
Impairment of Physiologic Functions is a Reliable Prognostic Indicator of Poor Outcome in Surgical Intensive Care Unit

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Identification of potential risk factors is useful for the effective and rational therapy in severely ill surgical patients. Determination of objective independent risk factors is a difficult task because of the presence of many confounding variables. The purpose of the study was to examine potential risk factors on the first day after admission and during stay in an intensive care unit (ICU). Independent predictors of ICU mortality were assessed using multivariate logistic regression analysis. All consecutively admitted surgical patients that stayed for more than 24 hours in the ICU were enrolled in a prospective observational study. The ICU mortality rate was 17%. The non-survivors were older than survivors ($p < 0.001$), had a higher SAPS II score ($p < 0.001$). Infection, severe sepsis ($p < 0.001$) on admission and during stay in the ICU were more common among non-survivors. The incidence of organ dysfunction on the first day and during the ICU stay was also greater among non-survivors. Multivariate analysis including first-day variables revealed that the SAPS II score ($p = 0.001$), central nervous system dysfunction ($p < 0.01$), pulmonary ($p < 0.05$), and intra-abdominal ($p < 0.05$) infection retained significance for mortality prediction. A second data set analysis including variables collected during the ICU stay showed that cardiovascular ($p < 0.001$), respiratory ($p < 0.01$) and central nervous system ($p < 0.001$) dysfunctions were independent predictors of ICU mortality. In conclusion, the severity of illness, the presence of infection and changes in the mental status on admission to the ICU were reliably related to the outcome. Abnormalities in organ system function, particularly dysfunction of the cardiovascular, neurological and respiratory systems were the major determinants of ICU mortality. We suggest that the severity of illness score, organ dysfunction and infection should be accounted for while predicting the outcome of patients in a surgical ICU.

Key words: outcome, organ dysfunction, infection, intensive care unit, SAPS II, severe sepsis, surgery

INTRODUCTION

Recent advances in initial resuscitation and intensive care have resulted in increased survival of critically ill patients with a wide range of surgical disease states. Risk scoring and outcome assessment is currently of particular importance in intensive care medicine and also in surgical practice. A number of

scores used to predict the outcome in specific conditions, such as the Injury Severity Score, the Ranson score for pancreatitis, the burns index, the Child classification of liver failure are widely used in surgical practice (1). Scoring systems that aim to predict outcome in severely ill patients were introduced in clinical practice two decades ago. These general systems are based on the physiological response to the illness or injury and mainly have been intended for critically ill patients. Most popular of them are APACHE, SAPS (2, 3).

Clinical research in intensive care is often focused on survival and physiologic impairment. Predic-

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ting mortality for patient groups becomes an important tool of intensive care practice. Mortality is the primary outcome for critical care research, because critical care therapy is directed at overcoming an acute life-threatening illness (4). Another important aspect in outcome analysis is the evolution or resolution of organ dysfunction. Critical care is a challenge to the outcome research, because the key variables of disease, patient population, therapy are difficult to define (5). The complexity of organ dysfunction in seriously ill patients, association between the variables cause difficulties in risk assessment.

Identification of potential risk factors is useful for the effective and rational medical therapy implementation in critically ill patients with reversible medical conditions. We have developed an extensive database to provide a more reliable assessment of outcomes in order to establish the priorities for evaluation of intensive care practices. The purpose of the study was to assess the outcome of surgical patients in the intensive care unit (ICU). The current study was designed so as to examine potential risk factors on the first day after admission, independently related to mortality in a cohort of surgical patients. Other risk factors available during stay in the ICU more strongly dependent on therapy and also related to the outcome were assessed.

MATERIALS AND METHODS

A prospective observational study was performed in the ICU of Vilnius University Emergency Hospital. The database for this analysis was collected as part of the Intensive Care European Network that was used to assess performance and quality of care throughout the network of European ICUs. Data collection took place from February 1998 through January 1999. All surgical patients consecutively admitted to the ICU were enrolled. Those who stayed in the ICU for less than 24 h were excluded from our study; for usually these were patients admitted for short monitoring or severely ill non-survivors.

The first set of the variables was recorded from the first 24 h period on admission to the ICU. The following variables were included: basic demographic characteristics (age, gender, comorbidities), reason for ICU admission, surgical status (surgical emergency or elective), anatomical sites of surgery (neurosurgery, vascular, abdominal, trauma, orthopedic, urological, gynecologic, and other surgery), acute medical diseases, severity of illness on ICU admission and pre-ICU infection. The patients were classified as surgical emergency, if they were added to the

operating theatre schedule no more than 24 h before surgery or operation was performed within one week on ICU admission. The assessment of the severity of illness on the ICU admission was measured by the Simplified Acute Physiology Scoring (SAPS) II system for all patients, using the most physiologically abnormal data collected in the first 24 h of intensive care treatment (3).

The second set of the variables recorded over the ICU stay included organ dysfunction and ICU-acquired infection. For the evaluation of the presence or absence of infection at admission and during the ICU stay, we used definitions recommended by the Center for Disease Control and Prevention (6). ICU-acquired was defined an infection not present on admission to ICU and developing 48 h or more after admission. Severe sepsis was diagnosed according to the ACCM-SCCM Consensus Conference recommended criteria (7). The presence of organ dysfunction was assessed on admission and daily during the ICU stay, using a Sequential Organ Failure Assessment (SOFA) score for each organ system >1 point (8): cardiovascular dysfunction defined as arterial hypotension requiring vasopressor infusion (any dose); respiratory dysfunction defined as a $\text{PaO}_2/\text{FiO}_2$ ratio of <300 mm Hg; renal dysfunction defined as a serum creatinine concentration >170 $\mu\text{mol/l}$ or oliguria as a diuresis of <500 ml/day; hepatic dysfunction defined as a serum bilirubin concentration >32 $\mu\text{mol/l}$; neurological dysfunction defined as a Glasgow Coma Scale of <13 points; coagulation dysfunction defined as a platelet count of <100 $\times 10^9/\text{l}$.

Patients were distributed into groups according to the outcome at discharge from the ICU: survivors ($n = 250$) or non-survivors ($n = 51$).

Statistical analysis. All continuous variables were presented as means \pm standard deviation (SD) and analyzed by the Student's *t* test. Univariate comparisons were performed to compare survivors and non-survivors at discharge. Categorical variables were expressed as actual numbers and percentages and compared using the χ^2 analysis or Fisher's exact test for a small sample size. *P* values less than 0.05 were considered significant for all tests. Odds ratio and 95% confidence interval for variables with a significant univariate association were calculated.

For multivariate regression analysis, each categorical variable was dichotomized by replacing it with the indicator of whether it was above or below its mean. Among strongly correlated variables reflecting similar process, *i.e.* the reason for ICU admission and the presence of organ dysfunction on the first ICU day, we selected one with the highest impact on

a dependent variable. Multivariate stepwise regression was performed on significant variables in two separate groups of variables. First, we used logistic regression analysis to determine the independent contribution of the variables from the first 24 h in the ICU to the prediction of ICU mortality. A second multivariate logistic regression analysis was limited to variables collected during the ICU stay. Mortality in the ICU was a dependent variable. Variables which had a significant association with mortality to a value of $p < 0.1$ on univariate analysis were entered into a stepwise multiple logistic regression and tested for significance. Odds ratios were used to estimate association between the independent determinants of mortality in the ICU. The discriminative power of the predicted probability of ICU mortality, derived from the variables entered into multivariate logistic regression analysis was tested by the area under the receiver operating characteristic (ROC) curve.

RESULTS

During a 12-month period, 673 surgical patients were entered to the database; 301 (45%) of these patients remained in the ICU for more than 24 h and were included into the study. The patient's demographic data, including previous health status, location before the ICU admission, reasons for admission, severity of illness, surgical status and anatomical site of surgery are shown in Table 1. Readmission accounted for 10% of all admission to the ICU. The most common comorbidities were arterial hypertension, malignancy and chronic obstructive pulmonary disease.

There was a clear predominance of emergency surgical patients; 87% of the patients were admitted directly from the operating room. The most frequent anatomical sites of surgery were of gastrointestinal category, accounting for 63% of all cases in the total sample.

The total of 154 (51%) of patients were infected on ICU admission. The most frequent sites were gastrointestinal (40% of patients), mainly peritonitis, and respiratory (12% of patients), mainly pneumonia. Severe sepsis on the first ICU day was present in 17% of patients, and additionally was diagnosed in 7% of patients during stay in the ICU. At

Characteristic	No. (%) or mean \pm SD
Age, years	63.4 \pm 16.6
Sex	
female	154 (51%)
male	147 (49%)
Readmission	31 (10%)
Comorbidities	
arterial hypertension	103 (34%)
malignancy	60 (19%)
chronic obstructive pulmonary disease	36 (12%)
Emergency surgery	234 (78%)
Elective surgery	67 (32%)
Type of surgery	
neurosurgery (nontrauma)	15 (5%)
vascular surgery	28 (9%)
abdominal	191 (63%)
trauma	41 (14%)
other	26 (9%)
Severity of illness on 1st ICU day, SAPS II score	32.8 \pm 16.2
Organ dysfunction on 1st ICU day, SOFA score	2.8 \pm 3.1

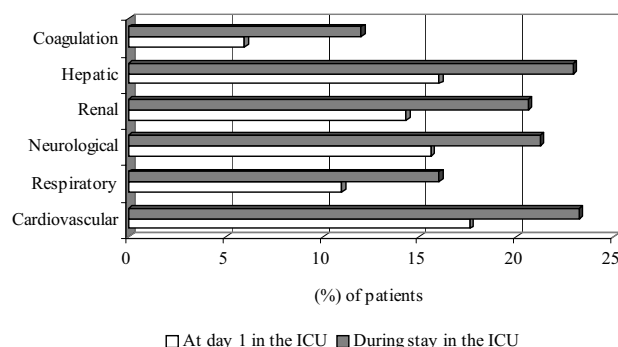


Fig. 1. Incidence of organ dysfunction on admission and acquired during stay in the intensive care unit in surgical patients

least one episode of ICU-acquired infection was detected in 22% of patients.

The incidence of organ dysfunction on the first day and during the ICU stay was greater among non-survivors than among survivors (Fig. 1). The acquired new cases of organ dysfunction were observed over the ICU stay for all organ systems. Arterial hypotension, impaired consciousness, increased concentration of creatinine and bilirubin were most frequent.

ICU mortality

51 (17%) patients died in the ICU. The non-survivors were older than survivors (71.2 ± 14.1 years *versus* 61.9 ± 16.7 years, $p < 0.001$). The mortality rate for emergency surgery patient group was lower than for elective surgery patient group (7.5% *versus* 19.7%, $p < 0.001$). The mean length of stay in the

ICU was 4.7 ± 5.3 days, and this was higher in non-survivors than in survivors (6.5 ± 5.9 days *versus* 4.4 ± 5.1 days, $p < 0.05$). Type of surgery was not significantly related to ICU mortality.

The SAPS II score was significantly higher among non-survivors than among survivors (51.8 ± 18.3 *versus* 29.0 ± 12.6 , $p < 0.001$). The ICU mortality increased linearly with the SAPS II score (Fig. 2).

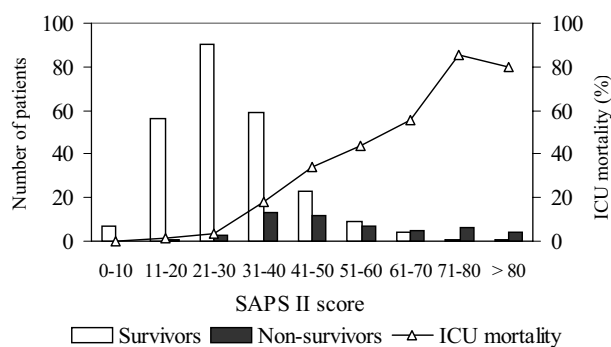


Fig. 2. Distribution of the Simplified Acute Physiology Score (SAPS II) in the first 24 h on admission and mortality in the intensive care unit

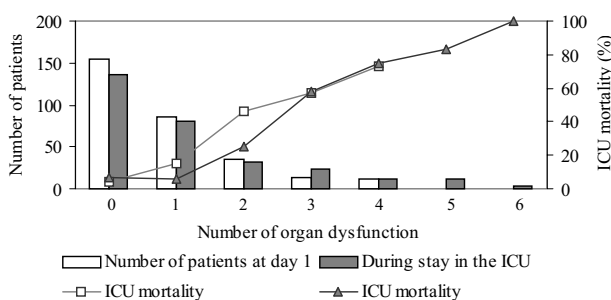


Fig. 3. Relationship between the number of organ dysfunctions and mortality on admission or during stay in the intensive care unit in surgical patients

During the stay in the ICU all organ dysfunction showed a significant relation to outcome ($p < 0.001$ for all six systems). A direct relationship between the number of organ dysfunctions on the ICU admission or during stay in the ICU and mortality was found (Fig. 3). Due to acquired new organ dysfunction, progression to more severe cases of multiple organ dysfunction was observed.

Outcome prediction

Variables collected on admission were analyzed as potential predictors of ICU mortality (Table 2). Advanced age, higher SAPS II score, emergency surgery, the presence of pulmonary and intra-abdominal infection, severe sepsis, the presence of all organ dysfunctions except hematological system were determined to be significantly associated with ICU mortality by univariate analysis. Multivariate analysis including these variables revealed that only SAPS II score ($p = 0.001$), central nervous system dysfunction ($p < 0.01$), pulmonary ($p < 0.05$), and intra-abdominal ($p < 0.05$) infection retained significance for the prediction of mortality among surgical patients admitted to the ICU (Table 3). The discriminative capability of these variables entered into multivariate analysis to predict the ICU mortality as tested by the area under ROC curve was 0.906 (95% confidence interval, 0.868–0.945, $p < 0.001$).

A second data set analysis included variables collected during the ICU stay (Table 4). By univariate analysis, a patient with severe sepsis, ICU-acquired pulmonary infection and bacteremia, with the presence of all organ dysfunction was statistically more likely to die in the ICU. However, multivariate analysis of these variables showed that cardiovascular ($p < 0.001$), respiratory ($p < 0.01$) and central nervous system ($p < 0.001$) dysfunctions were indepen-

	Nonsurvivors n (%)	Survivors n (%)	Odds ratio	95% confidence Interval	P value
Age, >63 years	40 (78.4)	135 (54.0)	3.10	1.52–6.31	0.002
Emergency surgery	46 (90.2)	188 (75.2)	3.03	1.15–7.98	0.017
SAPS II score, > 33	46 (90.2)	76 (30.4)	21.06	8.05–55.09	<0.001
Pulmonary infection	14 (27.5)	22 (8.8)	3.92	1.84–8.34	0.001
Intra-abdominal infection	33 (64.7)	89 (35.6)	3.32	1.77–6.23	<0.001
Severe sepsis	28 (54.9)	23 (9.2)	12.02	5.97–12.64	<0.001
Arterial hypotension, need for vasopressor infusion	26 (51.0)	27 (10.8)	8.59	4.36–16.94	<0.001
PaO ₂ /FiO ₂ ratio < 300 mm Hg	17 (33.3)	16 (6.4)	6.03	3.03–12.02	<0.001
Glasgow Coma Scale < 13	21 (41.2)	26 (10.4)	7.31	3.38–15.82	<0.001
Serum creatinine > 170 μmol/l or oliguria	18 (35.3)	25 (10.0)	4.91	2.42–9.96	<0.001
Serum bilirubin > 32 μmol/l	14 (27.5)	34 (13.6)	2.40	1.18–4.91	0.020

Table 3. Multivariate regression analysis of variables on admission to the intensive care unit independently associated with mortality

	Odds ratio	95% confidence Interval	P value
SAPS II score, > 33	8.22	2.49–27.16	0.001
Glasgow Coma Scale < 13	3.83	1.47–9.99	0.006
Pulmonary infection	3.43	1.20–9.79	0.021
Intra-abdominal infection	2.85	1.11–7.31	0.029

accepted in clinical practice in many European countries, such as the SAPS II system for the severity of illness and the SOFA score for organ dysfunction. The clinical and biochemical parameters collected for these patients can easily be obtained and routinely monitored during intensive care.

Table 4. Variables available during stay in the intensive care unit associated with mortality by univariate analysis

	Nonsurvivors n (%)	Survivors n (%)	Odds ratio	95% confidence Interval	P value
ICU-acquired pulmonary infection	17 (33.3)	23 (9.2)	4.94	2.40–10.17	<0.001
ICU-acquired bacteremia	11 (21.6)	18 (7.2)	3.54	1.56–8.06	0.004
Severe sepsis	39 (76.5)	33 (13.2)	21.37	10.16–44.95	<0.001
Arterial hypotension, need for vasopressor infusion	38 (74.5)	32 (12.8)	19.91	9.59–41.36	<0.001
PaO ₂ /FiO ₂ ratio < 300 mm Hg	29 (56.9)	19 (7.6)	16.02	7.76–33.10	<0.001
Glasgow Coma Scale < 13	36 (70.6)	28 (11.2)	19.03	9.27–39.06	<0.001
Serum creatinine > 170 µmol/l or oliguria	30 (58.8)	32 (12.8)	9.73	4.98–19.02	<0.001
Serum bilirubin > 32 µmol/l	23 (45.1)	46 (18.4)	3.64	1.93–6.89	<0.001
Platelet count < 100 × 10 ⁹ /l	17 (33.3)	19 (7.6)	6.08	2.88–12.83	<0.001

Table 5. Multivariate regression analysis of variables available during stay in the intensive care unit independently associated with mortality

	Odds ratio	95% confidence Interval	P value
Glasgow Coma Scale < 13	10.58	3.96–28.25	<0.001
Arterial hypotension, need for vasopressor infusion	8.49	2.75–26.23	<0.001
PaO ₂ /FiO ₂ ratio < 300 mm Hg	4.05	1.40–11.67	0.010

dent predictors of ICU mortality (Table 5). The area under the ROC curve for these variables was 0.954 (95% confidence interval, 0.930–0.979, $p < < 0.001$).

DISCUSSION

The present study was conducted to identify the most important factors related to mortality in severely ill surgical patients admitted to the ICU. Using demographic and clinical data on the patients available on admission and during stay in the ICU, we demonstrated that the outcome at the ICU discharge for the surgical patients studied was closely linked with the severity of illness, severe infection and organ dysfunction. As an Intensive Care European Network participant, we prospectively collected data at the ICU of Vilnius University Emergency Hospital. We used a well-known scoring system widely

Determination of the objective factors related to the outcome in critically ill patients is a problematic and difficult task because of the presence of many confounding variables significantly correlated with each other. A combination of factors must be taken into account to estimate a critically ill patient's prognosis in the ICU. Interpretation and comparison of risk factors between studies are difficult, not only because of different definitions and inclusion criteria, but also because of the specificity of patient population. Previous studies in the surgical ICU patients revealed a lot of risk factors contributing to decreased survival, but those are hard to interpret and compare, partly because of differences in the variables studied and interrelations between the variables.

To evaluate the precise role of the ICU characteristics, we undertook a study using strict criteria to define the severity of illness, infection and impairment of organ function. In addition, we tried to reduce the risk of identifying confounding variables. The study population was restricted to the ICU patients hospitalized for more than 24 h. Those patients were exposed similarly to the ICU-related risk factors, impact of disease severity and effect of therapy, excluding patients admitted for short monitoring and observation. We did not include variables

that depend on existing differences in clinical practice in many ICUs, such as the presence or absence of therapeutic procedures.

Important factors for outcome prediction using univariate analysis in our study were advanced age, emergency surgery, severity of illness on admission to the ICU, organ dysfunction (except the hematological system) and the presence of intra-abdominal and pulmonary infection on admission to the ICU. The relative importance of each selected variable from univariate analysis in relation to the ICU mortality was determined by using multiple logistic regression analysis which allows a simultaneous analysis of the variables and control of interrelations between the variables.

The scoring systems to be used in ICU usually include only data from the first 24 hours after admission, because the early changes in physiological variables are dependent on disease severity rather than treatment (9). The effects of surgical stress, anesthesia, postoperative pain and subsequent resuscitation may affect the physiological functions. Severity of illness defined by the SAPS II score was the most important variable to predict the outcome on the first ICU day. As expected, the multivariate analysis confirmed a strong relationship between the patient's likelihood of surviving to ICU discharge and acute physiological abnormalities as evaluated by the SAPS II system. The ability of the general severity scoring systems to predict the outcome was shown in our study and in other similar studies (10–12).

Our study showed that intra-abdominal and pulmonary infections were reliable determinants of the outcome. Severe sepsis was one of the strongest predictors of outcome in univariate analysis. After adjustment for other confounding variables, particularly for occurrence of organ dysfunction, sepsis was not independently associated with an increased risk of hospital mortality. Complications of severe sepsis were more powerful predictors of outcome than sepsis itself.

The importance of organ dysfunction in determining the outcome for patients requiring intensive care is well established. Kollef MH et al. also found the severity of illness and organ system derangement to be useful discriminators of outcome for ICU patients undergoing abdominal surgery (13). Similarly, in the report by Wickel DJ et al., disease severity and organ failure were the major causes of adverse outcome in patients with peritonitis (14). However, in many studies the outcome was not corrected for confounding factors. The univariate analysis, both in our previous work and in other studies, revealed that mortality was closely related to

the number of organ failure during stay in the ICU (15–17).

Identifying and monitoring the onset and resolution of organ dysfunction could optimize the management of severely ill surgical patients. The importance of individual organ system dysfunction as a determinant of mortality has been demonstrated for both surgical and medical ICU populations. Tran DD et al. found that coma on admission was one of most powerful predictive factors in determining the outcome for surgical patients following ICU admission (16). Barie PS and co-workers found that for patients with perforated gastrointestinal tract the identified hematological, central nervous system and respiratory dysfunctions were independently related to mortality (18). Kollef MH et al. using multivariate analysis and considering the patient's demographics, illness severity and organ system impairment showed that cardiovascular and neurological dysfunction remained significantly associated with mortality (19). In the present study we found that only abnormalities in the neurological, cardiovascular and respiratory functions were independently associated with ICU mortality after adjustment for sepsis and ICU-acquired infection.

These findings suggest that interventions aimed at prevention or treatment of these functions should receive the highest priority, because such measures offer the greatest potential benefit for patient's outcome. These data also may improve our ability to predict the clinical outcome for surgical patients who require admission to the ICU. In conclusion, the severity of illness, presence of infection and changes in the mental status on admission to the ICU were reliably related to the outcome. Abnormalities in organ system function, particularly dysfunction of the cardiovascular, neurological and respiratory systems, were the major determinants of ICU mortality. The prognostic capability of other organ dysfunction was less clear in this selected group of surgical ICU patients. We suggest that the severity of illness score, organ dysfunction and infection should be considered while predicting the outcome in critical care.

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FIZIOLOGINIŲ FUNKCIJŲ SUTRIKIMAI – PATIKIMI NEPALANKIOS PROGNOZĖS RODIKLIAI CHIRURGINIAMS INTENSIVIOS TERAPIJOS SKYRIAUS LIGONIAMS

S a n t r a u k a

Sunkių būklių chirurginių ligonių prognozei svarbių rizikos veiksnių nustatymas galėtų padėti pasirinkti efektyvią ir racionalią gydymo taktiką. Objektivus nepriklausomų rodiklių įvertinimas yra sudėtingas dėl didelės jų tarpusavio koreliacijos. Studijos tikslas – išanalizuoti rizikos veiksnius, nustatant pirmąją parą ir vėliau gydymo reanimacijos ir intensyvios terapijos skyriuje (RITS) metu. Nepriklausomi rizikos veiksniai buvo išskirti dauginės loginės regresijos metodu. Visi chirurginiai ligoniai, gydyti RITS ilgiau nei 24 valandas, buvo įtraukti į prospektivinę studiją. Ligonų mirštamumas RITS – 17%. RITS mirę ligoniai, palyginti su sveikstančiais, buvo vyresni ($p < 0,001$), jų būklės įvertinimas pagal SAPS II sistemą buvo blogesnis ($p < 0,001$), pirmą parą ir vėliau RITS dažniau pasireiškė organų disfunkcijos, diagnozuotos infekcijos ir sunkios eigos sepsis ($p < 0,001$). Daugine logine regresija buvo nustatyti pirmos RITS paros nepriklausomi mirštamumo rizikos veiksniai: SAPS II balų skaičius ($p = 0,001$), centrinės nervų sistemos disfunkcija ($p < 0,01$), plaučių ($p < 0,05$) ir intraabdominalinė infekcija ($p < 0,05$). Gydymo RITS metu tokiais rodikliais buvo kardiovaskulinės ($p < 0,001$), centrinės nervų sistemos ($p < 0,001$) ir respiratorinės sistemų disfunkcijos ($p < 0,01$). Ligonų būklių sunkumas, infekcijos ir sąmonės sutrikimai pradedant gydymą RITS bei organų disfunkcijų pasireiškimas gydymo RITS metu yra svarbiausi mištamumą nulemiantys rizikos veiksniai. Anksčiau ir adekvati organų funkcijų sutrikimų korekcija galėtų reikšmingai pagerinti chirurginių kritinių būklių ligonių išgytį.