrated that increase in age per year increases odds of 30-day in-hospital mortality. In terms of age, peritonitis has been reported to be common in all groups; however, elderly patients have a higher risk of poor outcomes [6,27]. We found mortality odds to increase 1.08 per 1 year in intra-abdominal sepsis patients. This might be associated with more prevalent co-existing diseases in the elderly population [28]. Another study report confirmed age as an independent risk factor of poor outcomes in peritonitis patients as well; however, it did not find co-morbidities to be a risk factor for increased mortality [6]. Since patients with a terminal phase of a malignant disease were excluded from our study; this might be the reason we did not find co-morbidities to be an increased mortality risk factor. Increase in age combined with septic shock showed the odds of mortality of 12.24 in abdominal sepsis patients (model 1).

There are various possible tools to assess perioperative risk such as the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM), Surgical Outcome Risk Tool (SORT), the risk calculator of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). All these scoring systems are quite complex and time consuming and each has its pros and cons. For instance, the APACHE II score, the POSSUM, and the ACS-NSQIP provide the individual risk of morbidity and

mortality [11,12,29,30], while the SORT score is not patient specific and only provides general risk of procedures [31]. The ACS-NSQIP tool does not account for urgency of procedure and is not validated for emergency surgery. We chose the ASA physical status and the APACHE II score to assess perioperative risk in our study as these tools are routinely used in our hospital. ASA physical status has a reliable and independent associations with post-operative medical complications and mortality across procedures [10,12,32]. The APACHE II score is accurate in predicting perioperative complications in the surgical patients [11,12]. Both higher ASA status and increased APACHE II score were associated with increased odds of 30-day in-hospital mortality in our study. Urgent laparotomy is associated with significant increased risk of mortality. Using the APACHE II score, the percent risk of mortality convertor to the estimated mortality of 26.5% was predicted for patients undergoing urgent surgery who had an APACHE II score of 13. Even though the mean APACHE II score was 13 in this study, the observed 30-day in-hospital mortality was 40%. This indicated that urgent laparotomy patients were associated with increased risk of mortality, and in combination with sepsis, the mortality risk increased even more.

Hyperthermia and hypothermia are both possible characteristics of sepsis [18,19,33,34]. Fever is more common and considered to be an adaptive response to infection, which indicates the activation of defense mechanisms of the body by augmentation of several factors of humoral and cellular immunity [18]. Even though hyperthermia increases the heart rate and elevates the oxygen demand and energy requirements of the tissues [33,34], we did not find an association of hyperthermia at admission to 30-day in-hospital mortality. However, the presence of hypothermia at admission was associated with an increase in odds of 30-day in-hospital mortality.

Worsening coagulopathy in the first 24 hours has been reported to prognose poor outcomes [35]. Increased INR is significantly and independently associated with the mortality rate in sepsis patients and is one of the variables included in the Sepsis Induced Coagulopathy score [36]. In our study, observed INR was significantly higher for non-survivors than survivors and the increase of INR above 1.2 increased odds of 30-day in-hospital mortality (OR 9.5, $P=0.007$).

We found the sudden drop in MAP (<65 mmHg) immediately post anesthesia induction to increase the odds of mortality. This finding was quite unexpected, as we had thought that hypotension on admission would increase the risk of poor outcomes, which was not confirmed in our study. Hypotension often occurs after induction of general anesthesia due to the vasodilatory effects of anesthetic agents [37]. While mild hypotension is not dangerous, a severe drop can cause hypoperfusion and ischemia of internal organs and induce shock.

A substantial problem is sepsis-related occult organ dysfunction [9]. This was noted in our study as well. As the study showed, 17 patients out of the 27 non-survivors had stable hemodynamics before surgery and the diagnosis of sepsis had not been considered in most of these patients. Overall, out of 52 patients who were hemodynamically stable preoperatively, severe post-induction hypotension was later registered in 27 of these patients (52%). Out of these 27 patients, 19 patients (70%) experienced severe post-induction drop in MAP that did not respond to fluids resuscitation and ended in septic shock during surgery. Manifestation of septic shock is associated with poor outcomes [25,26,38]. These results suggested that the severity of the condition had not been properly evaluated preoperatively. Moreover, this finding suggested that adequate fluid resuscitation had not been ensured before surgery. Pathophysiology of peritonitis is related to a large amount of exudate released into the peritoneal cavity. It induces intravascular fluid and protein displacement. This mechanism leads to reduced intra-vascular volume and severe hypovolemia [39]. When intra-abdominal infection is complicated by sepsis, one more mechanism of tissue hypo-perfusion and hypovolemia is activated. Immunologic reaction and endothelial cell dysfunction are common in sepsis [40]. Marked capillary permeability and fluid loss in the third space together aggravate hypovolemia even more. It is very important to start early and adequate fluid resuscitation as there are several mechanisms of fluid loss in peritonitis patients. One of the aims is to avoid tissue hypoperfusion that can lead to multi-organ failure and shock. International guidelines of sepsis and septic shock management recommend administering at least 30 mL/kg of intravenous fluids over 3 hours [41]. Our study found a substantial problem in failure to identify sepsis preoperatively.

Time plays a very important role in treatment of acute peritonitis. One of the main goals of the Surviving Sepsis Campaign is effective source control as soon as possible [41]. We found that delayed arrival to the hospital had a dramatic impact on patient outcomes. After having compared the time intervals from the beginning of severe abdominal pain to surgery, we discovered that symptoms that had lasted for more than 30 hours were associated with increased mortality. On average, patients in the non-survivor group presented to the operating theatre when symptoms had lasted for more than 50 hours compared to 28 hours in the survivor group. On average, it took about 4 hours in each group from diagnosis to surgery.

Limitations

We were unable to compare how the rate of unsuspected sepsis influenced the length of in-hospital or ICU stay. For example, if a patient who died on day 1 had length of stay of only 1 day, this would distort the interpretation of length of in-hospital stay for the purpose of the study.

Recommendations

We have identified clear triggers which can alert clinicians that a diffuse peritonitis patient is at a higher risk of 30-day in-hospital mortality. Some factors include age, higher ASA status and APACHE coagulation impairment on arrival, or symptoms duration, appeared to increase the odds of mortality and were patient depended. One area that could be changed, is timely antibiotic therapy. Antibiotics were administered approximately 2 hours earlier for patients who were diagnosed with intra-abdominal sepsis compared to misdiagnosed patients. In addition, a drop of MAP <65 mmHg post-induction was associated with increased risk of 30-day in hospital mortality. We hypothesized that this indicated insufficient fluid resuscitation preoperatively. Even though there are clear recommendations for management of sepsis and septic shock, sepsis is still misdiagnosed too often. We suggest considering SOFA score (calculation of which is quick and easy) for acute patients who demonstrate the aforementioned triggers because it might be lifesaving. Timely identifying patients with sepsis and activating sepsis protocol may increase survival rate of intra-abdominal sepsis patients.

Conclusions

The observed 30-day in-hospital mortality rate in this study was 40%. This study suggests a simple indicator for the risk for death for diffuse peritonitis patients complicated with sepsis. Severe hypotension post-induction was more frequent in patients who were not diagnosed with sepsis. Septic shock, increase in age per year, peritonitis symptoms lasting more than 30 hours, and severe hypotension post-induction had a negative prognostic value for mortality of intra-abdominal sepsis patients and was an alert for high 30-day mortality risk. There is a high number of unrecognized sepsis.

Conflict of interest

None.

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