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THE PREDICTIVE PERFORMANCE OF THE POSSUM SCORING SYSTEM AND EARLY INDICATORS OF PERIPHERAL PERFUSION FOR COMPLICATIONS AFTER MAJOR ABDOMINAL SURGERY

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ZNAČAJ POSSUM SKORA I RANIH POKAZATELJA PERIFERNE PERFUZIJE ZA PREDVIĐANJE POSTOPERATIVNIH KOMPLIKACIJA U HIRURGIJI DIGESTIVNOG SISTEMA

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Dedicated to my patients

THE PREDICTIVE PERFORMANCE OF THE POSSUM SCORING SYSTEM AND EARLY INDICATORS OF PERIPHERAL PERFUSION FOR COMPLICATIONS AFTER MAJOR ABDOMINAL SURGERY

Abstract

Postoperative complications are the major cause of postoperative morbidity and mortality and remain to be a serious burden for a healthcare system. The early identification of patients at risk may play a pivotal role in rational decisions regarding perioperative management. The aim of this study was to explore the characteristics of complications in high-risk patients after major abdominal surgery. We also assessed and compared the accuracy of the Clavien-Dindo classification (CDC) and the Comprehensive Complication Index (CCI) for evaluation of postoperative morbidity and the predictive performance of the POSSUM scoring system for complications and mortality. Finally, we wanted to explore the significance of early indicators of altered peripheral perfusion after major abdominal surgery for the occurrence of severe complications.

A prospective, observational, cohort study included 206 high-risk surgical patients undergoing major abdominal surgery at the Clinic for Digestive Surgery, Clinical Center of Serbia, from November 2016 to October 2017.

We found that the complication rate in our cohort was 60.7% and that the occurrence of complications was associated with the longer ICU stay ($p<0.001$), postoperative length of stay ($p<0.001$) and lower functional activity at hospital discharge ($p<0.001$). The CCI was shown to be of superior accuracy in high-risk patients with multiple complications compared to the CDC as it demonstrated a higher correlation to the resource utilization indicators ($p<0.001$). The POSSUM scoring system showed the sub-optimal performance for prediction of morbidity and mortality in this cohort of patients ($AUC_{morbidity}= 0.708$, O:E ratio=1.07; $AUC_{mortality}= 0.744$, O:E ratio=0.38). We found that the alterations of peripheral perfusion early after the operation were more pronounced in patients who developed more severe complications. Capillary refill time, central-to-peripheral temperature gradient, and venoarterial pCO_2 difference to arteriovenous O_2 content ratio on admission to the ICU after the operation, as well as serum lactate concentration and base excess 12 hours after the admission to the ICU were the independent predictors of severe complications. Finally, based on the preoperative, intraoperative, and postoperative variables, with the application of the machine learning algorithms, we developed a new model for the prediction of postoperative complications. The model was validated on the new set of patients and it demonstrated an excellent predictive performance (AUC=0.91; sensitivity 92%; specificity 78%; PPV 87%).

Key words: major abdominal surgery; postoperative complications; peripheral perfusion; POSSUM score

Scientific area: Medicine - Anesthesiology

ZNAČAJ POSSUM SKORA I RANIH POKAZATELJA PERIFERNE PERFUZIJE ZA PREDVIĐANJE POSTOPERATIVNIH KOMPLIKACIJA U HIRURGIJI DIGESTIVNOG SISTEMA

Sažetak

Postoperativne komplikacije su vodeći uzrok postoperativnog morbiditeta i mortaliteta i predstavljaju značajno opterećenje za zdravstveni sistem u celini. Rana identifikacija bolesnika sa povećanim rizikom može imati ključnu ulogu u donošenju racionalnih odluka u vezi sa perioperativnim lečenjem. Cilj ove studije bio je da ispita karakteristike komplikacija kod visokorizičnih bolesnika nakon velike abdominalne hirurgije. Takođe smo procenili i uporedili preciznost Clavien-Dindo klasifikacije (CDC) i Comprehensive Complication Index-a (CCI) za evaluaciju postoperativnog morbiditeta i ispitali prediktivne karakteristike POSSUM skora za komplikacije i mortalitet. Konačno, analizirali smo značaj ranih pokazatelja periferne perfuzije za pojavu teških komplikacija nakon velike abdominalne hirurgije.

Prospektivna, opservaciona, kohortna studija pratila je 206 visokorizičnih bolesnika podvrgnutih velikoj abdominalnoj operaciji na Klinici za digestivnu hirurgiju Kliničkog centra Srbije, od novembra 2016 do oktobra 2017.godine.

Pokazali smo da je učestalost komplikacija u našoj kohorti bila 60.7% i da je pojava komplikacija bila udružena sa dužim boravkom u jedinici intenzivnog lečenja (JIL) ($p< 0.001$), dužom postoperativnom hospitalizacijom ($p<0.001$) i nižim funkcionalnim kapacitetom na otpustu iz bolnice ($p<0.001$). Takođe je prikazano da je CCI prikladnija skala za visokorizične bolesnike sa udruženim komplikacijama u poređenju sa CDC jer je ispoljila jaču korelaciju sa parametrima hospitalizacije ($p<0.001$). POSSUM skor je pokazao suboptimalne karakteristike u predviđanju rizika za morbiditet i mortalitet u ovoj kohorti bolesnika ($AUC_{morbiditet}$ = 0.708, O:E odnos = 1.07; $AUC_{mortalitet}$ = 0.744, O:E odnos =0.38). Poremećaj periferne perfizije rano nakon operacije bio je izraženiji kod onih bolesnika kod kojih su se razvile teže komplikacije. Kao nezavisni prediktori teških komplikacija su se izdvojili vreme kapilarnog punjenja, centralno-periferni gradijent temperature i odnos venoarterijske razlike pCO_2 i arteriovenske razlike u sadržaju kiseonika na prijemu u JIL nakon operacije, kao i serumska koncentracija laktata i bazni eksces 12 sati nakon operacije. Konačno, na osnovu preoperativnih, intraoperativnih i postoperativnih varijabli, primenom algoritama mašinskog učenja, kreirali smo novi model za predviđanje postoperativnih komplikacija. Model je eksterno validiran i pokazao je odlične prediktivne karakteristike (AUC = 0.91; senzitivnost 92%; specifičnost 78%; pozitivna prediktivna vrednost 87%).

Ključne reči: velika abdominalna hirurgija; postoperativne komplikacije; periferna perfuzija; POSSUM skor

Naučna oblast: Medicina - Anesteziologija

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1. INTRODUCTION

1.1.POSTOPERATIVE COMPLICATIONS

1.1.1.Epidemiology and Significance

Surgery is an effective treatment option for a variety of diseases and today one can hardly imagine it be replaced by conservative treatment even in the categories of very old patients, with numerous comorbidities and advanced malignant diseases. Estimates are that every year more than 312 million operations are performed worldwide, although epidemiological studies indicate that as many as 4.8 billion of the world population has no access to any surgical treatment. [1,2] Elective non-cardiac surgery can now be considered safe, even if associated with the global mortality rate of 1-4%.[3–5] Abdominal surgery is amongst the most prevalent surgical fields and the associated mortality for hepatobiliary, colorectal and upper gastrointestinal surgery is 0.6%, 1.0% and 1.5%.[4] However, within the population older than 65 years of age, the 90-day mortality up to 40% after surgery such as esophagectomy and gastrectomy is described.[6] This information gains on importance bearing in mind that at this time one fifth of the population of Europe is over the age of 65, and that by 2050, this age group will constitute more than 30%.[7] Advances in surgery and anaesthesia, as well as improving perioperative care, will inevitably reduce the overall surgery-related mortality, while the improvements of the health care systems will make surgical treatment accessible to more people. It is foreseeable that postoperative complications will then be appearing in a significant number of patients.[2]

Postoperative complications are the leading cause of postoperative morbidity and mortality.[8] It has been shown that the occurrence of postoperative complications has a greater influence on long-term survival after surgery than preoperative patient condition and intraoperative events.[9,10] The economic consequences of the complicated postoperative course are enormous both for the patients and the health system.[11] Evidently, a large volume of surgical treatments will always be accompanied by complications, however their number and difficulty can be reduced by identifying patients with risk factors, early diagnosis, timely resolution, and by providing an adequate level of treatment such as placement in an intensive care unit (ICU).[12]

1.1.2.Definition and Classification of the Postoperative Complications

Mortality as a surgical outcome has long been the only measure of work quality and risk, associated with a particular operation.[13] Comparing the mortality rate after surgery between the states, hospitals and surgeons, provide information of importance to the patients, health system and institutions responsible for health policy. Death is an outcome incapable of subjective interpretation, dichotomous in its character and easily accessible in medical documentation, therefore being suitable as an indicator of the medical treatment outcome.[3] Drastic decline in mortality after elective surgery recognised in recent decades, in parallel with growing expectations of improved quality of surgical treatment and cost reductions, contributed to the shift of attention from mortality to other outcomes, such as morbidity, quality of life after surgery, length of hospitalisation and so forth.[14,15] Morbidity resulting from postoperative complications is the usual way of measuring an adverse effect of surgery. However, the absence of standardisation in defining and quantifying the complications that exists in the professional literature makes it impossible to compare results and make valid conclusions about the overall morbidity that accompanies certain operations. The analysis of 119 studies investigating short-term outcomes of esophagectomy, pancreatectomy and hepatectomy have shown that complications were defined in 34% of cases and their difficulty in only 20% of the studies.[16] Many authors inconsistently quantify complications as minor and major, or show only those which they evaluate as being significant, all the while omitting others with lesser clinical significance.[17,18] Undoubtedly, this leads to insufficient complications reporting, heterogeneity in reporting and more challenging interpretation of the surgical outcomes.

1.1.3. The Clavien-Dindo Classification

In 1992, with an aim to overcome these problems, a new proposal for classification of complications was presented.[19] At first, three different types of negative outcomes were defined: *complications, failure to cure, and sequelae*.[19,20]

The complication is defined as "any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise the failure to cure" .[21] Pancreatic fistula and intra-abdominal abscess after pancreatic resection are examples of the complications in

accordance with this definition.

Failure to cure is a failure of surgical therapy to meet the basic goal of the surgery.[19] The surgery may be unsuccessful, even though it is well performed and the postoperative course is complications free. An example of this would be R2 resection of pancreatic tumour, which has failed to reach an oncological aim of the surgery.

Sequelae is an outcome whose main feature is that it is inherent to the procedure.[19] As such, it is in a certain way anticipated, as well as being characterised by durability. Diabetes after total pancreatectomy or "short bowel syndrome" after extensive resection of the intestines are typical sequelae in the abdominal surgery.

The Clavien-Dindo Classification of Surgical Complications is a system that ranks complications based on the therapeutic interventions applied to their treatment.[19,20] In this way, it avoids subjectivity in the qualification of the severity of complications and allows for the recording of all relevant complications, especially in retrospective analyses, since therapeutic intervention data is usually well documented. The system consists of five levels of complications severity (I-V).[20] Grade I complications are all deviations from the ideal postoperative course without the need for a specific pharmacological or surgical and endoscopic treatment. Grade II represents complications requiring pharmacotherapy. Complications of Grade III are those that are treated by surgical, endoscopic or radiological intervention, either in the local (Grade IIIa) or general anaesthesia (Grade IIIb). Patients with Grade IV complications have a life-threatening condition due to mono-organ (Grade IVa) or multiorgan (Grade IVb) dysfunction and require treatment in an Intensive Care Unit (ICU). Grade V signifies the death of a patient. To each of the grades the suffix "d" can be added, indicating invalidity (disability) and defined as a temporary or permanent disorder of function that usually lags upon completion of the surgical treatment. (Table 1.1)

Since its publication and after the revision in 2004, The Clavien-Dindo Classification of Surgical Complications has gained great popularity as a way of assessing the quality of perioperative treatment and has been used as a basis for reporting complications in over 1000 papers in specialised literature for various areas of surgery.[17,22–25] In addition, it is used as a measure of quality of work in everyday practice and is supported by several professional associations.[26]

For a classification to be widely accepted, it is necessary for it to be precise, simple and

reproducible. Validation of The Clavien-Dindo Classification of Surgical Complications was first performed retrospectively in the cohort of patients undergoing general surgery when a positive correlation of the grade of complications with the length of hospitalisation and the complexity of the surgery was shown.[20,27]

Table 1. The Clavien-Dindo Classification of Surgical Complications[20]

Grade	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infection, which are being treated only locally.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anaesthesia Intervention under general anaesthesia
Grade IV Grade IVa Grade IVb	Life-threatening complication requiring ICU treatment Mono-organ dysfunction Multiorgan dysfunction
Grade V	Death of a patient
Suffix „d“	If the patient suffers from a complication at the time of discharge, the suffix „d“is added to the respective grade of complication. This label indicates the need for a follow-up with the aim to evaluate the disability.

Also, the reproducibility of the classification was demonstrated by the correct identification and classification of complications in the identical clinical scenario by surgeons with various experiences on all 5 continents.[20] Finally, the subjective severity-of-complication experience of the patients measured by the visual analogue scale has shown a high correlation with the grade of the Clavien-Dindo classification.[20] This provides for a possibility to use the classification while informing the patient on the surgical risk and postoperative morbidity

during joint decision- making about the surgery.

The important limitation regarding The Clavien-Dindo Classification is that with the aim of simplicity, the entire postoperative course is described with one and the most severe complication, while ignoring the significance of other, less severe ones.

As an example, in this way, the postoperative course of a patient who, after the total colectomy developed acute renal insufficiency (Grade IVa) as the only complication, is assessed as more severe, than the postoperative course of the patient who developed pneumonia (Grade II), deep venous thrombosis (Grade II), bleeding ulceration managed with the endoscopic haemostasis (Grade IIIa) and anastomotic breakdown that required surgical treatment (Grade IIIb).

The Clavien-Dindo classification is, in addition, an ordinal scale rather than a continuous one, so the difference between grades III and IV do not have to be the same as between grades II and I. This makes it difficult to apply it to the analysis and interpretation of the actual severity of the postoperative course.

1.1.4. The Comprehensive Complication Index

Recognising the significance of the appearance of multiple complications on the precise view of the postoperative outcome, as well as the fact that the patients and doctors have a different perception of the severity of complications, Ksenija Slankamenac and associates proposed, in 2013, a new comprehensive system for measuring the morbidity in surgery.[28,29]

The Comprehensive Complication Index (CCI) is created using a methodology widely used in economic sciences, which takes into account the perspective of the different stakeholders. In the first phase, doctors and patients, applying a numerical analogue scale, separately evaluated the severity of 30 postoperative complications suggested in the identical questionnaire. For each complication, a median-severity as assessed by patients and physicians was multiplied and for the patients with multiple complications these products were summed.[29] Finally, with the aim of easier clinical application, mathematical transformation has provided a linear scale at which "0" corresponds to the absence of complications and "100" to the death of a patient. The CCI takes into account all the complications occurring in the postoperative period, graded according to the Clavien-Dindo

classification. In a complex clinical scenario, in patients with multiple complications, the CCI value accurately describes postoperative morbidity as a relative contribution of less severe complications decreases with the increasing values of the score.[29] In a patient who has died as the consequence of numerous complications, morbidity can not be observed in this way only, because CCI resulting in a death of a patient is always 100, regardless of the severity and the number of complications that preceded it. (Table 1.2) Calculation of CCI for an individual or a group of patients is easy and can be done using a public online program (www.assessurgery.com).[29]

Table 2. Clinical examples of the CCI in cases with one or more complications after the total gastrectomy procedure

Outcome	**Complication**	**Clavien-Dindo Complication Grade**	**CCI**
One complication			
	Atelectasis	I	**8.7**
	Urinary infection	II	**20.9**
	Pneumothorax	IIIa	**26.2**
	Subfrenic abscess	IIIb	**33.7**
	Acute renal insufficiency	IVa	**42.4**
	Anastomotic breakdown	IVb	**46.2**
More complications			
Scenario 1	Arrhythmia due to hyperkalaemia	I	**15.0**
	Surface infections of the wound	I	
	Transitory confusion	I	
Scenario 2	Wound infection	I	**34.6**
	Pneumonia	II	
	Pancreatic fistula type B	IIIa	
Scenario 3	Transient increase in creatinine	I	**65.0**
	Tachyarrhythmia	II	
	C. dificille colitis	II	
	Bleeding	IIIb	
	CVC infection with septic shock	IVb	
Scenario 4	Pain	I	**81.9**
	Deep venous thrombosis	II	
	Anaemia	II	
	Pleural effusion	IIIa	
	Anastomotic leak	IIIb	
	Hyperactive delirium	IVa	
	Pneumonia with septic shock	IVb	

After the creation of the score, validation of the CCI for complications after the abdominal surgery was performed.[29] It has been shown that the score is suitable for use in randomised clinical trials as it reduces the required sample size when the overall postoperative morbidity is viewed as an outcome.[30] In patients undergoing esophagectomy, there was a stronger correlation of CCI with the length of hospitalisation, the frequency of reoperation and reintubation compared to the Clavien-Dindo classification.[31] The scale was used to demonstrate morbidity after hyperthermic intraperitoneal chemotherapy (HIPEC), for comparison of outcomes of open and minimal invasive esophagectomy, and risk factors for high CCI after hepatectomy were also examined.[32–34] A prospective study involving all operated patients at the Department of Surgery of the University Hospital in Zurich, has shown that concomitant complications occur in 44% of patients with complicated postoperative course and that CCI significantly improves the Clavien-Dindo classification while showing the outcomes of the surgery.[35] In this centre, both complication classification systems are used in daily work and in weekly analyses of hospital morbidity and mortality.[35]

1.2. COMPLICATIONS AFTER THE ABDOMINAL SURGERY

1.2.1. Introduction

Abdominal surgery is burdened with a significant morbidity because after the routine, major elective surgical procedures complications occur with an incidence of over 50%.[36,37] Etiology of the postoperative complications, both medical and surgical, is complex and multifactorial. The risk factors for complications include factors related to the patient, such as life expectancy, comorbidity, and functional capacity at the time of surgery. Then, there are the surgery related factors, complexity of surgery, localisation, and the degree of urgency. Finally, the occurrence of complications is affected by the organisation of the perioperative care and availability of an adequate level of care.[8,38] It is very likely that not all of the factors that contribute to the complications can be fully comprehend, nor all the mechanisms that explain their occurrence can be identified.

There are numerous studies that point to the link between the global oxygen delivery to the tissues (DO_2) and unfavourable surgical outcome.[39,40] Changes that occur in the splanchnic circulation during major surgery can at least partially explain significant morbidity after abdominal surgery, and very frequent gastrointestinal complications after non-abdominal

operations as well.[41]

1.2.2. Splanchnic Circulation and the Significance of Changes in Gastrointestinal Perfusion

Splanchnic circulation is a complex system that plays a major role in maintaining basic functions of the digestive tract, such as digestion and absorption, preservation of the mucosal membrane, secretion and motility, as well as numerous liver functions. It comprises blood flow to the abdominal gastrointestinal organs including liver, spleen, pancreas, and stomach, small and large intestines. The splanchnic system receives about 25% of the cardiac output across the first three major branches of the abdominal aorta: truncus coeliacus, superior and inferior mesenteric arteries. About a fourth of the arterial flow through the splanchnic region is immediately directed to the liver via the hepatic artery, the branch of the celiac artery.[42] The other three quarters arrive to the liver after the perfusion of the digestive organs, via the portal vein system.

Digestive organs make up about 10% body weight, but contain about 25% of the total blood volume. In the condition of the sympathetic stimulation, nearly two thirds of the splanchnic blood volume can be autotransfused into systemic circulation within just a few seconds, which is more than 800 ml of blood in a normally nourished adult.[43] Therefore, the splanchnic circulation is an important reservoir of blood for the entire circulatory system and is highly adaptive thanks to the physiological functions performed by the digestive system.

Flow regulation through splanchnic circulation is performed by acting of the internal (local metabolites with myogenic activity), external (autonomic nervous system) and humoral factors (locally produced or circulating vasoactive substances).[42] The ability of catecholamines to increase the cardiac output largely depends on the compliance, capacity and volume of blood in the splanchnic circulatory system. Depending on the type of catecholamines and the density of adrenoreceptors in the blood vessels, the effect on the arteries may be constriction or relaxation. The dominant effect catecholamines produce on the large veins in the form of venocostrition, by increasing pressure in these blood vessels, efficiently displacing splanchnic blood into the systemic circulation. With this mechanism, during the physical activity, the volume of blood in the splanchnic circulation is decreased by 35%.[44] Hypovolemia causes activation of the sympathetic nervous system and increased concentration of the circulating catecholamines. The suppression of blood from the body

reservoirs (predominantly splanchnic veins) into systemic circulation is a form of compensation for the reduction of circulating volume. A study analysing the effects of controlled hemorrhage in dogs has shown that bleeding of such a size to cause the reduction in mean arterial pressure by 50% produces a reduction in the cardiac output by 50% and almost 90% reduction in the splanchnic volume of the blood.[45] It has also been shown that moderate hypervolemia and hypovolemia that have no significant effect on cardiac output, significantly decrease the intestinal blood volume.

The effects of catecholamines applied in the state of hypovolemia depend on the available amount of blood in the splanchnic resevoir. Under conditions of very severe hypovolaemia, when homeostatic mechanisms for maintaining blood pressure and cardiac output have already led to its significant discharge, the ability of exogenous catecholamines to improve systemic hemodynamics by modulating splanchnic flow rapidly decreases.[43] Maintaining perfusion of the heart and brain can then partially be provided with large doses of catecholamines through further increase of systemic vascular resistance in the splanchnic region and other vascular beds. However, such an intensive vasoconstriction may have a detrimental effect on digestive organs due to severe ischemic injury.

Hypoperfusion often occurs during major surgeries in general anesthesia as well as in the course of critical illness and the resulting non-occlusive mesenteric ischemia has different consequences for the digestive organs. Under the conditions of splanchnic hypoperfusion, the integrity of the intestinal villi and mucous barrier is disturbed and the conditions for the formation of bacterial translocation and the release of proinflammatory cytokines are created. The current theory is that the proinflammatory mediators and bacteria from ischemic intestine are not transmitted by portal blood flow, but by the mesenteric lymphatic system.[46] As these directly enter into ductus thoracicus and then into v.subclavia, the first changes as a consequence of mucosal barrier damage usually occur in the lungs in the form of acute respiratory distress rather than on the liver as it could be expected.[46] Reperfusion of the splanchnic region is causing the emergence of events that begin by creating free radicals, which cause tissue damage and neutrophil activation.[42] The release of the inflammatory mediators, increased endothelial adhesion and increased vascular permeability are steps that can lead to the development of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction.

It is clear that surgical manipulation has a direct mechanical effect on the splanchnic

circulation. Hemodynamic effects of the laparoscopic surgery depend primarily on the pressure of the insufflation that usually ranges from 12-15mmHg and the type of the gas used. Interestingly, although muscle relaxants do not have any direct effect on hemodynamics, the use of a deep neuromuscular block provides better surgical conditions with lower insufflation pressure and better splanchnic perfusion than moderate muscular block.[47]

The technique of anesthesia and the choice of the anesthetic influence as well. It is expected that epidural blockage through the sympathetic and reduction of peripheral vascular resistance can cause an increase in splanchnic flow. However, systemic effects in the form of moderate mean arterial pressure reduction and cardiac output decrease potentially oppose this effect. One of the few studies directly measuring the flow in the inferior mesenteric artery (AMI – Acute Mesentric Ischemia) and the erythrocyte flux in colon serosa has shown that thoracic epidural anesthesia induces a flow decrease in AMI accompanied by the lowering of the mean arterial pressure.[48] Re-establishing the normal flow was impossible to achieve by infusion of fluids nor by increasing the cardiac output, but exclusively by the use of vasopressors.[48]

Vasoactive drugs, which have a broad application both in anesthesia and in critically ill patients, have their own effect on the splanchnic perfusion. It has been shown that noradrenaline, the first-line vasopressor in septic shock, has minimal effect on mesenteric flow, but in combination with dobutamine it improves the splanchnic perfusion.[49] Dopamine is traditionally attributed to be acting protectively on the splanchnic bed via D1- and D2-receptors-mediated vasodilation. It has been shown, however, that although dobutamine and dopamine inotropic effect increase cardiac index and improve global hemodynamics, they do not have an effect on the increase of the flow in gastrointestinal mucosa, pancreas and kidney in septic patients.[50] Adrenaline and phenylephrine reduce splanchnic perfusion.[51]

Mechanical ventilation of the lungs during anesthesia and in the intensive care unit, by increasing intrathoracic pressure, has an effect on systemic circulation and flow through the gastrointestinal tract. The application of large tidal volumes and high inspiratory and end-expiratory pressures reduces splanchnic perfusion. Repeated recruitment maneuvers reduce oxygen delivery to the splanchnic region, even though leading to the over-all improvement in oxygenation, while spontaneous breathing tests favorably affect the gastrointestinal flow.[52]

Data on events in splanchnic circulation during abdominal operations can mostly be found in

the studies on experimental animal models. Thus, it has been shown that the maintenance of normovolemia is not enough to prevent intestinal hypoperfusion during and after the digestive tract operation.[53] Because of the changed vasoregulation, the redirection of the flow from the superior and inferior mesenteric arteries to the organs supplied by the blood through the celiac artery occurs. Such redistribution of the flow causes signs of borderline perfusion of the intestinal mucosa despite normovolemia.[53] Brügger et al demonstrated that changes in the regional gastrointestinal flow after fluid-challenge occur independently of changes in stroke volume (SV).[54] This leads to an important conclusion that if intraoperative fluid resuscitation is guided by changes in SV exclusively, as required by the "goal-directed fluid management" protocols, an opportunity may be missed for optimising splanchnic perfusion during abdominal operations.

The awareness of the importance of perfusion of the digestive tract for successful abdominal surgeries and events in critical illness has contributed to the creation of numerous measuring techniques of the flow through the splanchnic circulation.[55] Unfortunately, these methods are only tested on animal models. The only technique that has been introduced in clinical practice is gastrointestinal tonometry for measuring intraluminal CO2 based on the observation that under the conditions of compromised local perfusion, CO2 production increases and pH decreases due to conversion to anaerobic metabolism.[56] However, the widespread use of gastric tonometers has not survived to this day, in part due to certain technical limitations and partly due to the problems with the interpretation of the results and the fact that this method does not provide additional information in relation to some routine analyses, such as arterial blood gas testing.

Because of the inability to perceive directly and reliably the flow through splanchnic circulation, the microvascular flow analysis is performed in other vascular beds. Especially attractive, for the ease of its accessibility, is sublingual capillary bed, therefore, various methods of evaluating microvascular flow are applied in clinical practice through information obtained from this vascular network.[57] However, it must be taken into account that the sublingual bed significantly differs from the anatomically distant, distal parts of the digestive tract, as well as its likelihood to exhibit a different sensitivity to hypoperfusion under stress conditions.

Given the critical importance of adequate local perfusion for the healing of gastrointestinal anastomosis, it can be concluded that there is still a large gap in understanding of all of the

mechanisms, which contribute to maintaining the optimal splanchnic flow and the great need for a reliable and simple method that can be used for monitoring.

1.3. RISK ASSESSMENT IN ABDOMINAL SURGERY

1.3.1.“High-risk “ Surgical Patient

In literature, we can often come across the term "high-risk patient" concerning a particular surgery. Despite the widespread use of the term, there is still no clear definition of what this risk exactly implies.[58] Different participants in the process of treatment may have a different perception of the risk.[59] When the operation is in question, the patient considers the risk of failure of the surgery, long-term disability or absence from work. An anaesthesiologist is thinking about the risk of unfavourable events during surgery and the immediate postoperative course, while for the surgeon the concept of risk is often associated with the inability to carry out the planned surgery and surgical complications that will require long-term engagement and unforeseeable consequences. For an intensivist, the risk is associated with a potentially long-term stay in the intensive care unit, while for the hospital management the risk of an intervention is an outcome, which will be worse than that of the competitive hospitals and will infer unplanned costs. However, the common denominator of all these qualms is the chance of occurrence of the postoperative complications, including those most severe, with a deadly outcome. The qualification of the perceived risk for complications as "high" is also subject to individual interpretations. When individual patient risk is being assessed, it is usually considered high if it is higher than expected for the population. More precisely, if the risk is above the two standard deviations compared to the risk expected for the entire population undergoing that particular type of surgery.[59] This mathematical approach is not an ideal way to treat the problem of quantifying risks because population risk is most commonly unknown and is expected to vary in different environments.

Assessment of the risk for postoperative morbidity and mortality is a mandatory part of the preoperative evaluation according to the latest guidelines.[60] This procedure is of an outmost importance for precisely identifying those patients who will benefit from additional specialist check-ups and preoperative examinations, as well as the application of various interventions aiming to optimise the condition in order to reduce the risk to available evidence from the literature. Risk assessment is also important in terms of resource planning and determination

of the required postoperative care level. Finally, there is the highest level of recommendation that the perioperative risk information is to be presented to each patient during the preoperative interview.[60] In most countries, it is legally binding to provide adequate information and obtain consent for each medical intervention. As means to ensure better information immersion on perioperative risk, additional information resources, such as multimedia content on the Internet, is also provided.[61]

If the assessed risk for a particular operation is very high for a patient or unacceptable for the institution, consideration may be given to postponing surgery or choosing an alternative, less invasive treatment.

1.3.2.Risk Assessment in the Preoperative Period

1.3.2.1.Determining Functional Capacity

The highest extent of information based on which a high-risk surgical patient is identified is obtained in the preoperative period. Risk assessment at this stage is of the outmost importance because risk-based decisions can be made to modify the treatment plan and take measures to improve the patient's condition with an intent of reducing the risk.

Evaluation of preoperative functional capacity is, according to the recommendations of the European Society of Cardiologists and the European Society of Anaesthesiology (ESC / ESA), the first step in preoperative risk assessment.[62] Functional capacity is measured by metabolic equivalents (METs) and one MET matches the basal metabolism level. Although its objective measurement is achieved by cardiac stress tests, it can be quite well estimated based on the patient's ability to perform various activities from everyday life.[63] The Duke Activity Status Index is a validated and simple questionnaire that provides quick insight into the state of functional capacity. (Table 2.1) As one MET coresponds to the requirement for the resting state (3.5ml / kg / min), different degrees of stress correspond to multiplies of the basal metabolic levels.[64] Thus, self-maintenance of the hygiene corresponds to 2 METs, a 100m long walk at a speed of 3-5km / h requires 4 METs, while an intense physical activity during sports performance requires more than 10 METs.[62] Metabolic demands during the postoperative response to stress have been increased, so the ability to climb two sets of stairs is commonly used as a discriminator, thus corresponding to the consumption of more than 4 METs.[65] Several prospective studies have shown the correlation of stair-climbing capacity to

unfavourable outcome after the non-cardiac surgery.[66,67] This simple test, in which the symptoms appear to limit stairs climbing, has shown a positive predictive value of 82% for the occurrence of pulmonary and cardiac complications after major non-cardiac surgery.[65] The inability to climb up the stairs has shown an impact on overall mortality after thoracic surgery, probably because it leads to a linear increase in minute ventilation, which is of critical importance for this category of patients.[67] Such an effect, however, is not recorded in other types of non-cardiac surgery.[65] It should be borne in mind that the functional capacity is not only about the performance of the cardiovascular system, since it also depends on the function of the respiratory system, nutritional status, certain medications, and may be limited due to neurological disorders, orthopaedic immobilisation and other reasons.

Table 3. The Duke Activity Status Index[63,68]

The Duke Activity Status Index	
METs	Activity
Less than 4 METs	Can You… 1. Take care of yourself (eat, dress, bath, use toilet)? 2. Walk indoors around the house? 3. Walk a block or two on ground level at 4-5 km/h? 4. Do the light work around the house like dusting or washing dishes?
4 METs	5. Climb a flight of stairs or walk up the hill? 6. Do moderate work around the house like vacuuming, sweeping floors, or carrying groceries?
6 METs	7. Do heavy work around the house like scrubbing floors, or lifting or moving heavy furniture? 8. Do moderate yard work like raking leaves or weeding? 9. Have sexual relations?
8 METs	10. Participate in moderate recreational activities like golf, bowling, dancing, or throwing a baseball or football?
10 METs	11. Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing? 12. Run a short distance?

Wiklund and associates, in their analysis of 5939 patients, 633 of whom had a major abdominal surgery, found a low predictive value of the functional capacity of the METs for

postoperative complications.[68] The same author has shown significant differences in the estimation of METs in the range of 4-8 by the different doctors.[68]

According to the valid recommendations, it can be said that if the estimated functional capacity is more than 10 METs, the prognosis is good, regardless of the existence of coronary disease, cardiomyopathy or additional risk factors.[62] Conversely, if it is lower than 4-6 METs, the existence of other risk factors and the type of the planned surgery will determine the definitive risk, but such a patient requires additional evaluation.[62,64]

1.3.2.2. ASA Classification

American Society of Anaesthesiologists Physical Status Classification – ASA classification is the oldest and probably the most widely used risk classification applied on patients undergoing surgery and anaesthesia. It was created in 1941 when the American Association of Anaesthesiologists instructed a committee of three doctors (Meyer Saklad, Emery Rovenstine and Ivan Taylor) to study and propose a system that would enable anaesthesiologists to determine the risk for the upcoming operation based on data on the overall health status of the patient..[69] Although the original intention of the author was to come up with an estimate of the "operational risk", they quickly gave up on this intention facing difficulties in regards to classifying the operation and due to awareness of the large variation of practice in various hospitals. For these reasons, a classification system with gradations, which are not in correlation with the type of surgical intervention, the competence of the anaesthesiologist and the surgeon, or the type of anaesthesia the patient will receive, was devised. The original ASA classification had 6 classes (Classes 5 and 6 referred to the emergency surgery for patients who would otherwise be classified as Class 1 or 2, or Class 3 or 4, respectively).[69] The first revision was done in 1963, and with minor changes, remains in use to this day.[70] (Table 2.2)

Affiliation to a particular ASA class is a piece of data that is probably contained in any anaesthesia chart in the world. In a retrospective study by Hackett and associates, analysing more than two million patient histories, a strong predictive ability of the ASA classification for complications and mortality in all types of surgery has been demonstrated.[71] The risk for medical complications for classes 2,3,4 and 5 was 2, 5, 17, and 63 times higher than in class 1.[71] It has also been proven that the ASA class correlates well with the functional capacity and that is, in a similar way, associated with the postoperative outcome in abdominal and

urological surgery.[72]

There is also an interesting analysis of Hopkins and associates who were investigating the impact of the ASA class on 48-hour mortality by comparing their findings with a large historical cohort from almost 50 years ago.[73] The increase in mortality with the rising of the ASA class was shown, without a difference in the two cohorts, except for that it was significantly higher for the class 5 in the contemporary cohort compared to the historical one.[73] However, there are studies that have failed to demonstrate good predictive characteristics of the ASA classification for postoperative morbidity and mortality after major abdominal surgery.[74] The fact is that in published studies there was a very large variation in mortality rates for different ASA classes (7.8-25.9% for ASA 4, 9.4-57.8% for ASA 5).[75]

Table 4. ASA Physical Status Classification System (last amended October 2014)

ASA Class	**Definition**
1	A normal healthy patient
2	A patient with mild systemic disease without substantive functional limitations
3	A patient with severe systemic disease with substantive functional limitations
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive without the operation
6	A declared brain-dead patient whose organs are being removed for donor purposes

The addition of suffix "E" denotes emergency surgery *(*when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

Subjectivity is the characteristic of the ASA classification. There is also a potential for significant variation in determining the affiliation of a patient to an ASA class. The research conducted among the members of the Finnish Association of Anaesthesiologists has shown a significant variation in the ASA classification between the employees of the university hospital and smaller regional hospitals.[76] In contrast, a very good alignment in the classification of patients undergoing urgent gastrointestinal surgery in 19 hospitals in Japan has been presented.[77] The highest degree of disagreement with the ASA class assignment was

noticed among the various specialists, anaesthesiologists and internists during the preoperative consultation, while the significant difference was not observed between the anaesthesiologists with different work experience.[78] It is likely that these differences are partly encouraged by the fact that the classification itself does not take into account many factors, such as gender, age, type and extent of surgery, specificities related to perioperative care, and the term "systemic disease" contained in class 2 description and 3 are not precisely defined.

It should be mentioned that the ASA classification is a classification system, and not a score, and since its first publication it is clear that in terms of its predictive characteristics (sensitivity, specificity, positive and negative predictive value) it does not provide reliable prediction of outcomes for individual patients. However, it has been used to create models that more reliably predict postoperative morbidity and mortality.[79]

1.3.2.3. Risk scores for Cardiac Events in Non-Cardiac Surgery

The estimates are that approximately 10 million people who are undergoing a major non-cardiac surgery each year worldwide experience a serious undesirable cardiac event within the first 30 postoperative days.[60] For this reason, risk assessment for undesirable cardiac events is an important part of the preoperative assessment. In the previous decades, several scales for assessing the said were proposed, based on multivariate analysis of data from observational studies. "Multifactorial Index of Cardiac Risk in Noncardiac Surgical Procedures", known as Goldman score, classifies patients into one of four classes of significantly different risk for severe and potentially fatal postoperative cardiac events centred around the presence of 9 identified predictors.[80] (Table 2.3). As 28 out of a total of 53 points available for assignment could potentially be controlled, it allows the elective surgery to be postponed until the cardiopulmonary status stabilisation. Although proved to be superior to the ASA class in prediction of undesirable cardiac event, ASA classification was better in predicting the overall postoperative mortality.[81] About then years later, Detsky and associates, after validating Goldman score in their patient population, suggested their own modification as Detsky score, which has also found the wide application among cardiologists in preoperative evaluation.[82] In order to simulate the risk of cardiac complications after non-cardiac surgery, Lee analysed a small number of predictors, creating a risk scale known as The Revised Cardiac Risk Index (RCRI).[83] This scale has gone through numerous external validations, as well as the further attempts at simplification or elaboration in the sense of

more precise risk definition of the surgery itself and by adding age, increasing its predictive characteristics for cardiac complications.[84,85] Goldman Scale, Detsky Scale, and Lee RCRI are supported by the European Society of Cardiologists as identification tools for patients requiring additional preoperative cardiac evaluation, pharmacotherapy or some other risk reduction strategy for cardiac complications.[62]

Table 5. Goldman Cardiac Risk Index [80] and The Revised Cardiac Risk Index [83]

Goldman Cardiac Risk Index (1977)		**The Revised Cardiac Risk Index (1999)**	
Risk factor	**Points**	**Risk factor**	**Points**
Third heart sound (S3)	11	High-risk type of surgery	1
Elevated jugular venous pressure	11	Ischaemic heart disease	1
Myocardial infarction in past 6 months	10	History of congestive heart failure	1
ECG: premature atrial contractions or any rhythm other than sinus	7	History of cerebrovascular disease	1
ECG shows > 5 premature ventricular contractions per minute	7	Insulin therapy for diabetes	1
Age > 70 years	5	Preoperative serum creatinine > 177μmol/l	1
Emergency procedure	4		
Intra-thoracic, intra-abdominal or aortic surgery	3		
Poor general status, metabolic or bedridden	3		
Risk of major complications or cardiac death		*Risk of major cardiac event*	
Class I= 0-5 points (1% complications)		Class I= 0 points (0.4%)	
Class II= 6-12 points (7% complications)		Class II=1 point (0.9%)	
Class III=13-25 points (14% complications)		Class III= 3 points (6.6%)	
Class IV ≥ 26 (78% complications)		Class IV= 4 points (>11%)	

Unfortunately, there are very few studies that have tried and succeeded in showing that the outcome can be corrected if this risk is known.[86,87] The fact is that the mentioned risk stratification scales were developed several decades ago, and since then the significant advances in cardiological diagnosis and therapy, operational techniques and perioperative

care have been achieved. The usage of biomarkers (troponin and NT-pro-BNP) in the stratification of perioperative cardiac risk, although widely used, still has not achieved the highest recommendation.[60] This points out to the need for a new predictive model that would allow more precise risk stratification, above all in terms of creating opportunities to improve outcomes.

1.3.2.4. Charlson Comorbidity Index

Charlson score (The Charlson Comorbidity Index) was created in 1987 with the aim of classifying the comorbidities affecting the mortality risk for longitudinal epidemiological studies.[88] The original index was created in the cohort of hospitalised internal medical patients and validated in surgical patients with various comorbidities after their discharge from the hospital during a long period of follow-up.[89] This index encompasses 17 comorbidities with the appropriate severity (1-6) assigned. The final score value is generated by summing of the assigned points and may have a value of 0 (without the accompanying diseases) to 29 (maximum severity of comorbidity). (Table 6)

More than 5,000 publications cited the Charlson index with the aim of showing the comorbidity of the patients covered by the examination. This score proved to be an independent predictor of pulmonary complications after abdominal surgery and the most important prognostic factor in older patients after colorectal cancer resection.[90,91] The influence of Charlson index on a complicated postoperative course has been verified after radical gastrectomy due to cancer and liver resection.[92] However, as well as the ASA classification, the Charlson index also did not show having an impact on the costs of hospitalisation and length of hospitalisation after elective surgery, such as laparoscopic cholecystectomy and colectomy.[93]

Table 6. Charlson Comorbidity Index[88]

Score	Comorbidity
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any malignancy
3	Moderate or severe liver disease (cirrhosis with ascites)
4	AIDS
	Metastatic solid tumour

Note: For each decade > 40 years of age one point is added to the score

1.3.2.5.Score for Prediction of Postoperative Respiratory Complications

Pulmonary complications after abdominal surgery occur with a frequency of up to 10-16%.[60,94] However, in some types of gastrointestinal surgery, especially those in the upper abdomen and in esophagectomy, the incidence of even over 50% is recorded.[95] As the pulmonary complications may have a high severity, such as pneumonia or ARDS, and may require mechanical ventilation and extended hospitalization, the need for preoperative identification of patients with increased risk has been imposed. The ARISCAT score for pulmonary complications was developed in a prospective multicentre study, which included 59 randomly selected hospitals.[96] This score, in addition to preoperative characteristics (age, preoperative pulmonary function and anaemia), also takes into account the parameters related to the planned surgical approach, its duration and urgency. ARISCAT is an externally validated score and has demonstrated good predictive features in various types of surgery.[97,98]

ARISCAT was the basis for the identification of patients for whom the team of experts proposed a set of measures to reduce the incidence of postoperative pulmonary complications.[99]

1.3.3. Risk Assessment of Complications Based on Information from the Intraoperative Period

Preoperative patient evaluation is just one part of a large puzzle and we can intuitively conclude that it only partially affects the overall outcome of the surgical treatment. Although it is clear that the surgery and anaesthesia cause a strong physiological stress response, relatively few studies have examined how the information from an intraoperative period can help identify patients with elevated risk of postoperative complications. The factors that have been shown to have an impact on the outcome are the complexity and urgency of the surgery, its duration, tissue injury extent, undesirable intraoperative events, minimally invasive approaches, anaesthetic techniques and so on.[3,100] On the other hand, it is almost certain that all of the factors, which can influence the outcome, could never be taken into account in entirety nor objectively measured. A surgery is performed by people, professionals whose competence, interest, attention to detail, skill, mood, current fatigue level, and motivation have not been examined in a study in the context of risk for complications. In addition, there are some patient characteristics such as "tissue quality" and healing capacity that can not be characterised only by standard analysis. Consideration of the relevant information from the intraoperative period can help except in quantifying the overall risk, and in decision making on further treatment and providing an adequate postoperative care level.

1.3.3.1.Surgery Complexity

The risk that the patient bears is evaluated to the greatest extent in relation to the complexity of the surgery. In the literature, there is no final agreement about what represents a "major" surgery.

In 1917, in his letter to the editor of the journal Annals of Surgery, Dr Robert Earl addresses a request for explanation to be given to him of what constitutes a minor and what a major surgery, as according to the applicable law of the Minnesota State,by which the osteopaths are allowed to perform only a minor surgery.[101] Mr Lewis Pilcher, the editor, gave the following answer: “...I would say that major surgery includes all work requiring a general anaesthetic; all operations which involve openings into the great cavities of the body; all operations in the course of which hazards of severe haemorrhage are possible; all conditions

in which the life of the patient is at stake; all conditions which require for their relief manipulations, for the proper performance of which special anatomic knowledge and manipulative skill are essential."[101] To this over a 100 years old definition, not much could be added even today. However, due to the great development that surgery has achieved in the meantime, there was a need for a more precise definition of the complexity of the surgical treatment. Large hospitals and professional associations provided different classification of surgeries, resulting in a significant confusion in literature.[102] The fact that the complex surgery is associated with the greater risk for death, long-term hospitalisation and higher costs of treatment, have also been recognised by health insurance funds thus creating a practical classifications of surgical procedures according to complexity.[23] The British United Provident Association (BUPA) has divided surgical interventions into 5 classes according to complexity (minor, intermediate, major, major plus, and complex major) and this division has become an integral part of the operational risk assessment.[79] The mortality after some of the undelayable surgeries is much higher than the elective, and for this reason there are subdivisions of surgeries according to the degree of urgency.[79,103]

1.3.3.2.Hospital Volume and Surgeon Volume

A number of operations of a particular type performed in a hospital, as well as the number of interventions made by a certain surgeon, are among the most important factors affecting the hospital mortality rate. An analysis of over 2.5 million Medicare insured patients operated in hospitals across the United States has unambiguously pointed to the inverse relationship between the hospital volume and mortality rate.[104] When hospital volumes are divided into quintiles, the biggest difference in mortality was observed in esophagectomy (23.1% at very low volume vs 8.1% at very high volume) and pancreatectomy (17.6% vs. 3.8%).[104] The need for centralisation of the certain types of surgery derives from the evidence that mortality after major oncological surgeries can be reduced by up to 50% if a certain number of surgeries per centre each year is guaranteed.[105] Significantly lower mortality after radical gastrectomy in the high-volume hospitals in Germany is primarily attributed to the ability to adequately treat the postoperative complications.[106] Schmidt and associates study, which analysed the results of 1003 duodenopancreatectomies in two long observation periods in the same center, took into account the hospital volume, surgeon's experience, and surgeon's volume.[107] These authors have clearly shown that the number of duodenopancreatectomies performed annually in the centre is the only factor influencing mortality, but that even in the "high-volume" centre the surgical experience is of undeniable significance because this variable has

determined total morbidity rate.[107] The significance of surgical volume was also confirmed in a large systematic analysis for almost all types of surgeries, as well as in a study that has shown that switching of the high-volume surgeons for pancreatic surgery in a low-volume centre did not result in a change in results.[108,109]

The surgeon's experience also depends on the learning curve while adopting a new surgical technique. Usually, the parameters used to measure reaching a plateau on the learning curve are the duration of surgery, length of hospitalization, or the percentage of conversion for laparoscopic procedures. It is considered that 30-35 operations are required to master the laparoscopic rectal surgery.[110] Perhaps during the analysis of the learning curve, the postoperative complications should be considered. They certainly speak more of the quality of work than the speed at which the surgery is completed.

1.3.3.3. Unfavourable Intraoperative Events

Many intraoperative events that deviate from the standard course of the surgery may have an effect on the occurrence of the postoperative complications. It has been shown that even short-term intraoperative hypotension significantly increases the chance of myocardial ischemia and acute renal insufficiency.[111]

Surgical Apgar score has emerged relying on the neonatal Apgar score with the aim of enabling the surgical team to evaluate in a simple and reliable way the patient’s condition at the end of the surgery, his risk of postoperative complications, and propose accordingly a further treatment plan.[112] This simple score obtained as a result of multivariate logistic regression analysis takes into account only three factors: intraoperative blood loss, heart rate and blood pressure. (Table 7) The authors have shown that the score has excellent predictive characteristics for postoperative morbidity because the incidence of severe complications was 58.6% in patients with a 0-4 score and 3.6% in those with a score of 9-10. Also, the score was predictive for mortality in cohorts of patients undergoing general and vascular surgery ($p<0.0001$).[112]

The score has been validated in several studies, and one of them suggests that for each patient with the score lower than 4 an intensivist consultation is needed in order to arrange the patient's intensive care unit addmission for the further follow-up.[113]

Table 7. Surgical Apgar Score (Gawande et al)[112]

	0 points	1 point	2 points	3 points	4 points
Estimated blood loss (ml)	>1000	601-1000	101-600	≤ 100	-
Lowest mean arterial pressure (mmHg)	< 40	40-54	55-69	≥70	-
Lowest heart rate (beats/min)	>85	76-85	66-75	56-65	≤ 55

Surgical score= sum of the points for each category

Occurrence of pathologic bradyarrhythmia, atrioventricular block, and asystole also receive 0 points

Retrospective analysis from the Columbia University Medical Centre, which covered the seven-year period, has shown that the surgical Apgar was closely associated with a ICU triage decision immediately after a high-risk abdominal surgery.[114]

1.3.4. Risk Stratification Systems for Complications that Combine Preoperative and Intraoperative Factors

1.3.4.1. Shoemaker Criteria

Shoemaker and associates have proposed a list of criteria for "high-risk" patients who undergo elective or emergency surgery based on mortality rate analysis from the previous years.[39] He had observed that the mortality in patients who fitted one or more criteria from the list was around 30%. Approximately 7% of patients in general surgery could fall into high-risk criteria, but they accounted for 82% of total mortality. The purpose of this list was to define inclusive criteria for the needs of randomised studies, which tested the strategies for supranormal oxygen delivery to tissues that were shown to be effective in the previous studies. **(**Table 8**)** Other authors have also used similar the criteria for defining the high-risk patients in randomised trials, but this list was rarely used in routine stratification of risk. [115] It does not allow for the risk grading, but only states its presence or absence, and is, besides, complicated for practical application.

Table 8. „High-risk“ patient criteria (Shoemaker et al)[39]

“High-risk” criteria
• **Previous severe cardiorespiratory illness** (acute MI, COPD, stroke, etc.) • **Extensive ablative surgery planned for carcinoma**; e.g. esophagectomy and total gastrectomy, prolonged surgery (>8h) • **Severe multiple trauma**; e.g. > 3 organs or > 2 systems, or opening 2 body cavities • **Massive acute blood loss** (>8 units), Blood volume <1.5L/m^2, Hct <20% • **Age over 70 years and evidence of limited physiologic reserve of one or more vital organs** • **Shock**: Mean arterial pressure <60mmHg; CVP < 15 cmH_2O and urinary output<20ml/h • **Septicaemia**, positive blood culture or septic focus, WBC>13000, spiking fever to 38.3˚C for 48 hour, and hemodynamic instability • **Respiratory failure**: e.g. PaO_2 <60 mmHg on FiO_2 > 0.4, Qs/Qt>30%, mechanical ventilation needed>48h • **Acute abdominal catastrophe with hemodynamic instability**: e.g. pancreatitis, gangrenous bowel, peritonitis, perforated viscus, GI bleeding • **Acute renal failure** (Blood urea nitrogen > 17.8 mmol/l; creatinine 265.2 μmol/l) • **Late stage vascular disease involving aortic disease**

MI-myocardial infarction; COPD-Chronic obstructive pulmonary disease; CVP-central venous pressure; Hct-Haematocrit; PaO_2 – arterial partial pressure of oxygen; FiO_2-Inspired fraction of oxygen; Qs/Qt –shunt fraction; GI-Gastrointestinal

1.3.4.2. The Surgical Risk Scale

Based on the clinical experience that the physical status and comorbidity, together with the surgery volume and degree of urgency, determine the final outcome, Sutton and associates with their methodology of logistic regression analysis created a sketch for predicting postoperative mortality. [79] This score uses only three readily available parameters: ASA class, urgency category according to the National Confidential Enquiry into Perioperative Deaths (NCEPOD) and the surgery volume in accordance with the British United Provident Association (BUPA) classification. (Table 9) In the validation set, the authors showed a good score calibration and good predictive performance in low-risk categories. The score is obtained by a simple addition of the points, and the mortality risk is less than 1% if the score is < 9.[79] It is unclear why, according to the BUPA classification, laparoscopic cholecystectomy is classified as major plus surgery, in the range of gastrectomy, and greater complexity than open cholecystectomy. The reasoning of a clinician would probably be different.

Table 9. The Surgical Risk Score (Sutton et al)[79]

	Description	Score
CEPOD		
Elective	Routine booked non-urgent case, e.g. varicose veins or hernia	1
Scheduled	Booked admission, e.g. cancer of the colon or AAA	2
Urgent	Cases requiring treatment within 24±48h of admission, e.g. obstructed colon	3
Emergency	Case requiring immediate treatment, e.g. ruptured AAA	4
BUPA		
Minor	Removal of sebaceous cyst, skin lesions, oesophagogastric duodenoscopy	1
Intermediate	Unilateral varicose veins, unilateral hernia repair, colonoscopy	2
Major	Appendectomy, open cholecystectomy	3
Major plus	Gastrectomy, any colectomy, laparoscopic cholecystectomy	4
Complex major	Carotid endarterectomy, AAA repair, limb salvage, anterior resection of the rectum, oesophagectomy	5
ASA-PS		
I	No systemic disease	1
II	Mild systemic disease	2
III	Systemic disease affecting activity	3
IV	Serious disease but not moribund	4
V	Moribund, not expected to survive	5

CEPOD- Confidential Enquiry into Perioperative Deaths; AAA-Abdominal Aortic Aneurysm; BUPA– British United Provident Association operative severity score; ASA-PS- American Society of Anaesthesiologists Physical Status

1.3.4.3. Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM score)

In 1991, Graham Copeland, a urologist from Liverpool, described a scoring system for tracking outcomes in surgery.[116] He named it the **P**hysiological and **O**perative **S**everity **S**core for the **E**numeration of **M**ortality and **M**orbidity and used the acronym POSSUM under which the score is known. A cohort of surgical patients from the general hospital served for a retrospective analysis of 62 individual factors (48 preoperative and 14 intraoperative). In a prospective analysis, in the next 6-month monitoring period, by multivariate discriminatory analysis, the number of factors was reduced and only independent predictors were included in the final model.[116] Each independent variable was given a value on the exponential scale (1, 2, 4, 8), and physiological score was created with 12 variables each having 4 gradations. It was immediately noted that this preoperative physiological score, although having good predictive characteristics for the general population of the patients, shows significant group differences in relation to the characteristics of the surgery. By further analysis, an "operative score" was created with 6 variables and was added to physiological. (Table 10 and 11) Physiological and operative POSSUM scores are obtained by adding points in each group and then these values are entered to the following formula for calculating the probability of morbidity and mortality:

$$p = \frac{e^y}{1+e^y}$$

; where p represents the probability of outcome (mortality or morbidity);

y (morbidity) = -5.91+(0.16 x Physiological score) + (0.19 x Operative score);

y (mortality) = -7.04 + (0.13 x Physiological score) + (0.16 x Operative score)

POSSUM score is currently validated in colorectal surgery, liver resection, pancreas, oesophagus, vascular surgery, orthopaedics, in urgent surgeries due to peritonitis, in geriatric population.[117–122] It was also used to compare the efficiency of various hospitals, surgeons, and various levels of postoperative care (intensive care vs. ward).[123–125] As a method for comparing the different populations of patients, POSSUM has found a very wide application in professional literature. However, when assessing an individual risk there are certain limitations in the interpretation of results.

Table 10. Physiological POSSUM (Copeland)[116]

Variable	1	2	4	8
Age (years)	≤ 60	61-70	≥ 71	-
Cardiac signs **Chest radiograph**	Normal Normal	Cardiac drugs or steroids -	Oedema, Warfarin Borderline cardiomegaly	Elevated JVP Cardiomegaly
Respiratory symptoms and signs	Normal	SOB exertion, Mild chronic obstructive airways disease	SOB stairs, Moderate chronic obstructive airways disease	SOB rest, Any other change
Systolic BP (mmHg)	110-130	131-170 100-109	≥ 171 90-99	≤ 89
Pulse (bpm)	50-80	81-100 40-49	101-120	≥ 121 ≤ 39
Glasgow coma score	15	12-14	9-11	≤ 8
Urea (mmol/l)	≤ 7.5	7.6-10	10.1-15	≥ 15.1
Na^+ (mEq/l)	≥ 136	131-135	126-130	≤ 125
K^+ (mEq/l)	3.5-5	3.2-3.4 5.1-5.3	2.9-3.1 5.4-5.9	≤ 2.8 ≥ 6.0
Hgb (g/dl)	13-16	11.5-12.9 16.1-17	10-11.4 17.1-18	≤ 9.9 ≥ 18.1
WCC ($x10^{12}$/l)	4-10	10.1-20 3.1-3.9	≥ 20.1 ≤ 3	-
ECG	Normal	-	Atrial fibrillation (60-90)	Any other change

JVP-jugular venous pressure, SOB-shortness of breath, BP-blood pressure, bpm-beats per minute, WCC-white cell count, ECG-electrocardiogram

Table 11. POSSUM Operative Severity Score (Copeland)[116]

Variable	1	2	4	8
Operative* magnitude	Minor	Intermediate	Major	Major +
Operations within 30 days	1	-	2	>2
Blood loss per operation (mls)	≤ 100	101-500	501-999	≥ 1000
Presence of malignancy	No	Primary cancer only	Node metastases	Distant metastases
Timing of operation	Elective	-	Emergency, resuscitation possible, operation<24h	Emergency, immediate operation < 2 hours

* Moderate severity: appendectomy, cholecystectomy, mastectomy, transurethral resection of prostate; Major surgery: any laparotomy, bowel resection, choledochotomy, peripheral vascular procedure; Major + surgery: any aortic procedure, abdominoperineal resection, pancreatic or liver resection, oesophagectomy

A part of these constraints stems from the equation derived from the logistic regression. Specifically, the lowest possible risk for the death outcome that can be predicted (when all physiological score parameters are normal and when the surgical severity is minimal) is 1.05%. This is an unacceptably high risk for a healthy patient undergoing a minor intervention. Many studies have shown that POSSUM predicts significantly higher mortality and morbidity than observed (over predicts) in low-risk categories.[126] This was also noticed by Prytherch and his associates, so they carried out a prospective analysis of the POSSUM score in a large cohort of surgical patients, which resulted in the remodelling of the mortality score equation.[127] The score was given a name P-POSSUM, applying the same predictors as POSSUM but with greater precision in predicting mortality in low-risk patients than the original POSSUM score.[117,127] The P-POSSUM score is derived only for mortality prediction, not postoperative complications.

As a score, which resulted from a patient cohort analysis from a general hospital, POSSUM contains variables that are not relevant to prediction of outcome in specific patient populations. Glasgow Coma Score (GCS) is an integral part of the physiological score, but the patients who undergo elective major surgery in which it is below 8 are extremely rare. In addition, for orthopaedic procedures the variable "peritoneal contamination" is insignificant. Therefore POSSUM variants are proposed for use in esophagogastric (O-POSSUM) or colorectal (CR-POSSUM) surgery.[128,129]

The lack of POSSUM is also due to the fact that some variables are not available immediately after the end of surgery (lymphadenopathy and distant metastases), which sometimes makes it difficult to apply it in the early identification of the patients at risk. Also, computing the predicted risk for mortality and morbidity requires a lot of time.

Although the official anaesthesia chart of the Clinical Centre of Serbia contains a section for the record of the POSSUM, it is unlikely that it has ever been filled. Possible reason is that the score has never been validated in our population.

1.3.4.4. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Surgical Risk Calculator

In 1996, the American Congress passed a law requiring all Veterans Affairs (VA) hospitals to submit reports on surgical treatment results for comparison with the national average. Based on the results of a major study (National Surgical Risk Study), from which various models for outcome prediction were derived, taking into account the severity of the patients' condition, in 1994 the National Surgical Quality Improvement Program (NSQIP) was organised.[130] This programme entails collecting relevant data pertaining to each operation performed in the Veterans Affairs hospital system. The data are forwarded to the co-ordination centres and from them the hospitals receive periodic reports in the form of observations relating to the expected morbidity and mortality (O: E ratio). With regards to this and other parameters, the quality of work of an institution is assessed. It has been noted that in the first ten years since the start of NSQIP, 30-day mortality rate after major surgery dropped by one third and morbidity by 45%.[131] One of the greatest achievements of NSQIP is generation of the databases of undeniable significance, with high quality information on millions of operations performed at VA hospitals.[131] Based on this information, the ACS NSQIP surgical risk calculator was created.[100] This calculator is based on a series of demographic, clinical and laboratory indicators and calculates the risk of death and numerous individual complications for almost all types of surgeries except for trauma and transplantation.[100] The risk is expressed in percentages, and the chance of a certain outcomes qualifies as average, below or above the average. The calculator provides a prediction of the length of hospitalisation. The prediction of outcome is made by including 21 preoperative risk factors in different formulas obtained by statistical modelling. The calculator allows the surgeon to increase or decrease the calculated risk within a given confidence interval for a certain outcome if he considers that some significant parameters for a particular patient are not taken into account.[100] ACS

NSQIP Surgical Risk Calculator is available on the website http://www.riskcalculator.facs.org. The great advantage of the calculator is that it is comprehensible, thanks to the technical solution and its visual acceptability for the patient, thus enabling discussion of the foreseen risks by providing the complete information.

The analysis of the ACS NSQIP score in South Korea has shown that it has good predictive characteristics, not only for the complications but also for remote oncological outcomes after cephalic duodenopancreatectomy due to pancreatic cancer.[132] On the other hand, this risk calculator did not demonstrate predictive ability for any specific type of complications, and it has demonstrated only moderate estimate for mortality in old patients who underwent the spine surgery in China.[133]

It is unlikely that any country in the world has a database as comprehensive as NSQIP. Therefore, it remains for the ACS NSQIP Surgical Risk Calculator yet to be validated through large prospective studies for the evaluation of its application possibilities in patients from other health systems.

1.3.5. Risk Assessment of Complications based on Information from the Early Postoperative Period

1.3.5.1.Risk Factors Related to the Postoperative Process of Care

A large observational study by Pearse et al showed that one relatively small group of patients who account for about 12% of all hospital admissions is responsible for over 80% of deaths after surgery.[8] This group was identified as high-risk surgical patients by the authors. Further analysis showed that the highest mortality was observed in those patients who were urgently accepted in the Intensive Care Unit (ICU) due to postoperative complications and after the initial treatment at the ward.[8,38] This study, as well as the later EUSOS study, attracted the attention of the public due to the fact that about 75% of the patients who died did not have any access to the ICU.[3] Such data on mortality and triage after general surgery were compared to cardiac surgery practice. Mortality after the aortocoronary by-pass is maintained at around 2% worldwide, despite the fact that the patients usually have many associated comorbidities.[134] Unlike general surgery, cardiac surgery is determined by the available resources in ICU, because every patient is routinely admitted in ICU after surgery. Such findings have posed the question of whether treatment in ICU for high-risk patients after general surgery could improve the outcome. Unfortunately, the answer to this question can not be obtained by randomised studies because of the unethical nature of triage in randomized

trials.

Staying in ICU also has a number of well-known adverse effects, such as risk for nosocomial infections, long-lasting immobilisation, excessive sedation, and psychological sequelae.[135] It has been shown that hospitals in which the rate of admission to ICU is the highest have poorer results in the treatment of pneumonia.[136] A study investigating the relationship between ICU and mortality after five types of surgery (open aortic aneurysm surgery, endovascular aortic aneurysm, duodenopancreatectomy, cystectomy and esophagectomy) showed a large variation between hospital use of ICU resources for these operations ranging from 5-100%.[137] No correlation was found between the rate of use of ICU and mortality for any of these surgeries. However, this study only included insured persons over the age of 65, and lacked the data on the time of their stay in ICU (immediately after surgery or during a postoperative course). An observational study involving 45,000 patients in 27 countries showed a greater incidence of the fatal outcome in patients with planned admission to ICU immediately after surgery.[138] The hospital level analysis did not establish a correlation between the death outcome and the planned ICU stay, or for treatment of complications, and concluded that scheduled admission to ICU did not improve the outcome after the surgery.[138] What the critique of this study might be is that it did not take into account equipment and personnel standards in the ICU and in the surgical wards, which likely show huge variations between hospitals in the countries covered.

To what extent the elements of the postoperative care influence the outcome also point out the findings of the studies that show that the greatest mortality after elective surgery is recorded in patients treated at the end of the working week and on the weekends, as well as during the month of August.[139,140]

1.3.6. Peripheral perfusion disorders

Based on the evidence that the peripheral perfusion disturbance, accompanied by decreased oxygen delivery, has a significant influence on the development of organ dysfunction and mortality in critically ill patients, a hypothesis has been made that the early detection of the deteriorated tissue perfusion may help identify surgical patients at risk for complications.[141,142] The tissue hypoxia after the surgical trauma is due to the inability to increase the oxygen supply to the tissues or its extraction in conditions of increased oxygen demand.[39] Today there are many techniques for assessing the adequacy of tissue perfusion

and oxygenation.[143,144] The fact is that orthogonal polarization spectroscopy, laser Doppler flowmetry, near-infrared spectroscopy, and peripheral perfusion index cannot yet be considered as the standard monitoring tools in surgical intensive care units. Therefore, the significance of other, clinically easily available signs of disturbed tissue perfusion for the identification of patients with a risk of postoperative complications has been studied. This allows further study of strategies for correction of the observed disorders with the aim of improving the postoperative outcome.

The subjective assessment of peripheral perfusion is one of the basic elements of a physical examination that must be adopted by each and every medical student. There are numerous examples in the literature in which the state of shock is depicted in very detailed descriptions of its appearance, colour and heat of the skin and mucosa. One of the pioneers of US military surgery,dr Nicholas Senn, describes the condition of the soldiers injured in the American-Spanish War in 1898:„... The patient lies on the ground, motionless. He has lost little blood, but his lips are pale...the hands are cold, and the pulse at the wrist cannot be felt. The respirations are irregular...it takes repeated questions to elicit the simplest answer.“[145] More than a century later, Lima with associates, in a prospective observational study, proves the importance of physical examination in the discrimination of hemodynamically stable critical patients and those who develop severe organ dysfunction.[146] In this study, the subjective assessment of the adequacy of perfusion is correlated with objective parameters such as the capillary refill time, body temperature gradients, and the noninvasively measured peripheral perfusion index.[146]

1.3.6.1. Capillary refill time

Henry Beecher introduced the capillary refill time in clinical practice on the basis of his research of only 100 seriously injured patients.[147] He qualitatively labeled the time needed to return the colour of the nail capillary bed after the compression, as "normal", "clearly slow" and "very sluggish" and this correlated with the shock of "mild", "moderate", and "severe degree".[147] The physiological explanation of this phenomenon is based on the existence of different degrees of vasoconstriction that accompany shock states and dehydration. Although the author did not numerically quantify the capillary refill delay, in most subsequent studies, the threshold value is 2 seconds.[148] However, it has been shown that normally the time of capillary filling varies significantly depending on the gender, the temperature and the age of the patient.[149] The increase in ambient temperature with each degree in the average increases the capillary refill time by 1.2%, regardless of the body temperature.[150] On the other hand, the

increase in body temperature by 1 degree shortens the capillary refill time by an average of 5%, non-co-dependent of the ambient temperature.[150] Meta-analysis by Fleming et al characterized the capillary refill time as a "vital sign" for children of all ages because if prolonged, it was coupled with a fourfold greater chance of death.[151] It has also been shown that delayed capillary refill time has a positive predictive value of 93-96% to point to the central venous blood saturation less than 70%.[151] With regard to high specificity, this indicator has low sensitivity so that the normal values do not exclude the existence of perfusion disorders.[151] Problems linked to the capillary refill are also related to the relative subjectivity in the assessment, as well as the lack of conformity with the length of compression and the site at which the tests are being conducted. In any case, this is a simple and quick test but we cannot yet be sure if within a matter of seconds, while we are actually doing it, we get clinically relevant data on peripheral perfusion or just a moment of time to peacefully consider what will our next step in the care of a critical patient be. It is possible that the objectivities of this method, the quantitative capillary refill time (Q-CRT), which was shown to correlate well with lactate values and circulatory status, would help to eliminate some of the aforementioned shortcomings associated with this parameter.[152]

1.3.6.2. Temperature gradients

Body temperature is one of the most accessible vital parameters. However, the research carried out by the Thermoregulation in Europe Monitoring and Managing Patient Temperature Study Group has shown that the intraoperative temperature monitoring was one of the least monitored parameters.[153] This study, conducted in over 800 hospitals across Europe, showed that intraoperative temperature monitoring was conducted in 19.4% of patients and that some form of active heating was used in less than 40% of the patients.[153]

The normal core temperature is 36.5-37.3 °C, while the temperature of the periphery is 2-4 °C lower thanks to the thermoregulatory vasoconstriction mechanism with the aim of maintaining the core temperature.[154] There are many reasons to lose heat during operations under general or regional anaesthesia, and it typically occurs in 3 phases: at first quickly due to the thermal redistribution to the periphery, then slower due to the redistribution from the periphery to the environment, and ultimately very slowly because of the activation of peripheral vasoconstriction when the core temperature drops to 33-35˚C.[155] Heat loss, especially after prolonged surgery may result in the appearance of unintended perioperative hypothermia. Numerous studies have shown a negative influence of hypothermia on postoperative outcomes. The increased predisposition to bleeding and the need for

transfusions occurring in both non-intentional and intentional hypothermia are the result of temperature-dependent and enzymatically mediated coagulation disorders: modified platelet function, coagulation factor, and fibrinolytic activity.[156] In a randomized study, Frank et al showed that even mild hypothermia, with a 1.4 ° C core temperature reduction, contributes to a threefold increase in the chance of developing perioperative myocardial infarction.[157] This result can be attributed to the hemodynamic effect of hypothermia in the form of hypertension and tachycardia, as well as postoperative shivering which increases the accentuated postoperative oxygen consumption. Surgical site infection after colorectal surgery occurs with a frequency of about 10%, which, in the hypothermic conditions with a temperature drop of 1.9 ° C, increases by triple.[158] This can be explained by direct disturbance of the immune function, but also by the influence of hypothermia-induced vasoconstriction on the wound perfusion and reduction of tissue oxygen partial pressure. There is even a hypothesis that unintended hypothermia could be responsible for the appearance of tumor relapse and the appearance of metastases after oncological surgery, probably through suppression of T-cell immunity.[159] Postoperative shivering and feeling cold are not severe postoperative complications, but they are often described by the patient as the more unpleasant experience than pain. Long-term shivering as a compensatory mechanism increases oxygen consumption by 2-3 times.[160]

One very old study has shown that the temperature of the toe is very well correlated with the heart rate and that this correlation is even stronger when placed in the context of ambient temperature.[161] It has also been shown that early skin temperature measurement at the toe has good predictive characteristics for the outcome of a critically ill patient.[161] These findings were the basis for the introduction of temperature gradients for estimating peripheral perfusion because under constant ambient temperature, changes in skin temperature are the result of changes in the skin blood flow.[162] Usually, as temperature gradients we use the difference between the forearm-to-finger-tip (Tskin-diff) skin-temperature, the difference between central and peripheral temperature (dTc-p), and the difference between peripheral and ambient temperature (dTp-a). It is considered that dTc-p in patients with stable hemodynamic is 3-7 ° C, and that the gradient is increased when vasoconstriction occurs in order to perfuse vital organs and maintain a central temperature stable.[143] It was shown that the mean value of dTc-p during 24 hours after admission to ICU together with lactate concentrations and mean arterial pressure (MAP) is an ICU and hospital mortality predictor in septic patients.[141] Also, the dTc-p value greater than 5 ° C significantly correlates with

central venous oxygen saturation (ScvO2) and lactate concentrations in patients with septic shock.[163] Studies which were investigating the importance of temperature gradients in surgical patients mainly refer to cardiac surgery. However, Genderen with associates showed that peripheral perfusion disorders after major abdominal surgery, including temperature gradients, were associated with severe complications, independent of systemic hemodynamics.[142] New studies are needed to investigate the effectiveness of strategies which by influencing peripheral perfusion may contribute to improving postoperative outcomes. Several studies related to the use of vasodilators after initial resuscitation of septic patients showed that along with the decrease of dTc-p, there was also an improvement in flow through microcirculation.[51,164,165]

1.3.6.3. Serum lactate

Elevated lactate levels are frequently found in critically ill patients and often correlate with disease severity. Because of its prognostic role, lactate has been widely used as a biomarker for screening, diagnosis, risk stratification, and monitoring in critically ill patients. Moreover, lactate levels can be used for outcome prediction and as a surrogate endpoint to guide treatment.[166] The rationale for lactate monitoring in critically ill patients is based on the fact that hyperlactatemia is most often caused by tissue hypoperfusion and increased anaerobic glycolysis. Elevated lactate might also be due to increased aerobic glycolysis, i.e. pyruvate production is higher than the capacity of pyruvate dehydrogenases, which occurs as a response to cytokine release, increased circulated catecholamines, or the accumulation of leukocytes at the site of inflammation.[166] Whatever the underlying cause, early detection of hyperlactatemia has shown to be beneficial since lactate levels were strongly related to the Sequential Organ Failure Assessment (SOFA) score and outcomes in critically ill patients.[167,168] Multiple studies have evaluated the prognostic value of lactate in heterogeneous groups of critically ill patients, in the intensive care unit (ICU) and emergency departments.[169,170] Most of these studies involved patients with sepsis, trauma, shock, or severe respiratory failure. On the other hand, data on the significance of lactate monitoring in patients undergoing elective major non-cardiac surgery is scarce. It has been shown that hyperlactatemia occurs in more than a third of patients admitted to the ICU following the elective surgery.[171] Creagh-Brown et al. evaluated the effect of the peak serum lactate, in the first 24 hours of ICU admission after major gastrointestinal surgery, in a very large cohort of more than a hundred thousand patients from 249 hospitals in the United Kingdom.[172] They found that increased in-hospital mortality was associated with elevated lactate levels, with no

differences between elective and emergency surgery. Moreover, the positive linear relationship between the lactate levels and risk of mortality continued down into the normal range of lactate (<2 mmol/l). It has been demonstrated by that lactate levels measured 12 hours after ICU admission could discriminate between survivors and nonsurvivors in a group of high-risk, hemodynamically stable surgical patients.[173] Furthermore, persistent hyperlactatemia in the nonsurvivors at 48 hours correlated with a poor clinical outcome. These findings are attributed to a continuous and inadequate resuscitation that resulted in occult hypoperfusion. The assumption that hyperlactatemia results from oxygen debt is the ground for „lactate-guided" resuscitation protocols. However, not all studies showed good results with these protocols.[174] Postoperative hyperlactatemia may be due to different etiologies and measures that only target tissue hypoxia to resolve hyperlactatemia may yield unsatisfactory results. Increased serum lactate concentration after the elective surgery may be due to a local ischemia inherent in the surgical procedure, such as the pringle maneuver during hepatic resection. Early postoperative causes of hyperlactatemia may be the awakening from anesthesia, pain, and hypothermia with a resultant increase in the endogenous catecholamines. Intraoperative and postoperative catecholamine administration may also lead to hyperlactatemia.[175] It is therefore unlikely that the interventions aimed at increasing oxygen delivery can resolve the hyperlactatemia that arises in response to marked surgical stress, postoperative pain, or hypothermia. Whatever the underlying cause, elevated serum lactate levels on ICU admission following surgery should prompt clinicians to analyze all the possible etiologies and undertake various measures to control hyperlactatemia early.

1.3.6.4. Central venous oxygen saturation ($S_{cv}O_2$)

Mixed venous oxygen saturation (S_vO_2) represents the fraction of oxygenated hemoglobin in the pulmonary artery and it serves as an indicator of the global oxygen supply (DO_2) to oxygen consumption (VO_2) relationship. Since its measurement requires pulmonary artery catheter in situ which is rarely used nowadays during abdominal surgery, a central venous oxygen saturation ($S_{cv}O_2$) as its surrogate measured in the superior vena cava is a frequently used parameter to estimate global VO_2/DO_2 ratio. Normally, $S_{cv}O_2$ is about 2-3% lower than S_vO_2 , but it has been shown that they are highly correlated and change simultaneously across a wide range of DO_2/VO_2 ratios.[176,177] The normal value of $S_{cv}O_2$ is around 70-75% and it reflects the relationship of oxygen delivery and consumption of the upper part of the body.[178] This value is under normal conditions lower than S_vO_2 mainly due to the high oxygen

extraction in the brain compared to that in the splanchnic region. Factors that influence $S_{cv}O_2$ are cardiac output (CO), hemoglobin level, arterial oxygen saturation (SaO_2) and oxygen consumption.[179] Oxygen extraction ratio (O_2ER) which is a quotient of tissue oxygen consumption and supply (VO_2/DO_2) directly influences $S_{cv}O_2$.[180]

Since $O_2ER = \frac{VO2}{DO2}$, where:

$DO_2 = CO \times (Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2)$,

and $VO_2 = CO \times ((Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2) - (Hb \times 1.34 \times S_{cv}O_2 + 0.003 \times PcvO_2)$

(CO-cardiac output; Hb-hemoglobin concentration; SaO_2 –arterial oxygen saturation; PaO_2 – arterial partial pressure of oxygen; $S_{cv}O_2$- central venous oxygen saturation; $PcvO_2$-central venous partial pressure of oxygen)

It can easily be demonstrated that: $O_2ER = \frac{SaO2 - ScvO2}{SaO2}$

If we approximate that in a healthy individual SaO_2 is 1, the relation of $S_{cv}O_2$ to VO_2/DO_2 ratio becomes clear: $O_2ER = 1 - S_{cv}O_2$.[180]

Clinical situations where $S_{cv}O_2$ is higher than S_vO_2 are general anesthesia and traumatic brain injury, because of depressed cerebral metabolism and reduced oxygen extraction.[179] Different types of shock, characterized by a diversion of blood from splanchnic circulation and increased oxygen extraction cause a decreased inferior vena cava saturation, thereby lowering S_vO_2.[176]

It has been shown by many observational studies that low perioperative $S_{cv}O_2$ was independently associated with complications in high-risk patients after major non-cardiac surgery.[181,182] Several randomized trials aiming to improve oxygen delivery/consumption balance in high-risk surgical patients, with a goal-directed strategy using $S_{cv}O_2$ as an endpoint were able to demonstrate that this approach was associated with more interventions, more fluid boluses and a higher need for transfusion.[183,184] However, it resulted in less organ dysfunction, fewer complications, and better survival. Significant fluctuations in $S_{cv}O_2$ occur after major abdominal surgery, and a sudden drop can be observed particularly during the first postoperative hour.[184] This phenomenon can be attributed to an increased brain oxygen consumption during awakening from anesthesia, but also to hemodilution caused by aggressive fluid resuscitation leading to hemoglobin drop.[179] A recent animal study has shown that $S_{cv}O_2$ as a reflection of VO_2/DO_2 ratio during isovolemic anemia can be used as a

transfusion threshold better than hemoglobin level.[185]

However, it should be kept in mind that a normal $S_{cv}O_2$ does not rule out ongoing tissue hypoperfusion, particularly in conditions characterized with a heterogeneity of microcirculation and mitochondrial dysfunction.[177] Perioperative hemodynamic optimization requires cautious interpretation of $S_{cv}O_2$ taking into account all possible mechanisms interfering with oxygen delivery and consumption balance.

1.3.6.5. Venous-to-arterial carbon dioxide tension difference

Venous-to-arterial carbon dioxide tension difference (ΔPCO_2, CO_2 gap) is the difference between partial pressure of CO_2 (P_vCO_2) in mixed venous blood and the partial pressure of CO_2 (P_aCO_2) in arterial blood. Since central venous PCO_2 has shown strong accordance with mixed venous PCO_2, central venous-to-arterial carbon dioxide difference, calculated after simultaneous sampling of central venous and arterial blood, is equally reliable and much easier.[186] It should be noted that PCO_2 represents partial pressure of dissolved CO_2 which is only a fraction of total CO_2 , transported in blood also as bicarbonate and bound to plasma proteins (carbamino compounds).

$$\Delta PCO_2 = PcvCO_2 - PaCO_2$$

Normally, ΔPCO_2 values are between 2 mmHg and 6 mmHg.[187] According to the Fick equation, carbon dioxide production is a product of cardiac output and the difference between venous (central venous) and arterial CO_2 content:

$$VCO_2 = CO \times (CcvCO_2 - CaCO_2)$$

(CO – cardiac output; $CcvCO_2$ – carbon dioxide content in central venous blood; $CaCO_2$ – carbon dioxide content in arterial blood)

Since the calculation of whole blood CO2 content requires the use of complicated Douglas formula, it is more convenient to represent it with a surrogate measure, PCO_2.[188] The association of PCO_2 and total CO_2 content is curvilinear and influenced by oxygen saturation, hematocrit, pH and temperature.[189] Thus, it can be assumed that:

$\Delta PCO_2 = k \times (CcvCO_2 - CaCO_2)$, where k is a constant in physiological circumstances

After substitution of venous- to-arterial CO_2 content difference with PCO_2 into a modified

Fick equation, CO_2 gap can be calculated as follows:

$$\Delta PCO_2 = VCO_2 \times k / CO$$

As shown by the equation, ΔPCO_2 is linearly influenced by carbon dioxide production (elimination) and inversely related to cardiac output. However, changes in constant k dependent on oxygen saturation, and varying CO_2 production cause different effects of cardiac output on ΔPCO_2 in normoxic and hypoxic conditions.[189]

Under normal (normoxic) circumstances, the CO_2 production during oxidative metabolism is directly related to oxygen consumption (VO_2). The relationship (ratio) of VCO_2 and VO_2 can be represented with the respiratory quotient (R) which ranges from 0.7 to 1 depending of the main energy source (lipids or carbohydrates). Decrease of cardiac output leads to a rise of venous CO_2 content and the resultant increase in ΔPCO_2 due to a stagnation phenomenon.[190] However, this relationship is curvilinear, meaning that the sharp increase in ΔPCO_2 occurs in the lowest ranges of cardiac output.[189]

The relationship between ΔPCO_2 and the cardiac output becomes more complex in hypoxic conditions when VCO_2 is not constant. Decrease in VO_2 during hypoxia is associated with reduced aerobic VCO_2 production.[191] Anaerobic generation of carbon dioxide may take place in such circumstances, but it is debatable to what extent it contributes to changes in ΔPCO_2. During tissue hypoxia with reduced blood flow, widening of CO_2 gap can be attributed mainly to the inadequacy of venous blood flow to wash tissue CO_2, and to a much lesser extent to a rise in venous CO_2 content from the increased production. On the other hand, tissue hypoxia with preserved or increased blood flow results in normal or decreased CO_2 gap.[192] Therefore, ΔPCO_2 shouldn't be regarded as a reliable indicator of tissue hypoxia.[193]

It should be kept in mind that during tissue hypoxia, a decrease in VO_2 is greater than that of VCO_2 due to some anaerobic production of carbon dioxide. The resultant change in the respiratory quotient, may, therefore, indicate the existence of tissue hypoxia.[194] The respiratory quotient (VCO_2/VO_2 ratio) is not routinely measured in everyday practice, but it can be substituted as follows:

(1) $VO_2 = CO \times (CaO_2 - CvO_2)$

(2) $VCO_2 \propto CO \times \Delta PCO_2$

It is obvious from these equations that ΔPCO_2/ Ca-vO_2 ratio may be employed as an indicator

of the global tissue hypoxia. It has been shown that $\Delta PCO_2/Ca\text{-}vO_2$ ratio was able to detect ongoing tissue hypoxia in critically ill patients with normalized cardiac output, and to predict the development of hyperlactatemia better than CO_2 gap alone, and $Ca\text{-}vO_2$ alone.[195] The other studies demonstrated that this ratio detected the VO_2/DO_2 dependency far better than $ScvO_2$ and serum lactate.[177,196] The interpretation of CO_2 gap and $\Delta PCO_2/Ca\text{-}vO_2$ ratio should consider the other hemodynamic and metabolic parameters. A resuscitation algorithm for septic shock patients was proposed, based on ΔPCO_2 and oxygen-derived parameters.[193] (Figure 1)

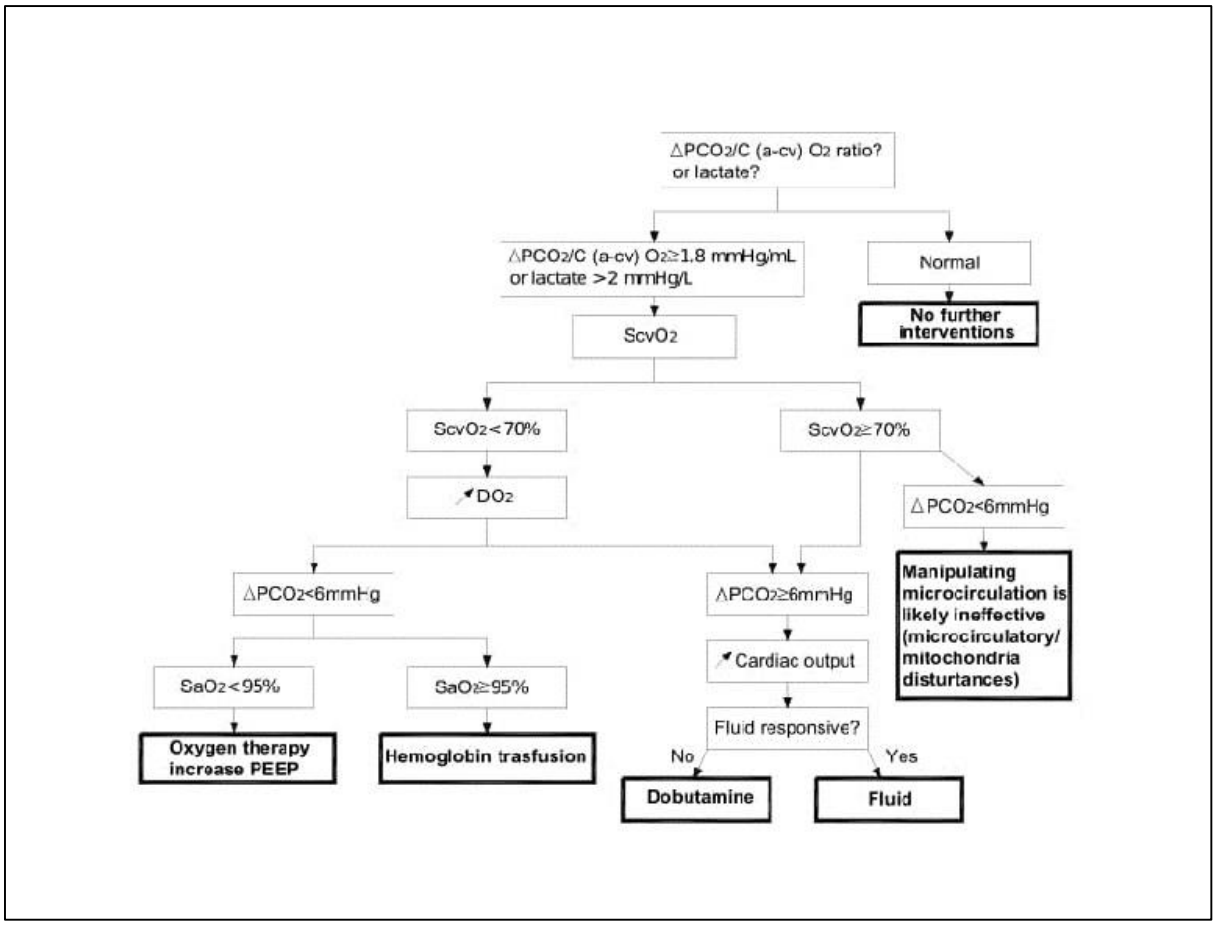

Figure 1. Protocol for hemodynamic optimisation guided by venoarterial CO_2 tension difference (Mallat, 2016)[177]

Data on the usefulness of CO_2 gap monitoring during resuscitation originate mostly from trials involving patients with septic shock or critically ill patients. There isn't much data on

the value of this parameter in high-risk surgical patients. However, there are studies that showed that an increased CO_2 gap during an early postoperative period was associated with the occurrence of postoperative complications.[197] These studies were also able to demonstrate that the CO_2 gap may serve as a complementary tool to $ScvO_2$ during goal-directed hemodynamic optimization in high-risk patients following major surgery.[198] Further studies are needed to elucidate the role of this easily obtainable parameter in guiding resuscitation during the postoperative period in an attempt to reduce the incidence of postoperative complications.

2. AIMS

1. To evaluate the incidence and type of postoperative complications after high-risk major abdominal surgery and to analyze their association with the intensive care unit and hospital length of stay, mortality, and functional activity on discharge.

2. To assess the accuracy of The Clavien-Dindo Classification (CDC) and The Comprehensive Complication Index (CCI) in evaluation of postoperative morbidity in high-risk patients undergoing major abdominal surgery and to compare the impact of the two scales on resource utilization indices.

3. To validate the use of the POSSUM scoring system in predicting postoperative morbidity and mortality after major abdominal surgery.

4. To determine the clinical relevance of markers of tissue perfusion (capillary refill, central-to-toe body temperature gradient, serum lactate, and CO_2 gap) and their repeated assessment during the first postoperative day for the occurrence of severe complications.

5. To identify preoperative, intraoperative, and early postoperative risk factors for complications after high-risk major abdominal surgery and to develop a new model for prediction of complications.

6. To validate the model on a new set of patients.

3. METHODOLOGY

This was a prospective, observational study conducted at the Clinic for Digestive Surgery, Clinical Center of Serbia, which is a tertiary care university hospital, over a two-year period (November 2016-October 2018). The study was performed in collaboration with the Georgia Tech University, M. Stewart School of Industrial & Systems Engineering, Atlanta, GA, USA. The Ethics Committee of the School of Medicine, University of Belgrade (reference number 29/XI-13) approved the study, and the informed consent was obtained from all included patients.

3.1.Patient selection

The study enrolled all consecutive adult patients (older than 18 years) if they fulfilled the following inclusion criteria:

1. Elective major or major + abdominal surgery

2. Surgery duration > 120 minutes

3. Evidence of limited physiologic reserve of one or more organs as reflected by ASA≥2 or the age >70 years

4. POSSUM predicted mortality > 3%

5. A planned postoperative ICU stay of at least 24 hours

Major and major + surgery were defined according to the criteria of Copeland et al.[116] The examples of major surgery in our cohort were: bowel resection, splenectomy, hepaticojejunostomy. Oesophagectomy, gastrectomy, hepatic and pancreatic resection, abdominoperineal resection, pelvic exenteration, and multiorgan resections were classified as major + surgery. If a patient underwent major surgery, the criterion of ASA > 2 or the age over 70 had to be met. If major + surgery was done, the ASA could be ≥ 2. All other criteria were obligatory.

The following exclusion criteria were used:

1. Emergency surgery

2. ICU admission after an operation performed in another hospital

3. Known peripheral arterial occlusive disease

4. The absence of central venous line (if it has not been inserted during the operation)

A final decision to enroll a patient was made at the end of the operation, after computation of the POSSUM predicted mortality. Along with other inclusion criteria present and nonexistence of exclusion criteria, the patient was considered a suitable candidate for further follow-up.

3.2. Data collection

Clinical and demographic data were recorded in several time points: before surgery, during the operation, on admission to the ICU (H0), twelve hours after the admission (H12), and on the first postoperative day (H24).

A questionnaire containing basic demographic and clinical data was completed before the operation. For each patient, the following preoperative data were obtained: gender, age, length of preoperative hospitalization, body mass index (BMI), ASA score, and functional status (graded as independent, partially dependent, and totally dependent). Comorbidities were recorded as present or absent. The presence of respiratory, cardiovascular (hypertension, coronary artery disease, congestive heart failure, valvular disease, other), diabetes (with or without end-organ damage), chronic renal disease, liver disease, neurologic, psychiatric, endocrine, and a systemic connective tissue disease was further noted. Obesity was defined as a BMI >30 and recorded if present, as well as malnutrition, defined as a BMI<18.5. Besides, weight loss before admission, smoking status, and alcohol consumption were also documented. A section related to chronic therapy contained the information about the number of drugs that the patient regularly takes, as well as previous corticosteroid and antibiotic therapy. Chemotherapy or radiotherapy that preceded hospital admission were also documented.

The following laboratory data were recorded:hemoglobin (g/l), white blood cell count (WBC), platelet count, albumin (g/l), urea (mmol/l), creatinin (μmol/l), INR, AST, ALT ,and CRP.

Finally, the physiologic part of the POSSUM score was calculated before the operation.

During the operation, following variables were recorded: type of surgical disease (benign or malignant), site of surgery (oesophagogastric, hepatic, pancreaticobiliary, colorectal,

multiorgan resection, and other), surgical approach (midline laparotomy, subcostal laparotomy, thoraco-abdominal, minimally invasive), duration of operation in minutes (from anesthesia induction until the skin closure), type of anesthesia (general or combined with epidural), the use of intraoperative warming, and the amount and type of administered fluids. The occurrence of intraoperative adverse events was noted too. Hypotension was defined as systolic blood pressure (SP) < 90mmHg or 20% lower than basal SP for more than 15 minutes. Hypertension as SP > 160mmHg for more than 15 minutes. Hypoxia as SpO2 < 90% measured by pulse oximetry. Hypercapnia as etCO2 > 6.0 kPa for more than 15 minutes. Bleeding and hypotension requiring vasopressor use were also considered as adverse events.

At the end of the surgery, the operative part of the POSSUM score was calculated, and finally, the POSSUM predicted morbidity and mortality for each patient.

Anesthetic drugs and techniques, intraoperative monitoring, and fluid management were selected on the discretion of the attending anesthesiologist. Different surgical teams performed the operations. Most of them are high-volume surgeons for the type of surgery they execute.

The patients were transferred to the ICU immediately after the end of surgery.

Standard hemodynamic monitoring, upon admission to the ICU, included continuous monitoring of the electrocardiogram, invasive monitoring of blood pressure, pulse oximetry, and central venous pressure (CVP). Concurrently, an arterial and venous blood sample was taken for blood gas analysis, including blood glucose and lactate concentration. (Radiometer ABL700, Radiometer Medical, Copenhagen, Denmark). The CO_2 gap was calculated as the difference between central venous partial pressure of carbon dioxide and arterial partial pressure of carbon dioxide. A skin temperature probe (Mon-A-Therm skin temperature probe, Covidien, UK) was attached to the patient's toe to measure the peripheral temperature and remained for the next 24 hours. The central temperature was obtained with an electronic epitympanic thermometer (Genius^{TM} 2 Tympanic Thermometer, Covidien,UK). A temperature gradient (deltaT) was calculated as the difference between the central and peripheral temperature (˚C). A capillary refill time (CRT) was measured simultaneously, and it was defined as the time (in seconds) needed for a nail capillary bed to regain its color after the pressure was applied to a fingertip to cause blenching. All of these recordings were done within the first 10 minutes after the admission to the ICU.

Twelve hours later (H12) all measurements were repeated to obtain data on: heart rate (HR), systolic pressure (SP), mean arterial pressure (MAP), CVP, pH, base excess (BE), arterial partial pressure of oxygen (p_aO_2), CO_2 gap, anion gap (AG), lactate concentration, CRT, and deltaT.

On the first postoperative day (H24) we collected data on vasopressor use, transfusion, a total amount of intravenous fluids for the 24-hour period, urine output, and output via abdominal or thoracic drains. Fluid balance was calculated as a difference between the amount of infused fluids and output by urine and drains for the 24 hours, starting from the onset of surgery. Laboratory analyses included the same measurements as preoperatively. We used data from the last 24 hours to calculate the Simplified Acute Physiologic Score (SAPS II) for each patient.

Since this was not an interventional study, patients were treated according to the local practice during their ICU stay. They were monitored and resuscitated to achieve usual hemodynamic goals and the target values were as follows: mean arterial pressure (MAP) of 65mmHg, central venous oxygen saturation ($S_{cv}O_2$) of 70%, urine output of 0.5-1.0 ml/kg/h, and hematocrit (Hct) of 25%. No specific algorithm was used to achieve these hemodynamic goals and laboratory values, and the use of intravenous fluids, vasopressors, inotropes, diuretics, antihypertensives, and packed red blood cells (PRBC) was guided by the assessment of the attending intensivist. Results of the assessment of peripheral perfusion (CRT, deltaT, CO_2 gap, and lactates) were not directly used to guide patient management at the ICU.

3.3.Follow-up

Patients were followed during their ICU stay and after transfer to the surgical ward for the occurrence of postoperative complications. All complications (medical and surgical) were recorded as well as their treatment.

A complication was defined as „any deviation from the normal postoperative course“ including asymptomatic complications.[20] A clear distinction was made from sequela that is inherent to the procedure or „failure to cure“ situation. These were not classified as complications.

More specifically, we used the European Perioperative Clinical outcome (EPCO) definitions of perioperative outcome measures, issued by the European Society of Anaesthesiology –

European Society of Intensive Care Medicine (ESA-ESICM) joint task force, to define each medical postoperative complication.[199] To define anastomotic leak we used the proposed definitions of the relevant International Study Groups for different fields of digestive surgery.[200,201]

According to the treatment applied, each complication's severity was classified with appropriate Clavien-Dindo (CD) grade. The highest CD grade was finally retained and assigned to the patient.

Patients were followed during the entire hospitalization, until discharge from the hospital or death, or if the readmission occurred within the 30 days after the index surgery.

To assess the impact of complications on a patient-centered outcome, we estimated the functional capacity on discharge with one of three grades: independent, partially dependent (walks with assistance), or totally dependent (bedridden). We also recorded the discharge location (home or other institution).

Hospitalization indices that were documented on discharge were: ICU length of stay (LOS), postoperative LOS, and a total hospital LOS.

Following discharge, we entered CD grade of every single complication that an individual patient developed into an online database created on the website www.assessurgery.com, to calculate the Comprehensive Complication Index (CCI) per patient. The CCI®-calculator is a registered trademark and is owned by the University of Zurich.

3.4.Validation of the POSSUM and the P-POSSUM score

For each patient Physiologic and Operative Score were derived using data collected preoperatively and at the end of the operation. Predicted mortality and morbidity were calculated using logistic regression equation as follows:

$$p = \frac{e^y}{1+e^y}$$

where p is predicted mortality or morbidity and y is the linear combination of predictors.

For POSSUM morbidity: y= -5.91+(0.16 x Physiologic Score) + (0.19 x Operative Score);

For POSSUM mortality: y= -7.04 + (0.13 x Physiologic Score) + (0.16 x Operative Score)

For P-POSSUM mortality: y= -9.37 + (0.19 x Physiologic Score) + (0.15 x Operative Score)

The ability of the scores to predict morbidity and mortality were tested through three characteristics: discrimination, the observed to expected mortality (morbidity) ratio (O:E ratio), and calibration.

Discrimination of the models was assessed by the area under a receiver operating characteristic (ROC) curve. A traditional academic scale was used to classify the area under the curve (AUC) and assess the performance of the test (< 0.6 – F (failed); 0.6-0.7 – D (poor); 0.7-0.8 – C (fair); 0.8-0.9 – B (good); 0.9-1.0 – A (excellent)).

We split patients into 4 groups according to the predicted risk of the outcome (death, complication). Expected number of deaths (or patients with complications for POSSUM morbidity) for each risk group was calculated by multiplying the number of patients in a group with the predicted average risk in that group. The ratio of observed to expected (O:E) outcome (death or complication) was then calculated for each risk band and for the entire cohort.

Calibration of the model was assessed by the Hosmer-Lemeshow (HL) test, to calculate HL statistic and the p-value. The Hosmer-Lemeshow statistic is calculated using the formula given below:

$$H=\sum_{q=1}^{Q}\frac{(\text{Observed.1-Expected.1})^2}{\text{Expected.1}}+\frac{(\text{Observed.0-Expected.0})^2}{\text{Expected.0}},$$

where Q is the total number of probability intervals. We compared the computed Hosmer-Lemeshow statistic to a chi-square distribution with Q-2 degrees of freedom (DF) to calculate the p-value. Poor calibration was considered when $p \leq 0.05$.

3.5. Development of a model for prediction of complications

Model development procedure consisted of first selecting predictors from 107 candidate covariates, then fitting the logistic regression model on the training data, and last rounding the model coefficients to the closest integers or other simpler numbers. The finalized model was both validated on the training set and a testing data set.

3.5.1.Variable selection

Variable selection was challenging in this study. The challenges included: 1) The covariates could be intuitively divided into three groups according to the time when they were measured

or collected: preoperative, intraoperative, and postoperative. Ideally, we wanted to select predictors from all of the three groups to take into account patients' conditions at all times; 2) Forty-nine out of 206 patients didn't have all of the 107 covariates, and therefore we could not simply delete those with missing data. To solve these challenges, we conducted variable selection within each group of covariates and then combined them together. Besides, median imputation was used in dealing with missing data.

The procedure of variable selection within each covariate group (Preoperative, Intraoperative, and Postoperative) was in order of the following three steps:

- Step 1: We compared candidate covariates across patients with and without complications, and selected the ones that were significantly different across those two groups. The numeric variables were compared using Mann Whitney Wilcoxon test and the Student's t-test, and categorical variables were compared based on chi-square test. P value less than 0.05 was considered as being significant.
- Step 2: After filling in the missing data with column median, we checked the correlations of the covariates selected from step 1. Selection among the highly correlated ones (correlation coefficient >=0.6) was based on clinical interpretations and domain knowledge.
- Step 3: Among the covariates from step 2, further conducted variable selection was based on statistical algorithms, LASSO or stepwise regression.

After within-group selection, we combined the selected covariates from each group, and then applied statistical algorithms (LASSO or stepwise regression) to determine the final predictors.

Specifically, a Lasso logistic regression model aims to minimize the sum of the negative log-likelihood function and the L_1 norm scaled by a tuning parameter λ:

$$-\sum_{i=1}^{N}(y_i \log(\hat{p}_i) + (1-y_i)\log(1-\hat{p}_i)) + \lambda \sum_{j=0}^{p}|\beta_j|,$$

where $\hat{p}_i = \hat{P}(y_i = 1) = \frac{1}{1+e^{-(\beta_0+\beta_1 X_{i1}+\cdots+\beta_p X_{ip})}}$, y_i is the binary outcome (either 0 or 1), p is the total number of covariates, β_0 is the intercept, and $\beta_j's$ (j > 0) are the coefficients of the covariates. The parameter λ is a tuning parameter controlling the extent of the shrinkage. The

result is an estimate of the β coefficients, with several coefficients potentially shrunk to zero. This coefficient shrinkage is the mechanism by which covariates selection occurs, with those covariates with zero coefficients being removed from the model. Larger tuning parameter λ will lead to less selected variables, and the value of λ will be determined by the following cross-validation procedure:

1. Set up a lambda candidate sequence;
2. For each lambda in the sequence, conduct a 10-fold cross validation, and calculate the mean cross-validated area under curve (AUC);
3. Repeat step 2 for 100 times and calculate the averaged "mean cross-validated AUC" for each lambda;
4. Select the best lambda to be the one corresponding to the largest averaged "mean cross-validated AUC".

These procedures in Lasso have been applied to select the covariates within each group (preoperative, intraoperative, …etc). The lambda candidate sequence was set to be from 0.001 to 0.1, with a step size 0.001. After within-group selection, the selected covariates from each group were combined, and the above Lasso procedures repeated to select the final predictors.

Lasso selected variables were finally used to build logistic regression model to predict complication occurrence.

Logistic regression model was fitted on the training data to predict the probability of developing a complication. The model has the form:

$$\log\frac{\hat{p}_i}{1-\hat{p}_i} = \hat{\beta}_0 + \hat{\beta}_1 X_{i1} + \cdots + \hat{\beta}_q X_{iq},$$

(1)

where X_{ij} is the jth predictor of patient i, with $j = 1, \ldots, q$ and q is the total number of predictors, and $\hat{p}_i$ is the predicted probability of developing complication ($y_i = 1$). The model was fitted on training data to obtain the estimated $\hat{\beta}$ coefficients.

3.5.2.Rounding the model coefficients

In order to simplify the model and make it easier to be implemented in real life, we rounded the coefficients in the fitted logistic regression model to some simpler numbers, without sacrificing too much prediction accuracy.

3.5.3.Model validation

The predictive model has been validated on both the training set and a testing set. The testing set consisted of 60 consecutive high-risk patients included with the same inclusion criteria as for the training set. Data on these patients were prospectively collected from September 2018 to December 2018. Only variables selected in the final model were recorded. These patients were followed for complications until hospital discharge. Given each subject i, we calculated the patient's predicted probability of developing complications, i.e. $\hat{p}_i$, using equation (1). The predicted complication was then obtained by comparing that probability with cutoff 0.5. In other words, if the predicted probability was over 0.5, then the patient was predicted as having complications. The model predictive performance was measured by prediction error rate, sensitivity, specificity, positive predictive value (ppv), and AUC.

3.6.Statistical analysis

Continuous data were presented as means ± standard deviations or medians (interquartile range) and analyzed using the Student's t-test or Mann-Whitney U-test depending on the normality of data distribution. Kolmogorov-Smirnov test was used to test the normality. Categorical data were analyzed with Chi-square or Fisher's exact test as appropriate. The differences between the grades of functional activity were tested with the Kruskal-Wallis test. A Spearman's rank test was used to asses the correlations between the CCI and the CDC, and to calculate the correlation coefficients of the two scales with the number of complications, ICU length of stay (LOS), postoperative LOS, hospital LOS, and the prolonged LOS. Correlation coefficients (r_s) of 0.10-0.29 ;0.30-0.49; and 0.5-1.0 were considered weak, moderate, and strong correlation, respectively. William's modification of Hotelling's test of equality of dependent correlation coefficients was used to test the difference between correlation coefficients of the CCI and the CDC with the above-listed variables.

To evaluate the validity of the POSSUM and the P-POSSUM for prediction of complications, ROC curve analysis was used to test the discrimination of the models. To test the difference between observed and expected morbidity and mortality, the Hosmer-Lemeshow test was applied as previously described. We considered that significant difference was present suggesting poor calibration if the p value was < 0.05.

To test the change of perfusion parameters over time Wilcoxon signed rank test was used. Univariate logistic regression was used to determine the significant predictors of the CCI>50.

Predictors with p values < 0.1 were entered in a multivariate analysis to determine predictors independently associated with the CCI>50. Odds ratios and 95% confidence intervals were calculated.

Lasso and stepwise algorithms were used to select variables and then fit the logistic regression model for the prediction of complications. The tunning parameter lambda and the final model were selected to have a large area under curve (AUC) but at the meantime keep the reasonable clinical explanations. 10-fold cross-validation was used for within sample validation of the model. Mean error rate, sensitivity, specificity, AUC were calculated for each testing set and then averaged across the testing data set. The error statistics from each cross-validation fold were further averaged. The model was validated in the new sample of patients. The area under curve and error statistics were calculated.

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk,NY), MedCalc, Version 18.11.6., and RStudio Version 1.1.453.

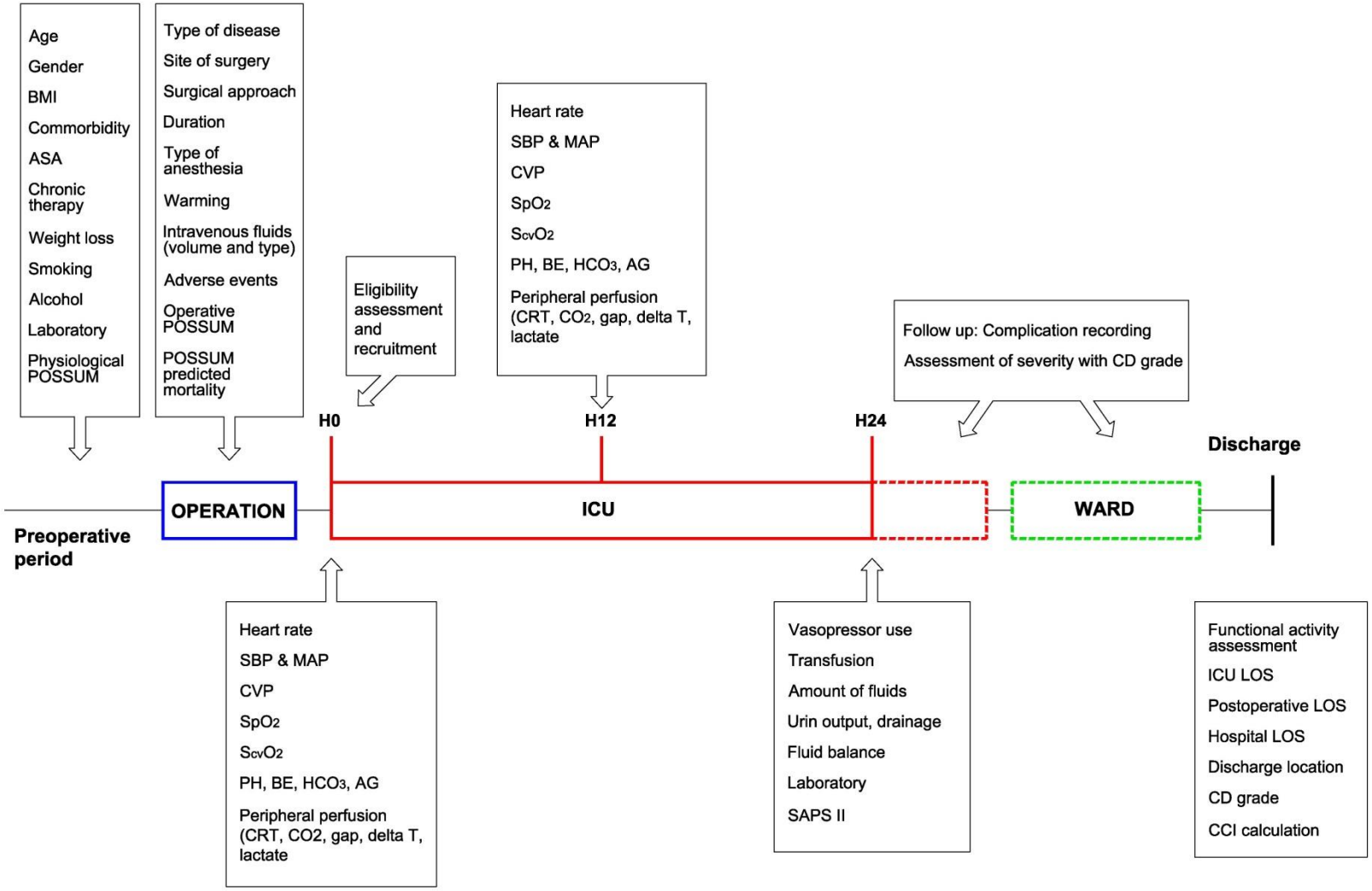

Figure 2. Study workflow; BMI-body mass index; SBP-systolic blood pressure; MAP-mean arterial pressure; CVP-central venous pressure; SpO2- arterial oxygen saturation; ScvO2- central venous oxygen saturation; BE-base excess; AG-anion gap; CRT-capillary refill time; delta T-central-to-toe temperature difference,; SAPS II – Simplified Acute Physiology Score; LOS – length of stay; CD – Clavien Dindo Classification; CCI- Comprehensive Complication Index

4. RESULTS

4.1.Demographic and clinical characteristics of the study cohort

During the study period, 4458 patients were operated in our hospital. Out of 856 patients admitted to the ICU following surgery and were screened for eligibility, a total of 206 patients met the inclusion criteria and were thus eligible for further analysis (Figure 3)

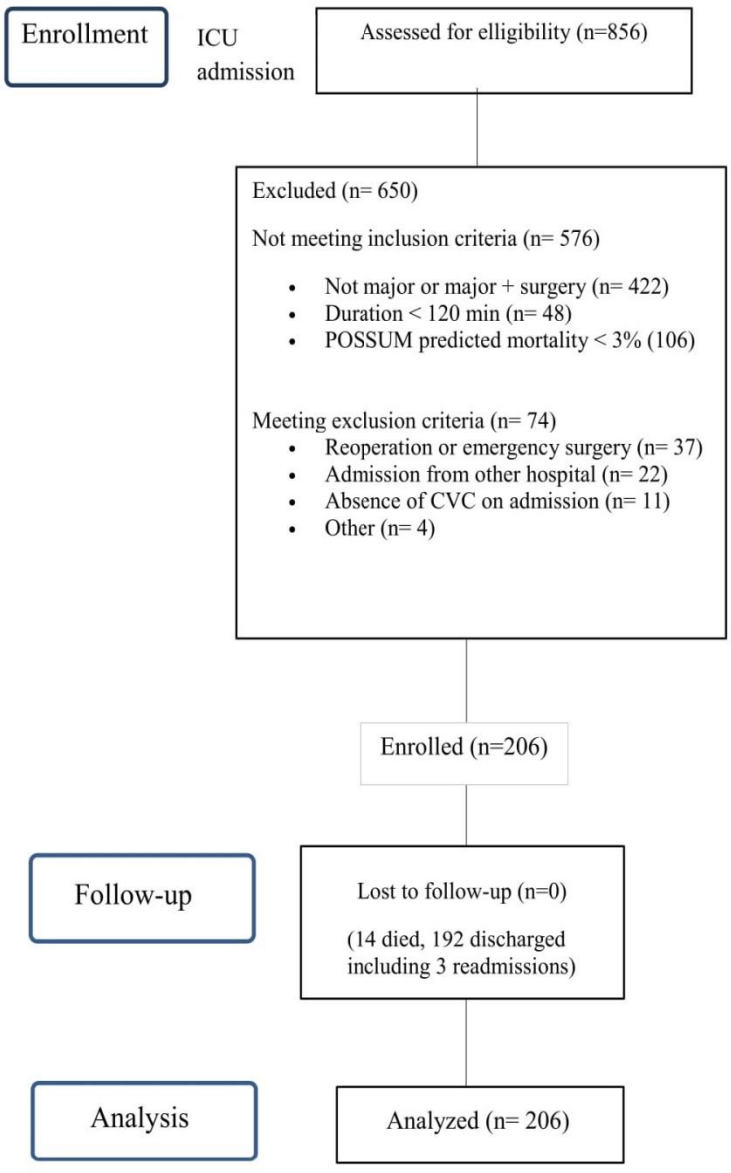

Figure 3. Flowchart of the study selection process

Baseline clinical and demographic characteristics of the study patients are summarized in table 12. One hundred thirty-three (64.6%) patients were male. Mean age of the patients in the cohort was 63.9 ± 11.8 years. Majority of patients were operated for cancer (188; 91.3%) and 33 (16.0%) of them had metastatic cancer. Comorbidity was present in 154 (74.7%) of patients, of whom 103 (50.0%) had ASA score 3 (89; 43.2%) or 4 (14; 6.8%). The overall POSSUM predicted morbidity was 57.9 % [38.0-76.3], while the POSSUM predicted mortality for the cohort was 13.2% [7.2-24.0]. Patients spent on average 8.0 [4.0-15.0] days in hospital prior to the scheduled operation.

Table 12. Baseline characteristics of the patients and preoperative laboratory findings

Characteristic	**Total (N=206)**	**Complications**		**p value**
		No (N=81)	Yes (N=125)	
Age (years)	63.9±11.8	62.8 ± 12.8	64.6 ± 11.2	0.292
Male gender	133 (64.6)	50 (61.7)	83 (66.4)	0.552
BMI	24.4 [22.1-27.3]	24.3 [21.3-26.8]	24.5 [22.1-27.7]	0.179
Functional status (< 4 METs)	31 (11.7)	11 (13.6)	20 (16.0)	0.694
Commorbidity	154 (74.7)	60 (74.1)	94 (75.2)	0.871
ASA				0.068
2	103 (50.0)	48 (59.3)	55 (44.0)	
3	89 (43.2)	27 (33.3)	62 (49.6)	
4	14 (6.8)	6 (7.4)	8 (6.4)	
Cancer	188 (91.3)	76 (93.8)	112 (89.6)	0.334
Metastatic cancer	33 (16.0)	9 (11.1)	24 (19.2)	0.122
Cigarette smoker	57 (27.7)	22 (27.2)	35 (28.5)	0.874
Alcohol consumption	79 (38.3)	29 (35.8)	50 (40.6)	0.557
Obesity	19 (9.2)	4 (4.9)	15 (12.0)	0.137
Malnutrition	21 (10.2)	11 (13.6)	10 (8.0)	0.240
Unintentional weight loss	69 (33.5)	25 (30.9)	44 (35.8)	0.546
Haemoglobin (g/l)	123.6±20.8	130.2±17.8	119.2±21.5	<0.001
WBC (10^9/l)	6.6 [5.0-7.5]	6.2 [5.0-7.7]	6.1 [4.8-7.1]	0.359
Platelets (10^9/l)	229.0 [177.0- 299.0]	244.0 [187.0-289.0]	222.0 [175.0-305.0]	0.375
Creatinine (μmol/l)	77.0 [60.0-89.0]	78.0 [64.0-88.0]	74.0 [58.2-92.5]	0.892
Urea (mmol/l)	6.3 [4.2-6.9]	5.7 [4.0-7.3]	5.3 [4.4-6.8]	0.625
Bilirubine (μmol/l)	12.6 [8.3-20.1]	13.1 [7.7-17.6]	12.6 [8.5-20.1]	0.520
Albumin (g/l)	36.8 ± 6.0	39.4 ± 4.3	35.1 ± 6.4	<0.001
CRP (mg/l)	9.9 [3.0-33.0]	5.9 [2.7-5.9]	11.2 [3.1-43.7]	0.025
AST (IU/l)	20.0 [16.0-32.0]	20.0 [15.0-32.0]	20.0 [17.0-29.2]	0.526
ALT (IU/l)	17.0 [12.0-32.0]	16.0 [11.0-25.0]	19.0 [13.7-33.2]	0.419
POSSUM predicted morbidity (%)	57.9 [38.0-76.3]	41.6 [30.6-61.5]	65.7 [50.0-80.9]	<0.001
POSSUM predicted mortality (%)	13.2 [7.2-24.0]	8.1 [5.6-14.7]	16.5 [10.7-27.9]	<0.001
Preoperative LOS(days)	8.0 [4.0-15.0]	5.0 [4.0-14.0]	9.0 [6.0-16.0]	0.002

Data are presented as mean ± standard deviation, number (%), or median [IQR]; BMI- Body mass index (kg/m^2); ASA- American Society of Anesthesiologists;WBC-white blood cell count; CRP-C-reactive protein; AST – aspartate aminotransferase; ALT- alanin aminotransferase; POSSUM-Physiological and operative severity score for enumeration of mortality and morbidity; LOS – length of stay

One hundred and twenty five (60.7%) patients developed at least one complication, including death in 14 (6.8%) patients. The remaining 81(39.3%) patients had no complications. Compared to patients without complications, patients with complications had significantly lower preoperative haemoglobin (130.2±17.8 g/l vs 119.2±21.5 g/l, p<0.001) and albumin levels (39.4 ± 4.3 g/l vs 35.1 ± 6.4 g/l, p<0.001), but a higher baseline CRP value (11.2 mg/l [3.1-43.7] vs 5.9 mg/l [2.7-5.9], p=0.025). The group of patients who developed complications had a higher POSSUM predicted morbidity (65.7 % [50.0-80.9] vs 41.6 % [30.6-61.5], p<0.001) and mortality (16.5 % [10.7-27.9] vs 8.1% [5.6-14.7], p<0.001), and a longer preoperative LOS (9.0 days [6.0-16.0] vs 5.0 days [4.0-14.0], p=0.002)

4.1.1 Comorbidities in patients with and without complications

Chronic health characteristics of study patients are presented in table 13. The most frequently encountered comorbidities were cardiovascular diseases (other than hypertension,i.e. coronary artery disease, valvular disease, cardiomyopathy, arrhythmias – 73 patients (35.4%)) and hypertension (64 patients (31.1%)). Patients with complications were more frequently diabetic (28 (22.4%) vs 5 (6.2%), p=0.002) and received more frequently a chronic corticosteroid treatment (7 (5.6%) vs 0 (0.0%), p=0.044).

Table 13. Patient's comorbidities and chronic therapy

Variable	Total (N=206)	Complications		p value
		No (N=81)	Yes (N=125)	
Commorbidity				
Hypertension	64 (31.1)	23 (28.4)	41 (32.8)	0.540
Cardiovascular	73 (35.4)	31 (38.3)	42 (33.6)	0.552
Pulmonary	30 (14.6)	11 (13.6)	19 (15.2)	0.841
Diabetes	33 (16.0)	5 (6.2)	28 (22.4)	0.002
Chronic renal disease	22 (10.7)	7 (8.6)	15 (12)	0.497
Liver disease	36 (17.5)	13 (16.0)	23 (18.4)	0.711
Neurologic disease	11 (5.3)	4 (4.9)	7 (5.6)	1.000
Psychosis	2 (0.97)	1 (1.2)	1 (0.8)	1.000
Endocrine disease	23 (11.2)	10 (12.3)	13 (10.4)	0.658
Other	18 (8.7)	6 (7.4)	12 (9.6)	0.586
Chronic therapy	138 (76.0)	58 (71.6)	80 (64.0)	0.290
Number of drugs	2.0 [0.0-4.0]	2.0 [0.0-3.0]	2.0 [0.0-4.0]	0.984
Corticosteroids	7 (5.6)	0 (0)	7 (5.6)	0.044
Chemotherapy	18 (8.7)	4 (4.9)	14 (11.2)	0.137
Antibiotic within 7 days	38 (18.4)	19 (23.5)	19 (15.2)	0.145
Physiological POSSUM	18.0 [15.0-22.0]	16.0 [14.0-20.0]	19.0 [16.0-23.0]	0.001

Data are presented as number (%) and median (IQR); POSSUM-Physiological and operative severity score for enumeration of mortality and morbidity

There were no other differences among patients with and without complications regarding preoperative health status. However, the physiological POSSUM score was significantly higher in patients who developed complications (19 [16-23] vs 16 [14-20], p<0.001).

4.1.2.Surgical and intraoperative characteristics of the study patients

Most operations were oesophagogastric (60 (29.1%); 28 esophagectomies and 32 gastrectomies) and colorectal (47 (22.8%)). There were no differences in the incidence of complications regarding the type of surgery, except the group of multiorgan resections where complications were recorded more frequently (13.6% vs 1.2%, p=0.002). Intraoperative warming was used in 104 (50.5%) patients, less frequently in patients who developed complications (44% vs 60.5%, p=0.023). Patients who developed complications, when compared to patients without complications had a longer operation (260 min [187-360] vs 210 min [137-300], p=0.002) and were more likely to receive more intraoperative fluids (4.0 l [2.5-5.7] vs 3.0 l [2.0-3.7], p<0.001). However, the amount of fluids adjusted to body weight and duration of operation (ml/kgxh) didn't differ between two groups. (10.7 ml/kgxh [8.1-16.7] vs 10.5 ml/kgxh [8.5-12.9], p=0.512). (Table 14)

Table 14. Surgical and intraoperative characteristics of the study patients

Variable	**Total (N=206)**	**Complications**		**p value**
		No (N= 81)	Yes (N=125)	
Type of surgery				
Esophago-gastric	60 (29.1)	29 (35.8)	31 (24.8)	0.116
Colorectal	47 (22.8)	20 (24.7)	27 (21.6)	0.614
Hepatic	30 (14.6)	11 (13.6)	19 (15.2)	0.841
Pancreatico-biliary	39 (18.9)	12 (14.8)	27 (21.6)	0.276
Multiorgan resection	18 (8.7)	1 (1.2)	17 (13.6)	0.002
Other	12 (5.8)	8 (9.9)	4 (3.2)	0.066
Approach				
Midline/subcostal	177 (85.9)	65 (80.2)	112 (89.6)	0.067
Thoracoabdominal	16 (7.8)	7 (8.6)	9 (7.2)	0.792
Minimaly invasive	13 (6.3)	9 (11.1)	4 (3.2)	0.037
Regional anesthesia	16 (7.8)	10 (12.3)	6 (4.8)	0.063
Advanced monitoring	13 (6.3)	4 (4.9)	9 (7.2)	0.573
Intraoperative warming	104 (50.5)	49 (60.5)	55 (44.0)	0.023
Duration of surgery (minutes)	240 [180-320]	210 [137-300]	260 [187-360]	0.002
Intraoperative fluid volume (l)	3.2 [2.2-4.8]	3.0 [2.0-3.7]	4.0 [2.5-5.7]	<0.001
Fluid volume (ml/kg/h)	10.5 [8.4-14.4]	10.5 [8.5-12.9]	10.7 [8.1-16.7]	0.512
Intraoperative adverse events	105 (51)	35 (43.2)	70 (56)	0.087

Intraoperative adverse events occurred in around half of the operations (51%). Hypertension (12.6%), bleeding (7.8%), and hypotension (6.3%) were the leading causes of intraoperative instability. (Figure 4). In 13 (6.3%) patients more than one adverse event was recorded during the operation. Although they were more likely to occur in patients with complications, the significance was not reached (56.0% vs 43.2%, p=0.087).

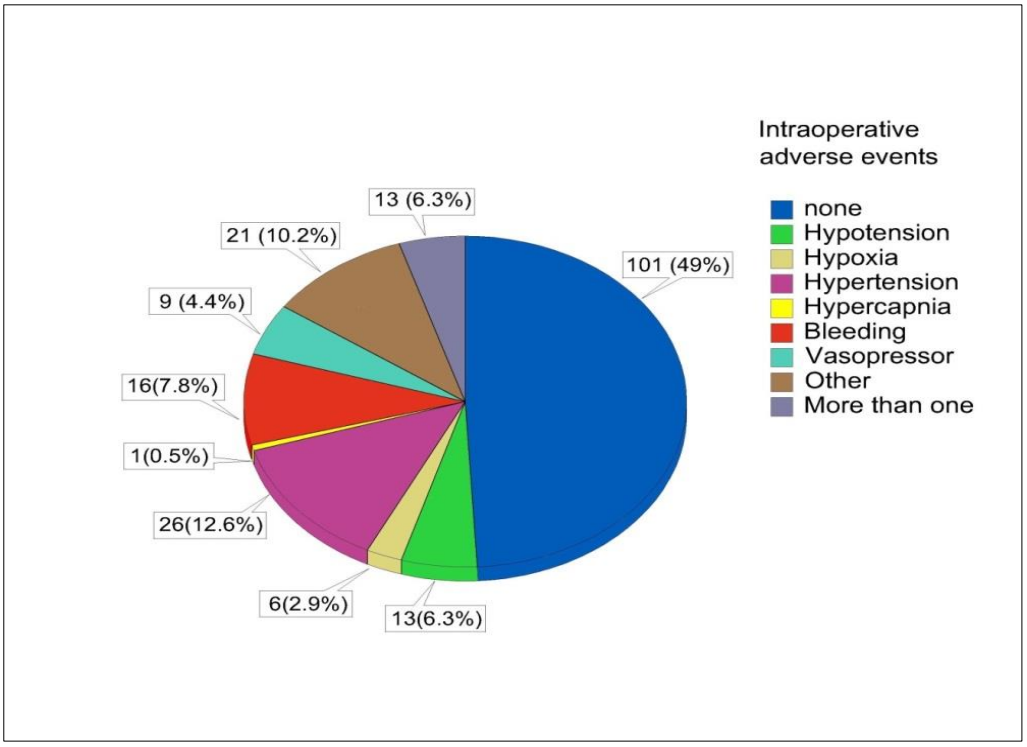

Figure 4. Intraoperative adverse events

4.1.3.Postoperative characteristics of patients on ICU admission

Postoperative characteristics of patients with and without complications on admission to the ICU are summarized in table 15**.**

On average, a mild inadvertent hypothermia was present, with no significant difference in patients with and without complications (35.6 ± 0.9˚C vs 35.8 ± 0.7˚C, p = 0.197). However, a peripheral (toe) temperature was significantly different in the two groups, resulting in a different central-to-toe temperature gradient (delta T) which was higher in patients with complications (9.0 ± 2.3˚C vs 7.7 ± 2.4˚C, p<0.001). In general, patients were normotensive on admission to the ICU with a mean MAP of 93.6 ± 18.5mmHg. Patients who developed

complications were likely to have a lower blood pressure (91.1 ± 19.2 vs 97.3 ± 16.9, p=0.016) and a higher heart rate (86 ± 7 vs 72 ± 12, p<0.001).

Table 15. Postoperative characteristics of patients on admission to the ICU

Variable	Total (N=206)	Complications		p value
		No (N=81)	Yes (N=125)	
Peripheral temperature (˚C)	27.2 ± 2.6	28.0± 2.6	26.6±2.4	<0.001
Central temperature (˚C)	35.7± 0.8	35.8 ± 0.7	35.6± 0.9	0.197
Delta T (˚C)	8.5 ± 2.4	7.7 ± 2.4	9.0 ± 2.3	<0.001
Systolic pressure (mmHg)	135.9 ± 26.3	141.2 ± 22.7	132.5 ± 27.9	0.016
MAP (mmHg)	93.6 ± 18.5	97.3 ±16.9	91.1 ± 19.2	0.016
Heart rate (bpm)	80.2 ± 17.5	71.8 ± 12.2	85.7 ± 7	< 0.001
SpO2 (%)	99 [97-100]	99 [97-100]	99 [97-100]	0.546
$S_{cv}O_2$ (%)	72.3 ± 9.7	72.3 ± 7.1	72.3 ± 11.1	0.999
pH	7.32 ± 0.07	7.34 ± 0.06	7.31 ± 0.08	<0.001
Base excess (mmol/l)	-6.2 ± 4.2	-4.2 ± 3.3	-7.5 ± 4.2	<0.001
PaCO2 (kPa)	5.1 ± 0.7	5.2 ± 0.7	5.0 ±0.7	0.015
PvCO2 (kPa)	6.1 [5.7 – 6.5]	6.2 [6.0 - 6.7]	6.1 [5.6 - 6.4]	0.004
CO_2 gap (mmHg)	8.1 ± 3.7	8.1 ± 4.1	8.1 ± 3.4	0.925
Anion gap (mmol/l)	11.7 [9.0-14.2]	11.2 [9.0-12.8]	11.8 [9.0-14.2]	0.224
Capillary refill time (s)	3.0 [2.5-4.0]	3.0 [2.5-4.0]	3.0 [2.5-4.0]	0.435
Lactate (mmol/l)	1.9 [1.2-2.5]	1.3 [1.0-2.1]	2.1 [1.4-3.2]	<0.001
Glycemia (mmol/l)	9.7 [8.1-11.2]	9.4 [8.0-11.0]	10.0 [8.1-11.5]	0.393
Intubated	140 (68.0)	93 (74.4)	49 (60.5)	0.045
Mechanical ventilation	77 (37.4)	25 (30.1)	52 (41.6)	0.141

Delta T – central-to-toe temperature gradient; MAP-mean arterial pressure; SpO2-oxygen saturation by pulse oxymetry; $ScvO_2$- central venous oxygen saturation; PaCO2 – arterial partial pressure of carbon dioxide; PvCO2- venous partial pressure of carbon dioxide; Data are presented as means ± standard deviation; medians [IQR] or number (%). P values were calculated with the Student's t-test, Mann-Whitney-Wilcoxon test or Chi-square

On admission to the ICU patients presented with a mild acidosis (pH 7.32 ± 0.07; BE - 6.2 ± 4.2 mmol/l). The acid-base disorder was more pronounced in patients with complications (pH 7.31±0.08; BE -7.5 ± 4.2 mmol/l vs 7.34 ± 0.06; -4.2 ± 3.3mmol/l, p<0.001). Compared to patients without complications, patients with complications had significantly lower both $PaCO_2$ (5.0 ± 0.7kPa vs 5.2 ± 0.7 kPa, p=0.015) and $PvCO_2$ (6.1 [5.6-6.4] kPa vs 6.2 [6.0-6.7] kPa, p=0.004). As a result, the CO_2 gap was not significantly different between them (p=0.925), though the average CO_2 gap (8.1 ± 3.7mmHg) was above the normal range. The median lactate on admission was 1.9 [1.2-2.5] mmol/l. Lactate concentration was significantly higher in patients with complications compared to patients without complications (2.1 [1.4-3.2]mmol/l vs 1.3 [1.0-2.1]mmol/l, p<0.001). Patients on admission didn't differ with regards to capillary refill time (p=0.435), glycemia (0.393), nor the rate of mechanical ventilation (p= 0.141).

4.1.4.Characteristics of patients 12 hours after the ICU admission

Twelve hours after the admission to ICU both patients' central (36.4 ± 0.6˚C) and peripheral (29.7 ± 3.9˚C) temperature increased showing no difference between patients with and without complications. Similarly, delta T decreased (6.6 ± 3.8˚C) in both groups. Though the temperature gradient was higher in patients with complications, the difference was non-significant (6.9 ± 3.9˚C vs 6.3 ± 3.7˚C, p=0.249). Compared to patients without complications, patients with complications tended to have a higher heart rate (84.0 ± 18.4 vs 76.2 ± 12.5, p<0.001) and a lower central venous oxygen saturation (71.8 ± 8.2 vs 74.4 ± 5.0, p=0.006). Patients with complications had lower pH (7.37±0.09 vs 7.40±0.06, p=0.003), more negative base excess (-4.6±6.1mmol/l vs -0.8±3.22 mmol7l, p<0.001), lower $PaCO_2$ (4.8±0.8 kPa vs 5.2±0.5 kPa , p<0.001) , lower $PvCO_2$ (5.8±0.7 vs 6.2±0.6 kPa, p=0.004) and a higher CO_2 gap (7.7 [5.7-9.2]mmHg vs 6.6 [4.1-8.7]mmHg, p=0.026).

Table 16. Postoperative characteristics of patients 12 hours after the admission to the ICU

Variable	Total	Complications		p value
		No (N=81)	Yes (N=125)	
Peripheral temperature (˚C)	29.7 ± 3.9	30.2 ± 3.68	29.4 ± 4.1	0.185
Central temperature (˚C)	36.4 ± 0.6	36.4 ± 0.5	36.3 ± 0.6	0.171
Delta T (˚C)	6.6 ± 3.8	6.3 ± 3.7	6.9 ± 3.9	0.249
Systolic pressure (mmHg)	124.6 ± 21.8	126.9 ± 17.7	123.1 ± 24.1	0.197
Heart rate (bpm)	80.8 ± 16.7	76.2 ± 12.5	84.0 ± 18.4	<0.001
SpO_2 (%)	99 [97-100]	99 [98-100]	99 [97-100]	0.768
$S_{cv}O_2$ (%)	72.8 ± 7.3	74.4 ± 5.0	71.8 ± 8.2	0.006
pH	7.38 ± 0.08	7.40 ± 0.06	7.37 ± 0.09	0.003
Base excess (mmol/l)	-3.1 ± 5.5	-0.8 ± 3.22	-4.6 ± 6.1	<0.001
$PaCO_2$ (kPa)	4.9 ± 0.7	5.2 ± 0.5	4.8 ± 0.8	<0.001
$PvCO_2$ (kPa)	5.9 ± 0.7	6.2 ± 0.6	5.8 ± 0.7	0.004
CO_2 gap (mmHg)	7.4 [5.1-9.1]	6.6 [4.1-8.7]	7.7 [5.7-9.2]	0.026
Anion gap (mmol/l)	9.7[8.3-11.1]	9.1 [7.5-10.8]	10.3 [8.7-11.5]	0.004
Capilary refill time (s)	2.5 [2.0-3.0]	2.0 [1.5-3.0]	3.0 [2.0-3.0]	0.002
Lactate (mmol/l)	1.2 [0.8-2.0]	0.9 [0.7-1.2]	1.7 [1.1-2.8]	<0.001
Glycemia (mmol/l)	8.1 [6.7-10.8]	7.5 [6.5-9.5]	8.2 [7.0-11.0]	0.009
Intubated	25 (12.6)	2 (2.5)	23 (18.5)	<0.001
Ventilation	18 (8.7)	2 (2.5)	16 (12.9)	0.010

Delta T – central-to-toe temperature gradient; MAP-mean arterial pressure; SpO2-oxygen saturation by pulse oxymetry; $ScvO_2$- central venous oxygen saturation; PaCO2 – arterial partial pressure of carbon dioxide; PvCO2- venous partial pressure of carbon dioxide; Data are presented as means ± standard deviation; medians [IQR] or number (%). P values were calculated with the Student's t-test, Mann-Whitney-Wilcoxon test or Chi-square

There were statistically significant differences 12 hours after ICU admission in anion gap (p=0.004), capillary refill time (3.0[2.0-3.0] s vs 2.0[1.5-3.0]s, p=0.002), lactate concentration (1.7 [1.1-2.8] mmol/l vs 0.9 [0.7-1.2] mmol/l, p<0.001), and glycemia (8.2 [7.0-11.0] mmol/l vs 7.5 [6.5-9.5]mmol/l, p=0.009) between patients who did and did not develop postoperative complications. Only two (2.5%) patients without complications required mechanical ventilation compared to 16 (12.9%) with complications (p=0.010). (Table 16)

4.1.5.Characteristics of patients on the first postoperative day

Characteristics of patients on the first postoperative day (24 hours after the operation) are shown in table 17.

Patients who developed complications were likely to receive more intravenous fluids (7.2 ± 2.6 l vs 5.7 ± 1.8 l, p<0.001) for the 24-hour period (including the operation), to have a higher drainage output (400[250-635] ml vs 250[150-350] ml, p<0.001), and a higher positive fluid balance (4.6 ± 2.4 l vs 3.2 ± 1.5 l, p<0.001).

Table 17. Postoperative characteristics on the first postoperative day

Variable	Total (N=206)	Complications		p value
		No (N=81)	Yes (N=125)	
Intravenous fluids (l)	6.6 ± 2.5	5.7 ± 1.8	7.2 ± 2.6	< 0.001
Diuresis (l)	1.9 [1.5-2.6]	1.8 [1.5-2.7]	2.0 [1.6-2.6]	0.654
Drainage output (ml)	300 [200-500]	250 [150-350]	400 [250-635]	<0.001
Fluid balance (l)	4.1 ± 2.2	3.2 ± 1.5	4.6 ± 2.4	<0.001
Vasopressor	21 (16.8)	0	0	<0.001
Transfusion	60 (29.1)	6 (7.4)	54 (43.2)	<0.001
Units of PRBC	0 [0-1]	0 [0-0]	0 [0-2]	<0.001
Hemostatic	11 (5.3)	3 (3.7)	8 (6.4)	0.533
Haemoglobin (g/l)	111.6 ± 17.1	117.6 ± 15.6	107.9 ± 17.0	<0.001
WBC (10^9/l)	11.3 [9.1-13.5]	11.1 [8.9-13.1]	11.4 [9.1-14.1]	0.276
Platelets (10^9/l)	209 [174-255]	221 [177-270]	209 [164-254]	0.384
Bilirubin (μmol/l)	14.9 [9.7-20.7]	11.2 [9.0-16.8]	15.3 [11.6-25.9]	<0.001
Urea (mmol/l)	4.7 [3.8-6.6]	4.5 [3.3-5.7]	5.3 [3.9-7.0]	0.013
Creatinine (μmol/l)	80.0 [64.0-97.7]	73.0 [64.0-82.0]	87.0 [64.0-104.0]	<0.001
AST (IU/l)	51.0 [23.2-140.0]	34.0 [23.0-132.5]	65.0 [23.5-166.5]	0.322
ALT (IU/l)	49.5 [15.0-159.7]	29.0 [14.0-129.7]	71.0 [18.5-171.0]	0.206
CRP (mg/l)	102.5 ± 34.2	95.7 ± 30.6	106 ± 35.7	0.054
Albumin (g/l)	31.1 ± 4.0	34.1 ± 2.5	29.2 ± 3.6	<0.001
SAPS II	19.0 [13.0-25.0]	16 [11.5-21.0]	22.5 [16.0-27.0]	<0.001

Data are presented as mean ± standard deviation, number (%), or median [IQR]; PRBC-packed red blood cells; WBC-white blood cells; AST – aspartate aminotransferase; ALT- alanin aminotransferase; CRP-C-reactive protein; SAPS II – Simplified Acute Physiology Score

Vasopressor use was recorded only in patients with complications (21 (16.8%) vs 0, p < 0.001).

Patients with complications had lower haemoglobin level (107.9 ± 17.0 g/l vs 117.6 ± 15.6 g/l, p<0.001) and were more likely to receive a transfusion (54 (43.2%) vs 6 (7.4%), p< 0.001). The number of blood units received by patients with subsequently complicated postoperative course was significantly higher. (Figure 5)

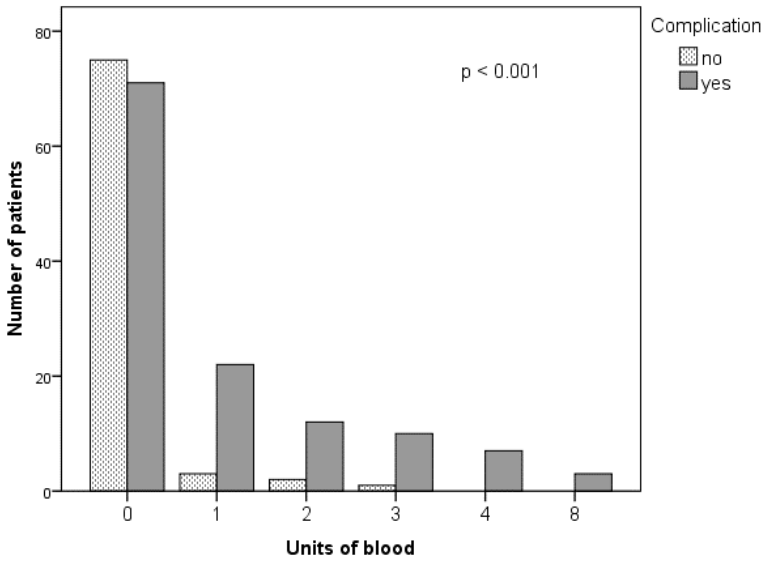

Figure 5. Number of units of PRBC received by patients with and without complications; p-value indicates the significance of difference between the patients with and without complications (Fisher's exact test)

Postoperative laboratory data revealed that bilirubin level was higher (15.3 [11.6-25.9] μmol/l vs 11.2 [9.0-16.8] μmol/l, p<0.001), as well as the creatinine level (87.0 [64.0-104.0] μmol/l vs 73.0 [64.0-82.0] μmol/l, p<0.001), whereas the serum albumin concentration was significantly lower (29.2 ± 3.57 g/l vs 34.1 ± 2.53 g/l, p<0.001) in patients with complications. The median SAPS II score was 19 [13-25], and, as expected, higher in patients in whom complications occurred (22.5 [16.0-27.0] vs 16 [11.5-21.0], p<0.001).

4.1.6. Type of postoperative complications

One hundred twenty-five patients (60.7%) developed a total of 424 postoperative complications. The most common complications encountered during the postoperative period were infections (72/424; 16.9%), followed by hematologic (69; 16.3%), cardiovascular (69;

16.0%), and pulmonary (65; 15.2%) complications. (Table 4) Anastomotic leak, a surgical complication in narrow context, occurred in 22 (5.2%) patients.

Table 18. Type of postoperative complications

Type of complication	***N (%)***
Infection	
SSI – superficial	23 (5.4)
SSI – organ/space	24 (5.7)
CVC associated blood stream infection	3 (0.7)
Urinary tract infection	7 (1.6)
Clostridium difficile infection	9 (2.1)
Unknown origin	6 (1.4)
Anastomotic leak	22 (5.2)
Bleeding/hematoma	11 (2.6)
Gastrointestinal	
Paralytic ileus	16 (3.8)
Nausea/vomiting	8 (1.9)
Non-infectious diarrhea	12 (2.8)
Liver disfunction	9 (2.1)
Cardiovascular	
Ischemia	12 (2.8)
Arrhythmia	36 (8.5)
Pulmonary embolism	4 (0.9)
Pulmonary edema	6 (1.4)
Cardiac arrest	2 (0.5)
Deep venous thrombosis	8 (1.9)
Pulmonary	
Pneumonia	18 (4.2)
Pneumothorax	2 (0.5)
Atelectasis	12 (2.8)
Pleural effusion	20 (4.7)
Bronchospasm	4 (0.9)
ARDS	3 (0.7)
Other	6 (1.4)
Acute kidney injury	10 (2.4)
Neurologic	
Stroke	5 (1.2)
Confusion/Delirium	16 (3.8)
Other	4 (0.9)
Hematologic	
Coagulopathy	16 (3.8)
Anemia	48 (11.3)
Other	5 (1.2)
Metabolic	25 (5.9)
Pain	12 (2.8)
Total	424 (100)

SSI-surgical site infection; CVC-central venous catheter; ARDS-acute respiratory distress syndrome; Data are presented as number of complications (percentage)

4.1.7. Length of ICU and hospital stay

The median ICU-LOS for the entire cohort was 2.0 days [1.0-5.0]. Ninety-four (45.6%) patients spent only one day in the ICU. (Figure 6) Postoperative LOS and total hospital LOS were 14.0 days [9.0-20.0] and 25.0 days [16.0-35.5].(Figures 7 and 8)

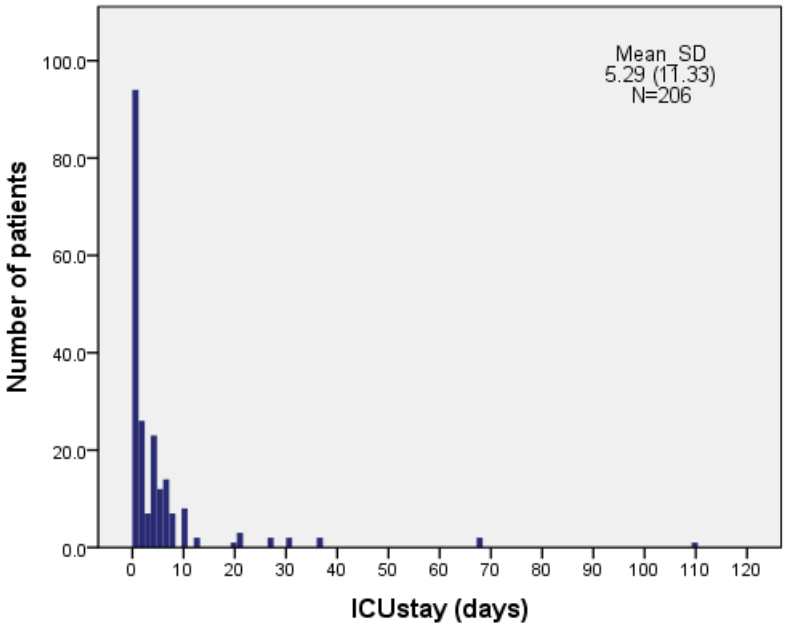

Figure 6. Histogram of ICU length of stay

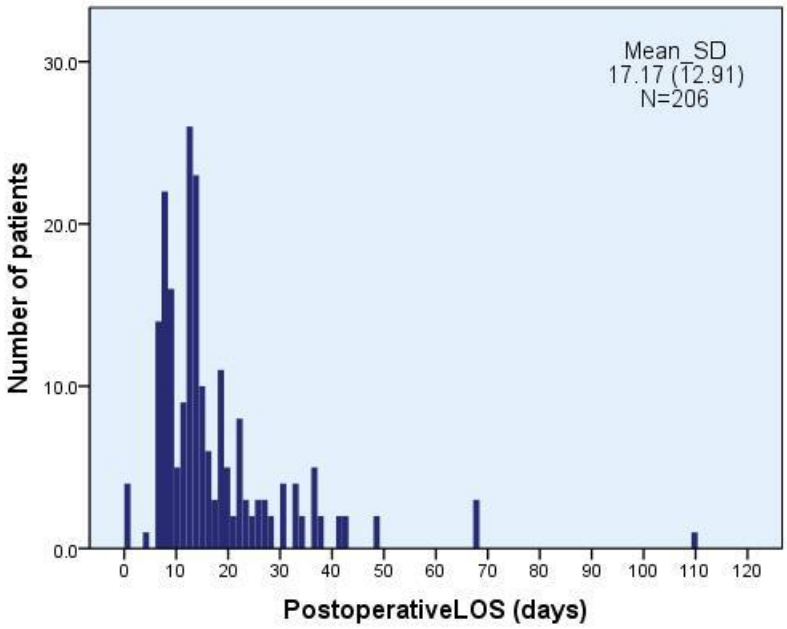

Figure 7. Histogram of postoperative length of stay

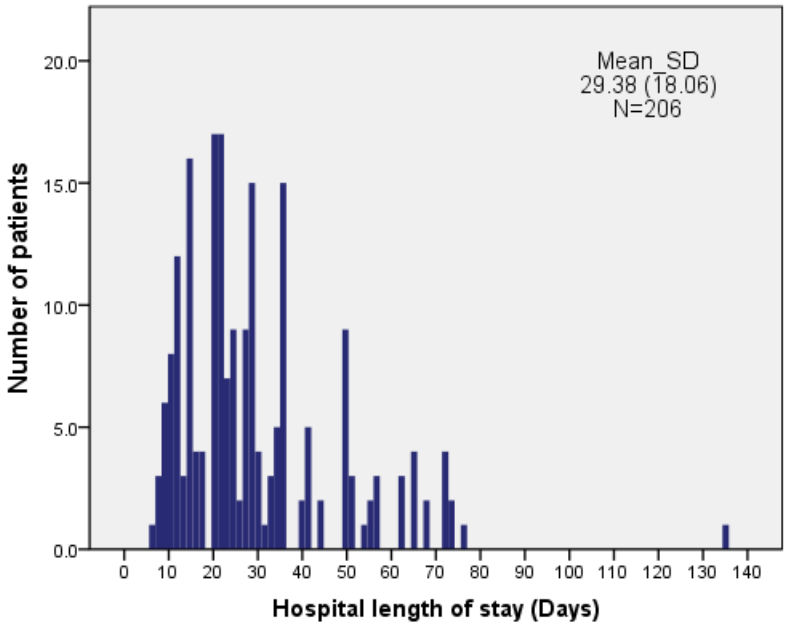

Figure 8. Histogram of hospital length of stay

A prolonged LOS was considered if it was longer than the median of the specific parameter. Therefore, a prolonged ICU-LOS, prolonged postoperative LOS, and prolonged hospital LOS were considered if they were longer than 2, 14, and 25 days, respectively. As expected all indicators of hospitalization were significantly greater in patients with complications. (Table 19, Figure 9-11) A prolonged ICU LOS was recorded in 75 (60%) patients with complications and in 11 (13.6%) patients without complications ($p < 0.001$). Higher proportion of patients with complications also had the prolonged postoperative LOS (61.6% vs 11.6%, $p<0.001$) and the prolonged hospital LOS (62.4% vs 25.9%, $p<0.001$) compared to patients with uneventful postoperative course.

Table 19. ICU LOS, postoperative LOS, and hospital LOS in patients with and without complications

Variable	Total (N=206)	Complications		p value
		No (N=81)	Yes (N=125)	
ICU LOS (days)	2.0 [1.0-5.0]	1.0 [1.0-1.0]	4.0 [2.0-7.0]	< 0.001
Postoperative LOS (days)	14.0 [9.0-20.0]	9.0 [8.0-12.0]	17.5 [13.2-27.0]	< 0.001
Hospital LOS (days)	25.0 [16.0-35.5]	16.0 [12.0-27.0]	29.0 [21.0-47.7]	< 0.001
Prolonged ICU LOS	86 (41.7)	11 (13.6)	75 (60.0)	< 0.001
Prolonged postoperative LOS	86 (41.7)	9 (11.1)	77 (61.6)	< 0.001
Prolonged hospital LOS	99 (48.1)	21 (25.9)	78 (62.4)	< 0.001

Data are presented as median [IQR] and number (%); LOS – length of stay

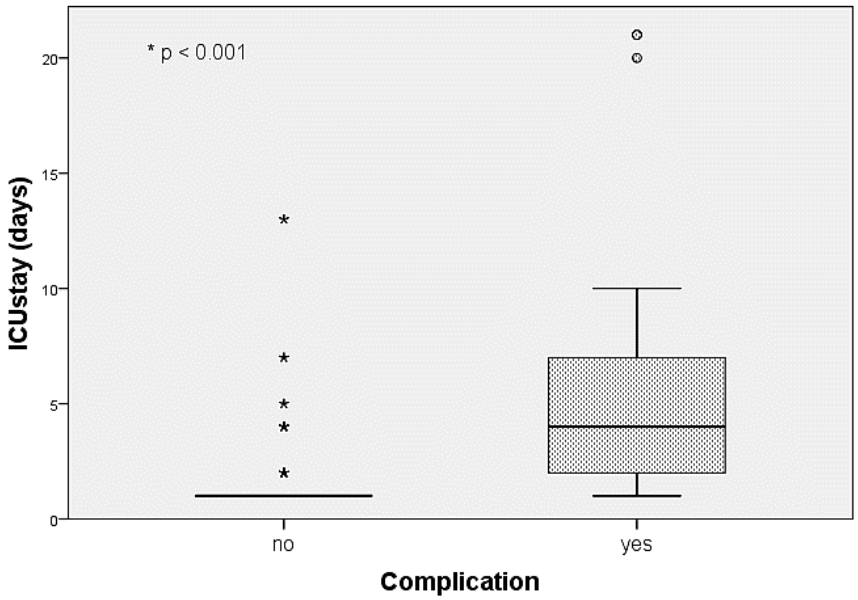

Figure 9. ICU LOS in patients with and without complications. Boxplots and T-bars represent the median ICU LOS, interquartile range and the extremes. * p-value (Wilcoxon rank sum test)

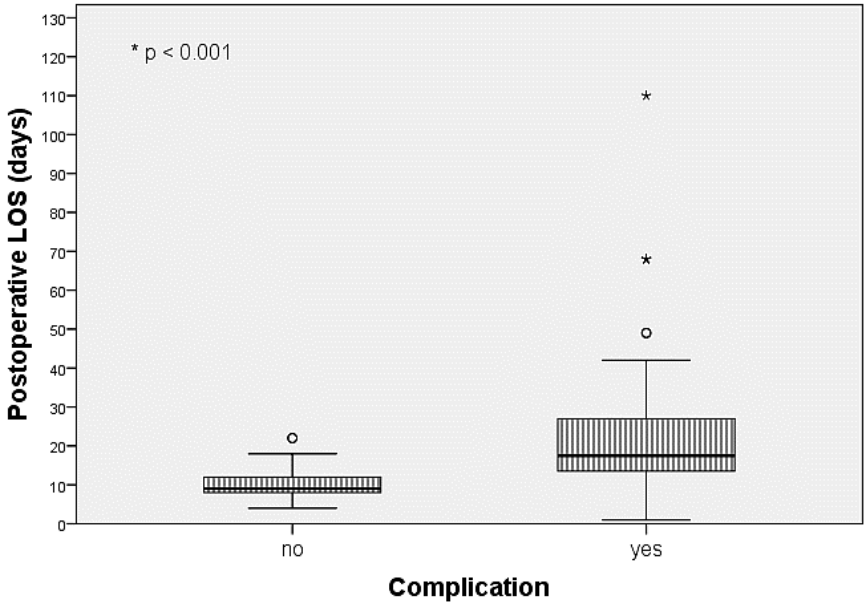

Figure 10. Postoperative LOS in patients with and without complications. Boxplots and T-bars represent the median postoperative LOS, interquartile range and the extreme values (minimum and maximum)

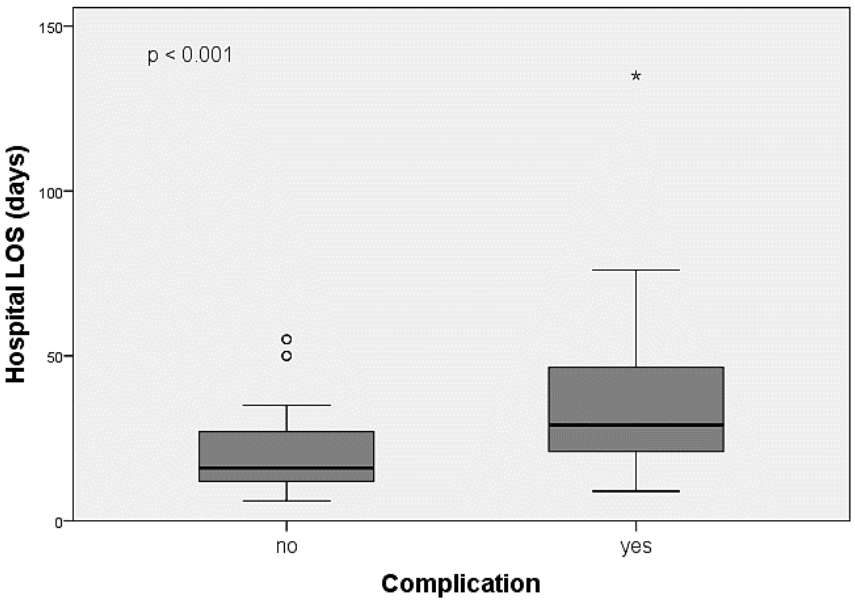

Figure 11. Hospital LOS in patients with and without complications. Boxplots and T-bars represent the median hospital LOS, interquartile range and the extreme values (minimum and maximum)

Kaplan-Meyer curve analysis showed that the patients with complications were more likely to stay hospitalized (log-rank test:p<0.001). The probability to stay hospitalized after 20 days reached 0 in patients without complications while it was around 50% in those who developed complications. (Figure 12)

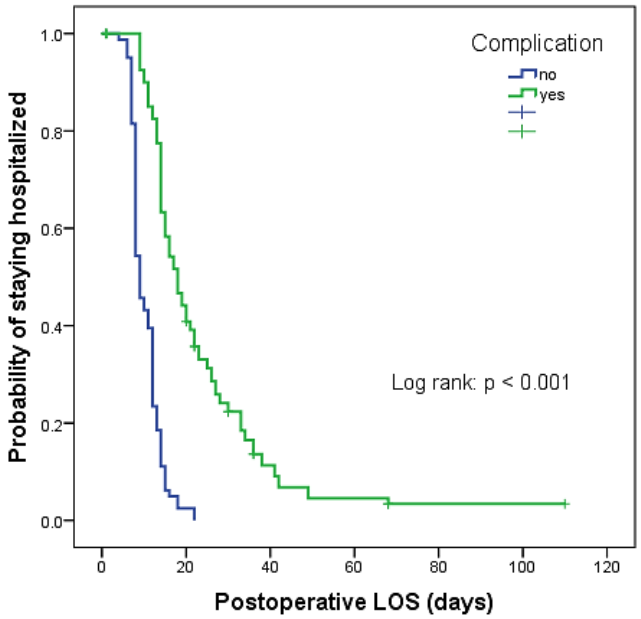

Figure 12. Kaplan-Meyer plots of postoperative length of stay according to the presence of complications

4.1.8. Functional activity on hospital discharge

The assessment of functional activity on hospital discharge in 192 patients who survived, demonstrated that 164 (85.4%) patients were independent, 18 (9.4%) patients were partially dependent (walk with assistance), and 10 (5.2%) patients were totally dependent (bedridden). The levels of functional activity were not equally distributed among patients with and without complications, as significantly more patients with complications were bedridden (9.0% vs 0%) and partially dependent (13.2 % vs 3.7%, p<0.001). (Figure 13)

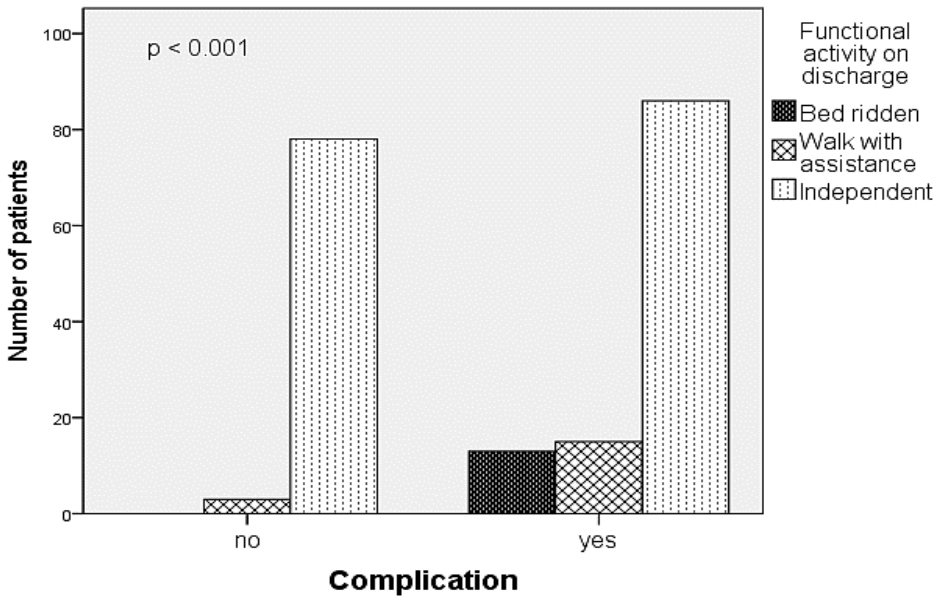

Figure 13. Functional activity on discharge in patients with and without complications

4.2. The assessment of the Clavien-Dindo classification (CDC) and the Comprehensive Complication Index (CCI) in evaluation of postoperative morbidity

4.2.1. Complication grading with CDC and CCI

The median CCI for the entire cohort was 20.9 [0-44.9]. The CD grade 0 was the most frequent (81/206; 39.3%). The highest CD grade among patients with complications was CD II (62/125; 49.6%). However, their median CCI was 29.6, ranging from 20.9 to 47.4. Table 20 shows the median CCI value and number of complications for the CD grade captured as the highest graded complication. The range of CCI values overlaps in all adjacent CD grades, except in the grade I and grade II. The median CCI for a CD grade IIIb is 52.0 and its range (39.7-65.4) extensively overlaps with those of the grade IIIa (26.2-54.2) and the grade IVa (47.3-

79.2). The table also shows the increasing number of complications with the higher Clavien-Dindo grade, with a median of 9 (2-12) complications in patients who died (grade V).

Table 20. The median CCI value and number of complications corresponding to the CDC grade of 206 analyzed patients

Clavien-Dindo grade	n (%)	Median CCI (range*)	Median number of complications (range*)
0	81(39.3)	0 (0-0)	0
I	4 (1.9)	10.4 (8.7-12.2)	1.5 (1-2)
II	62 (30.1)	29.6 (20.9-47.4)	2 (1-5)
IIIa	12 (5.8)	33.5 (26.2-54.2)	2 (1-5)
IIIb	16 (7.8)	52.0 (39.7-65.4)	3 (2-6)
IVa	13 (6.3)	65.2 (47.3-79.2)	5 (2-9)
IVb	4 (1.9)	65.2 (54.9-75.4)	4.5 (3-6)
V	14 (6.8)	100.0 (100.0-100.0)	9 (2-12)

*Range represents the extremes (minimum-maximum)

The comparison of the CCI values between the CD grades revealed a significant difference among all grades except grades IVa and IVb (the Mann-Whitney U-test; p=0.703). (Figure 14) Furthermore, a strong correlation of the CCI and the CDC was determined on Spearman's rank test with a correlation coefficient of 0.969 (p<0.01).

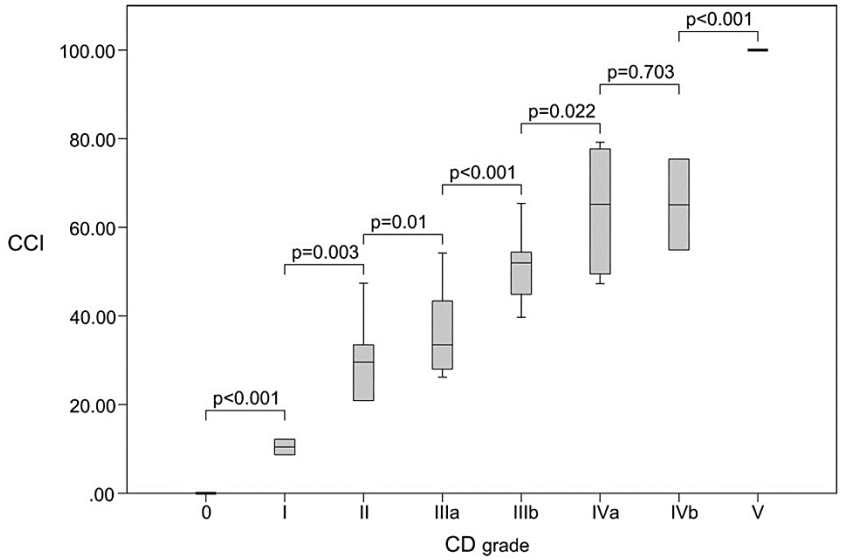

Figure 14. Comparison of the CCI values between the CDC grades. Boxplots and T-bars represent the median CCI, interquartile range, and the extreme values (min-max) for the CCI of each CD group. P values were calculated with the Mann-Whitney U-test

4.2.2.Number of complications and multiple complications

The median number of complications in the entire cohort was 1.0 [0-3.00], while it was 2.0 [2.0-4.0] in patients with complications. The rate of multiple complications was high as 100 (48.5%) patients developed more than one complication. (Figure 15)

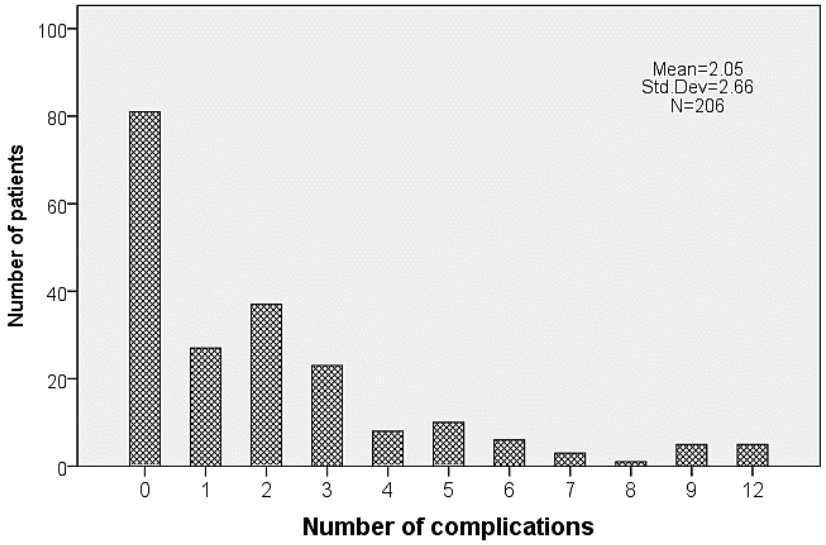

Figure 15. Number of complications in the study patients

The proportion of patients who suffered more than 3 complications rose significantly with the increasing CD grade ($p<0.001$) (Table 21)

Table 21. Number of complications according to the CDC grade

Number of complications	I (n=4)	II (n=62)	III (n=28)	IV (n=17)	V (n=14)
1	2 (50)	20 (32.3)	3 (10.7)	0 (0)	0 (0)
2	2 (50)	27 (43.5)	6 (21.4)	3 (17.6)	1 (7.1)
3	0 (0)	7 (11.3)	11 (39.3)	5 (29.4)	0 (0)
>3	0 (0)	8 (12.1)	8 (28.5)	9 (52.9)	13 (92.9)

n- number of patients (%)

Both classification systems correlated significantly with the number of complications (r_s for CCI 0.933; r_{s1} for CDC 0.869), but the correlation of the CCI was significantly stronger ($p<0.001$).

4.2.3. Correlation of number of complications, the CCI and the CDC with hospitalization indices

The pair-wise correlations between the number of complications and ICU LOS, number of complications and postoperative LOS, and number of complications and hospital LOS were significant and strong ($p<0.001$). The correlation coefficients were 0.55, 0.55, and 0.49, respectively. These were stronger than the correlations between the occurrence of any complication with the ICU LOS, postoperative LOS, and hospital LOS (r_1=0,25; r_2=0.43; r_3=0.40). (Table 22)

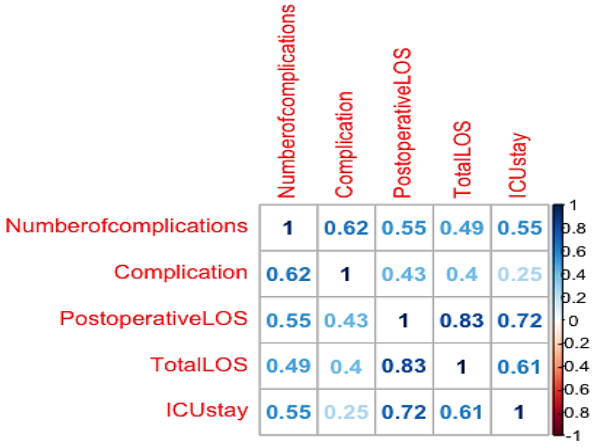

Table 22. Correlations of complication occurrence and number of complications with ICU LOS, postoperative LOS, and hospital LOS

A significant moderate and strong correlations of the CCI and the CDC were found with a Spearman's rank test with all hospitalization indices ($p<0.01$). A moderate correlation was found between the CCI and prolonged total LOS ($r = 0.450$) and the CD grade with the same parameter ($r = 0.432$). All other correlations were strong. The significantly stronger correlation of the CCI with the ICU LOS (0.670 vs 0.628, $p<0.001$), postoperative LOS (0.652 vs 0.630, $p=0.041$), prolonged ICU LOS (0.604 vs 0.555, $p<0.001$), and prolonged postoperative LOS (0.577 vs 0.555, $p=0.021$) was found. The rest of the correlations differences were not significant. (Table 23)

Table 23. Correlations of the CCI and the CDC with the parameters of hospitalization

Hospitalization parameter	CCI (r_{s1})	CD (r_{s2})	p value*
ICU LOS	0.670	0.628	< 0.001
Postoperative LOS	0.652	0.630	0.041
Hospital LOS	0.519	0.508	0.218
Prolonged ICU LOS	0.604	0.555	< 0.001
Prolonged postoperative LOS	0.577	0.550	0.021
Prolonged hospital LOS	0.450	0.432	0.105

All correlation coefficients were significant at the 0.01 level (2-tailed); *-p value was calculated with the William's modification of Hotelling's test of equality of dependent correlation coefficients

4.2.4. The association of the CCI and the CDC with patients' functional activity on discharge

The analysis of the CCI values and the CD grade according to the functional activity was performed for 192 patients who were alive on the day of hospital discharge. Ten patients (5.2%) were totally dependent (bedridden), 18 (9.4%) were partially dependent, while 164 (85.4%) were independent.The median CCI for the "independent", "partially dependent"and "totally dependent" patients was 20.9 [0.0-29.6], 47.3[20.9-54.4], and 59.6 [50.0-67.7] respectively. These values were significantly different (Kruskal-Wallis test, p<0.001). Similarly, the three groups based on functional activity at discharge differed in the Clavien-Dindo grade (Chi-square test, p<0.001). (Figures 16 and 17)

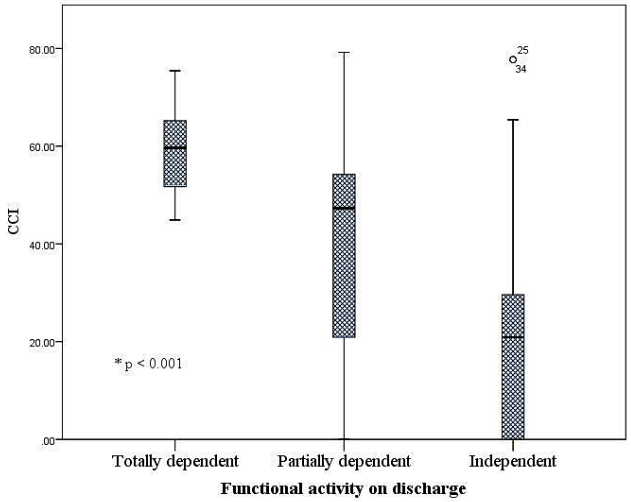

Figure 16.The CCI values in relation to functional activity on discharge from the hospital. Boxplots and T-bars represent the median CCI, interquartile range, and the extreme values;* p-value (Kruskal Wallis test)

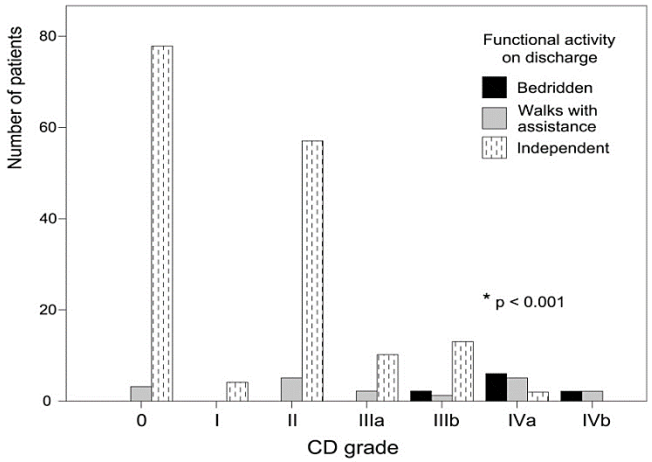

Figure 17. Functional activity on discharge of 192 analyzed patients in relation to the highest CD grade

4.3. Evaluation and validation of POSSUM and P-POSSUM score for prediction of in-hospital morbidity and mortality

4.3.1. Physiological and Operative Score distribution

The median Physiological score was 18 [15-22], with minimal score of 12 and maximal value of 54. It was significantly different between patients with and without complications (19 [16-23] vs 16 [14-20], p = 0.001) and also between patients who died and who survived (22 [16.7-34.5] vs 18 [15-22], p=0.034). The range of Physiological scores is presented in Figure 18.

The median Operative severity score was 16 [14-21]. The minimum value of the score was 7 and the maximum was 29. Similarly to Physiological score, patients with and without complications differed significantly with regards to the Operative score (15 [13-18] vs 18 [15-21], p< 0.001). The score was higher in deceased patients than in survivors (22 [15-25.2] vs 16 [14-20], p = 0.007). Figure 19 shows the distribution of patients according to the Operative score.

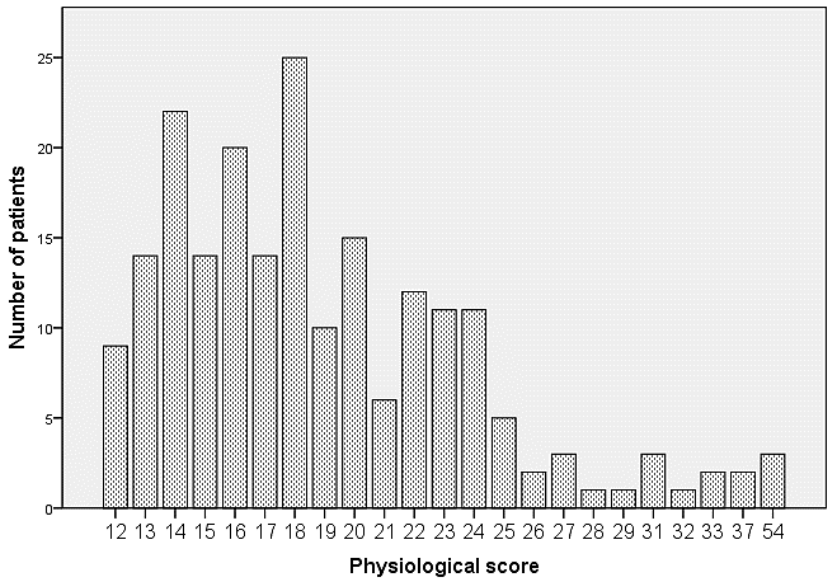

Figure 18. Distribution of patients regarding the Physiological score; Each bar represents the number of patients with corresponding score

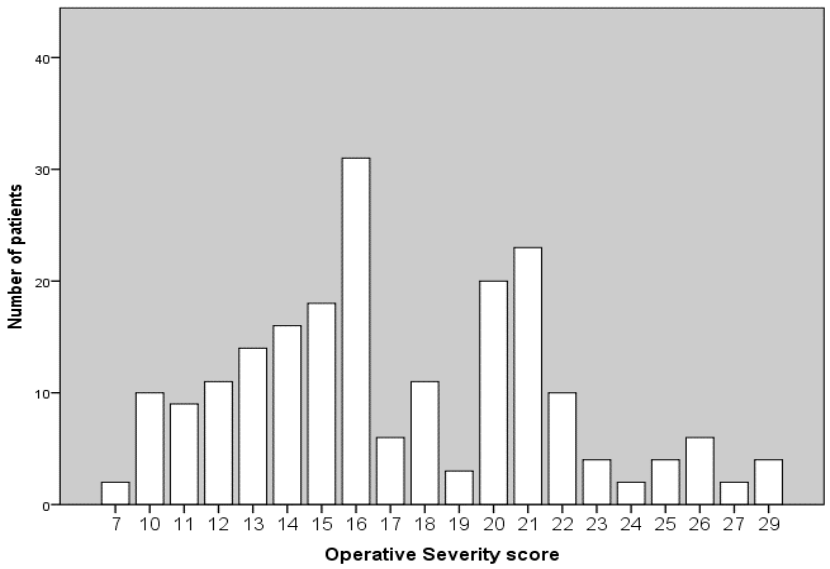

Figure 19. Distribution of patients regarding the Operative severity score; Each bar represents the number of patients with that score

4.3.2. POSSUM vs morbidity

The overall O:E ratio for morbidity was 1.07, meaning that the POSSUM score slightly underpredicted the occurrence of complication. It was particularly pronounced in the lowest risk group where the O:E ratio was 3.0. The calibration of the POSSUM score for morbidity was poor as assessed with the Hosmer Lemeshow test ($p<0.015$) (Table 24)

Table 24. The summary table of the three risk groups with predicted complications using POSSUM score and observed complications

Morbidity risk group (%)	Mean predicted morbidity (%)	Number of patients	Expected no. of patients with complications	Observed no. of patients with complications	O:E ratio
0 to ≤ 15	13.99	6	1	3	3.0
> 15 to ≤ 50	33.36	75	25	29	1.16
> 50 to ≤ 100	72.61	125	91	93	1.02
> 0 to ≤ 100	56.61	206	117	125	1.07

O:E – observed complications:expected complications; χ^2 5.85, DF 1, p=0.015

Discriminatory power of the POSSUM score in predicting morbidity was analyzed with the receiver operating characteristic (ROC) curve. The area under the curve (AUC) was 0.708 (95% confidence interval, 0.634-0.781) indicating fair performance. (Figure 20)

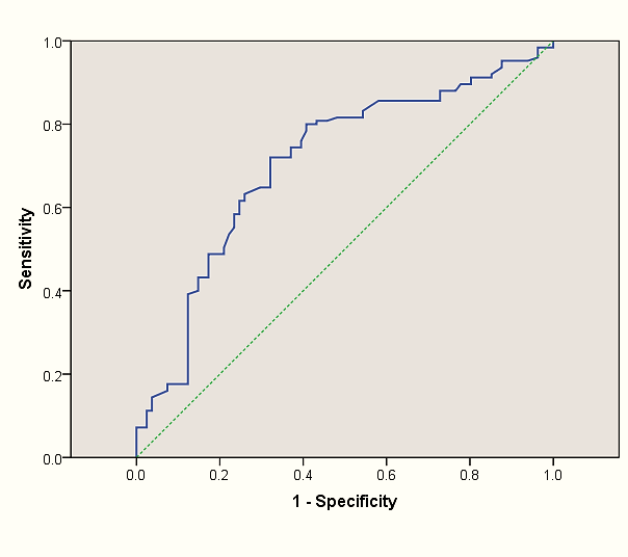

Figure 20. Receiver operating characteristic curve (ROC) for POSSUM morbidity

The best threshold to differentiate between patients with and without complications was determined by the Youden index. The selected threshold, corresponding sensitivity, specificity, positive predictive value (PPV) and Youden index are shown in table 25.

Table 25. Prognostic value of POSSUM for morbidity

Best threshold	*Sensitivity*	*Specificity*	*PPV*	*Youden index*
0.54	0.72	0.68	0.76	0.28

PPV –positive predictive value

4.3.3. POSSUM vs Mortality

The POSSUM score overestimated mortality since the overall O:E ratio was 0.38. The overprediction was present in all risk groups, except the group of the lowest risk where only 1 death was expected and occurred. The observed and expected proportions were significantly different across all POSSUM risk groups ($p< 0.001$), suggesting poor calibration. (Table 26)

Table 26. The summary table of the four risk groups of predicted mortality using POSSUM score and observed deaths

Mortality risk group (%)	**Mean predicted mortality (%)**	**Number of patients**	**Expected no. of deaths**	**Observed no. of deaths**	**O:E ratio**
0 to ≤ 5	3.54	29	1	1	1.0
> 5 to ≤ 15	9.41	84	8	2	0.25
> 15 to ≤ 50	25.81	86	22	8	0.36
> 50 to ≤ 100	77.70	7	5	3	0.60
> 0 to ≤ 100	17.75	206	37	14	0.38

O:E – observed deaths: expected deaths; χ^2=19.75, DF 2, $p< 0.001$

4.3.4. P-POSSUM vs Mortality

The P-POSSUM score has shown an underprediction in the lowest risk group (O:E ratio 1.67) and the overestimation of mortality in the middle-risk group (>15 to < 50%; O:E=0). However, the overall O:E ratio was 0.93. Since the p value calculated with the Hosmer Lemeshow test was 0.072, we could not reject the null hypothesis that the observed and expected proportions are the same across all P-POSSUM risk groups. (Table 27)

Table 27. The summary table of the four risk groups of predicted mortality using P-POSSUM score and observed deaths

Mortality risk group (%)	Mean predicted mortality (%)	Number of patients	Expected no. of deaths	Observed no. of deaths	O:E ratio
0 to ≤ 5	2.23	124	3	5	1.67
> 5 to ≤ 15	8.74	66	6	6	1.00
> 15 to ≤ 50	25.69	13	3	0	0
> 50 to ≤ 100	98.97	3	3	3	1.00
> 0 to ≤ 100	7.21	206	15	14	0.93

O:E – observed deaths:expected deaths; χ^2=5.27, DF 2, p=0.071

Discrimination of the POSSUM score and the P-POSSUM score in predicting mortality, analyzed with ROC curve was reasonable.(Figure 21)

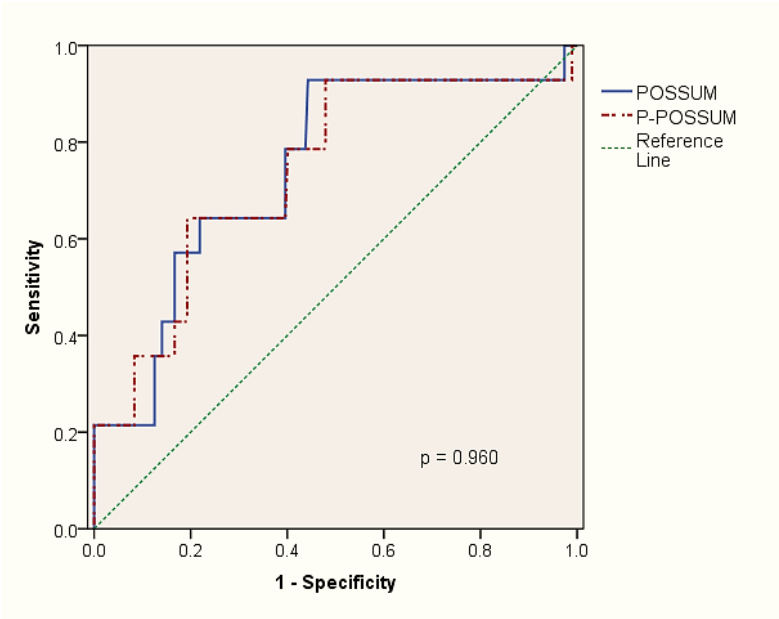

Figure 21. Receiver operating characteristic (ROC) curve for performance in mortality prediction of the POSSUM and the P-POSSUM score; There were no significant difference between the areas under the curve (AUC) of the two scores (z-statistic 0.0498, p=0.960)

The AUCs (95% CIs) of the POSSUM and P-POSSUM were not significantly different (0.744 vs 0.739, z-statistic 0.049, p= 0.960) (Table 28)

Table 28. Prognostic characteristics of the POSSUM and the P-POSSUM score for mortality

Score	*AUC*	*95% CI*	*S.E.*	*p value*
POSSUM	0.744	0.607-0.880	0.070	0.002
P-POSSUM	0.739	0.598-0.880	0.072	0.003

AUC- area under curve, CI-confidence interval, S.E. – standard error

4.4. Clinical relevance of the markers of tissue perfusion for the prediction of severely complicated postoperative course

According to our findings presented in chapter 4.2.1. a cut-off CCI of 50 was chosen to classify patients according to the overall burden of complications. This threshold was chosen because it corresponds to the CD grade IIIb (at least one complication requiring reoperation) or multiple complications of lesser severity. Out of 206 patients, 167 (81.1%) had the CCI ≤ 50. Thirty nine (18.9%) patients had CCI > 50. (Figure 22)

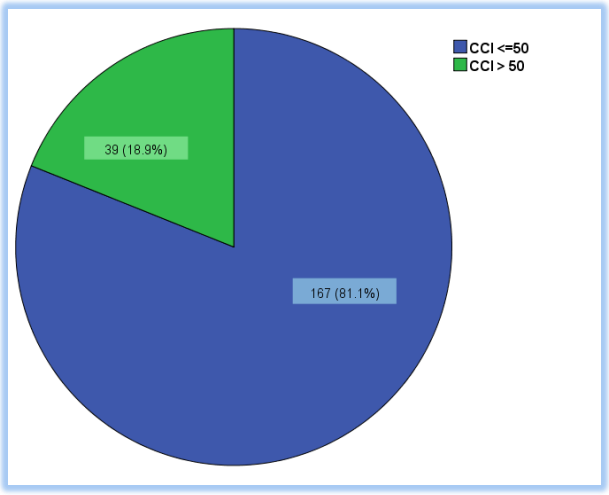

Figure 22. Distribution of patients regarding the CCI

Hemodynamic and data regarding peripheral perfusion of patients with CCI ≤ 50 and above 50 measured at two time points (on admission to the ICU and 12 hours later) are shown in table 29. Univariate analysis identified nine variables recorded on ICU admission associated with a more complicated postoperative course (CCI>50): peripheral temperature (p<0.001), central temperature (p=0.010), capillary refill time (p< 0.001), delta T (p<0.001), heart rate

(p<0.001), systolic pressure (p=0.008), base excess (p<0.001), CO_2 gap (p=0.027), and $PaCO_2$ (p=0.04). There were no significant differences on admission between these two groups of patients with regards to mean arterial pressure (p=0.386), $ScvO_2$ (p=0.676), PvCO2 (p=0.695), lactate concentration (p=0.106), and oxygen saturation (p=0.604). The analysis of data obtained 12 hours after the ICU admission has shown that seven variables were significantly different between patients with the CCI ≤ 50, and patients with the CCI > 50: systolic pressure (p=0.008), pH (p=0.001), base excess (p< 0.001), ScvO2 (p=0.004), pvCO2 (p=0.005), PvCO2 (p=0.005), PaCO2 (p<0.001), and lactate (p<0.001).

Table 29. Hemodynamic and peripheral perfusion parameters measured at two time points

	H0		H12	
Variable	**CCI ≤ 50**	**CCI > 50**	**CCI ≤ 50**	**CCI > 50**
Peripheral temperature (˚C)	26.74 ± 2.56	25.16 ± 1.36[a]	29.96 ± 3.91[b]	28.75 ± 3.86[b]
Central temperature (˚C)	35.70 ± 0.77	35.38 ± 0.88[a]	36.39 ± 0.51[b]	36.33 ± 0.75[b]
Delta T (˚C)	8.07 ± 2.41	10.22 ± 1.67[a]	6.43 ± 3.81[b]	7.58 ± 3.75[b]
Heart rate (bpm)	77.4 ±15.4	92.3 ± 20.9[a]	80.6 ± 16.0[b]	82.0 ± 19.8
Systolic pressure (mmHg)	138.2 ± 24.3	125.9 ± 31.8[a]	126.5 ± 19.3[b]	116.2 ± 29.0[a,b]
MAP (mmHg)	94.1 ± 16.1	91.3 ± 26.6	88.2 ± 15.2[b]	82.3 ± 24.2[b]
$S_{cv}O_2$ (%)	72.2 ± 9.4	72.9 ± 11.0	73.5 ± 6.4	69.7 ± 9.6[a]
Arterial pH	7.33 ± 0.07	7.30 ± 0.07[a]	7.39 ± 0.55[b]	7.34 ± 0.14[a,b]
BE (mmol/l)	-5.65 ± 3.82	-8.45 ± 4.88[a]	-2.12 ± 3.63[b]	-7.30 ± 9.07[a,b]
$PaCO_2$ (kPa)	5.11 ± 0.67	4.84 ± 0.71[a]	5.03 ± 0.65	4.55 ± 0.86[a]
$PvCO_2$ (kPa)	6.21 ± 0.63	6.16 ± 0.68	6.02 ± 0.62[b]	5.67 ± 0.86[a,b]
CO_2 gap (mmHg)	7.83 ± 3.83	9.28 ± 2.73[a]	7.21 ± 3.26[b]	7.99 ± 2.70
$\Delta pCO_2/C_{a-v}O_2$	1.84[1.42-2.20]	2.51[1.82-3.06][a]	1.92[1.36-2.28]	1.93[1.75-2.33][b]
SpO_2 (%)	99 [96-100]	99 [97-99.7]	98 [97-100]	99 [98 -99]
Capillary refill time (s)	3.10 ± 1.25	3.83 ± 1.12[a]	2.63 ± 0.97[b]	2.62 ± 1.07[b]
Lactate (mmol/l)	1.8 [1.1-2.5]	2.0 [1.6-2.5]	1.1 [0.7-1.7][b]	2.8 [1.7-3.4][b,c]

H0 – admission to the ICU; H12-12hours after ICU admission; Delta T – temperature gradient between central and peripheral temperature; bpm-beats per minute; MAP – mean arterial pressure; $S_{cv}O_2$ – central venous oxygen saturation; BE- base excess; $PaCO_2$ - central venous carbon dioxide tension; P_vCO_2 – central venous carbon dioxide tension, CO_2 gap – central venous-to arterial carbon dioxide gradient; SpO_2 – pulse oxymetry oxygen saturation; Data are presented as mean ± standard deviation or median [interquartile range]; [a] p value < 0.05 indicates significant difference between patients with CCI≤50 and CCI>50 (Student's t-test); [b] p value < 0.05 indicates significant difference between values at specific time points (H12 versus H0; Wilcoxon signed-rank test); [c] p <0.05 indicates significant difference between patients with CCI≤50 and CCI>50 (Mann-Whitney-U test)

These two groups didn't differ regarding the capillary refill time (p=0.926), central temperature (p=0.501), peripheral temperature (p=0.084), delta T (p=0.095), heart rate (p=0.627), mean arterial pressure (p=0.057), and oxygen saturation (p=0.641).

Changes in hemodynamic and perfusion parameters over time were compared using the paired samples Wilcoxon test (Wilcoxon signed-rank test). The analysis of the entire cohort showed that there was a significant difference ($p<0.001$) in all analyzed parameters from H0 to H12, except the heart rate ($p=0.127$), $S_{cv}O2$ ($p=0.921$), SpO2 ($p=0.383$), and $PaCO_2$ (0.307). In patients whose CCI was below 50, only three variables didn't change significantly over time: SpO_2 ($p=0.279$), $S_{cv}O2$ ($p=0.45$), and $PaCO_2$ ($p=0.683$). On the other hand, patients with a more complicated postoperative course (CCI>50) had nonsignificant change of 5 parameters: heart rate ($p=0.102$), SpO2 ($p=0.972$), $S_{cv}O2$ ($p=0.115$), PaCO2 ($p= 0.133$), and delta T ($p=0.064$).(Table 29)

Trends in capillary refill time, lactate concentration, delta T, and CO_2 gap during the first 12 hours in the ICU are shown in figure 24.

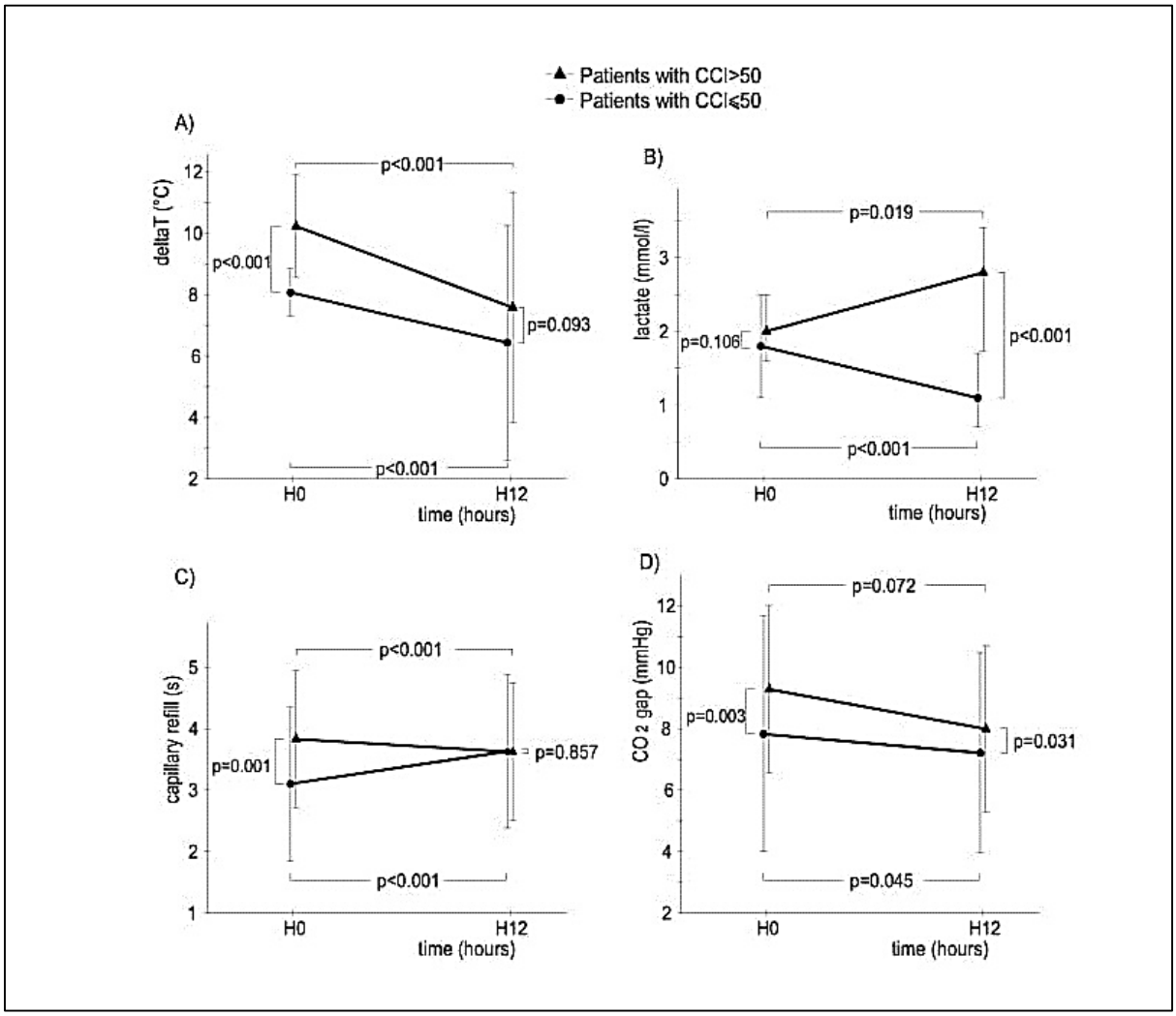

Figure 24. Trends in delta T , lactate, capillary refill time, and CO2 gap regarding to the severity of postoperative complications (CCI>50 vs CCI≤ ≤50)

Central-to-toe temperature gradient (Delta T) was significantly different between patients with CCI>50 and CCI≤50 on admission to the ICU (p< 0.001). It changed significantly (p<0.001) over time in both groups, and the difference bacame insignificant after 12 hours (p=0.093).

Lactate concentration which didn't differ between the two groups of patients on admission to the ICU (p=0.106), changed significantly over time in both groups, resulting in a significant difference , with higher values in patients with CCI > 50 (2.8mmol/l [1.7-3.4] vs 1.1mmol/l [0.7-1.7], p<0.001).

On the other hand, significantly different capillary refill time between groups on admission (p<0.001), has shown a significant decrease in CCI>50 group, and an increase in CCI≤50 group with a consequential non-significant values after 12 hours in the two groups (p=0.857).

Finally, although CO2 gap showed trend towards a decrease in both groups over time, it remained significantly different and higher in the CCI>50 group (8.9±2.7 mmHg vs 7.2±3.3 mmHg, p<0.031).

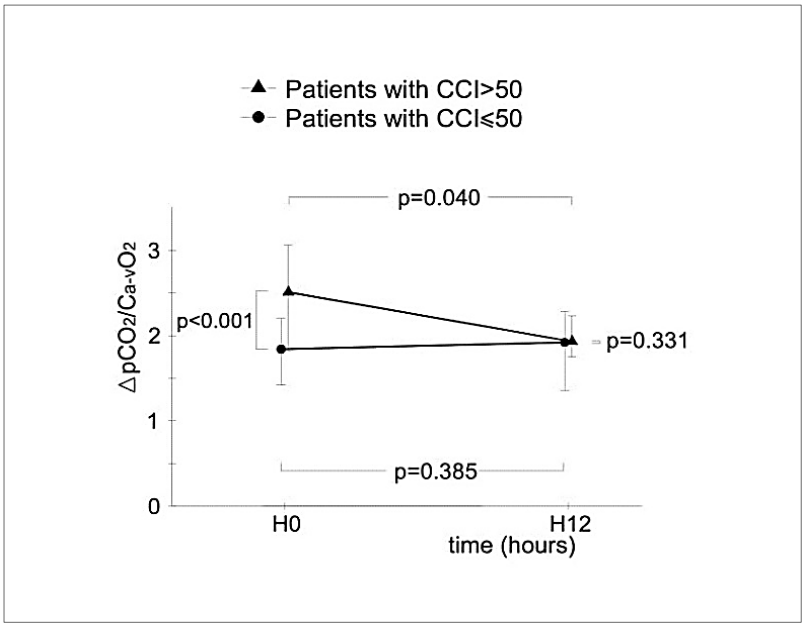

Figure 25. Trend in $\Delta PCO_2/Ca\text{-}vO_2$ with regard to the CCI (≤50 and >50); ΔPCO2-CO2 gap; $Ca\text{-}vO_2$ – central arteriovenous oxygen content difference

On admission to ICU, patients with CCI >50 had significantly higher $\Delta PCO_2/Ca\text{-}vO_2$ ratio (2.51[1.82-3.06]mmHg/ml vs 1.84 [1.42-2.20] mmHg/ml, p<0.001). The change over time in both groups resulted in nonsignificantly different values after 12 hours (1.93 [1.75-

2.33]mmHg/ml vs 1.92 [1.75-2.33]mmHg/ml, p=0.331).(Figure 25)

To test the ability of perfusion parameters on admission (H0) to the ICU and after 12 hours (H12) to discriminate between patients with more and less complicated postoperative course (CCI > 50 and CCI ≤ 50) we generated receiver operating characteristic (ROC) curves. (Figures 26 and 27) The area under the curve (AUC) for the occurrence of severe complications resulting in the CCI > 50 based on admission values of capillary refill time, lactate concentration, deltaT and CO2 gap was 0.666, 0.580,0.764, and 0.653, respectively. In other words, only deltaT could make a fair discrimination between the two outcomes. The other parameters' discriminative ability was poor.

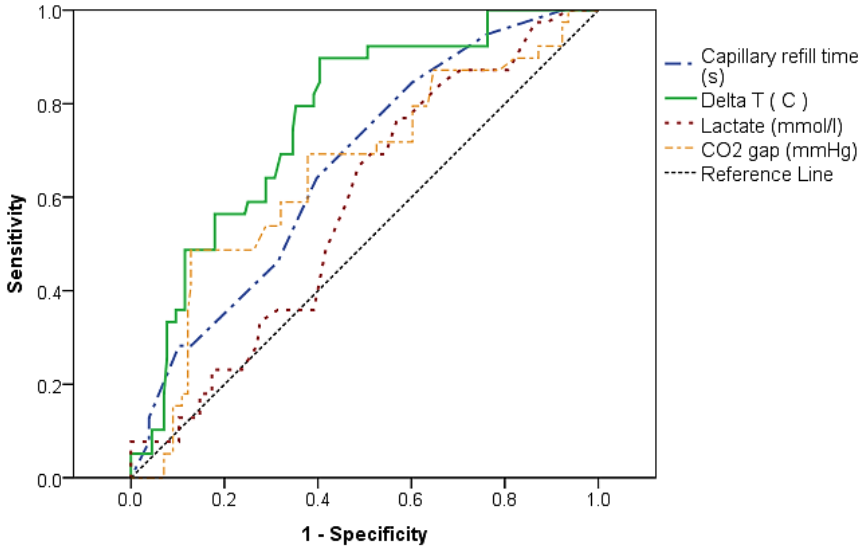

Figure 26. Receiver operating characteristic curve (ROC) comparing the ability of capillary refill time, delta T, lactate concentration and CO_2 gap to discriminate between patients with CCI ≤ 50 (n=167) and patients with CCI > 50 (n=39) on admission at the ICU. Area under the curve (AUC) was 0.666, 0.764, 0.580, and 0.653, respectively.

The area under the ROC curve for the CCI > 50 based on measurements 12 hours after admission (H0) for capillary refill time, lactate concentration, delta T, and CO2 gap were as follows: 0.497, 0.850, 0.612, and 0.618.

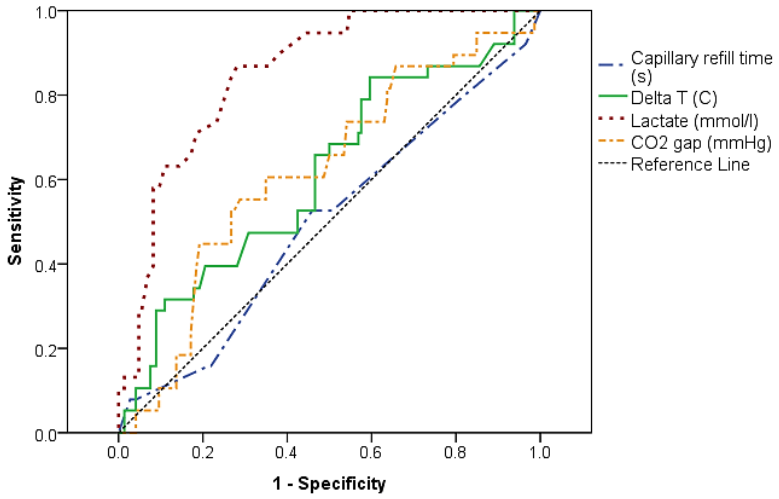

Figure 27.Receiver operating characteristic (ROC) curve comparing the ability of capillary refill time, delta T, lactate concentration, and CO_2 gap to discriminate between patients with CCI ≤ 50 and patients with CCI > 50 12 hours after the admission to the ICU. Area under the curve was 0.497, 0.612, 0.852, and 0.618, respectively.

The best threshold lactate value after 12 hours for discriminating between patients who will and who will not develop a seriously complicated postoperative course (CCI>50) was 1.65 mmol/l (sensitivity 84.2%, specificity 72.7%, PPV 64.0%). Of the 39 patients who developed the CCI>50, 33 had lactate concentration after 12 hours ≥ 1.65mmol/l.

Multivariate analysis included significant predictors from the univariate analysis. After checking for correlations, we decided to exclude pH since it was highly correlated to BE (r=0.741), mean arterial pressure since it correlated with systolic pressure (r=0.683), and peripheral temperature because of the strong negative correlation with delta T (r=-0.950). We adjusted for vasopressor use and transfusion because of their possible effect on perfusion parameters and the outcome. The results of the multivariable analysis are shown in table 30**.**

Multivariate analysis showed that Capillary refill time at H0 (OR 2.124; 95% CI 1.168-4.219, p=0.020), lactate concentration at H12 (OR 2.593; 95%CI 1.603-4.579, p<0.001), base excess at H12 (OR 0.824; 95% CI 0.678-0.968, p=0.024), and vassopressor use (OR 22.596; 95% CI 2.864-247.764, p=0.005) were independently associated with a more complicated postoperative course.

Table 30. Multivariate analysis of parameters associated with a severely complicated postoperative course (CCI >50)

	B (SE)	Odds ratio	95% confidence interval	p value
Constant	-8.421 (7.642)			
Capillary refill	0.753 (0.323)	2.124	1.128-3.998	**0.020**
Delta T	0.458 (0.020)	1.581	1.101-2.270	**0.013**
Heart rate	0.009 (0.018)	1.009	0.974-1.044	0.629
CO_2 gap	0.102 (0.115)	1.107	0.884-1.387	0.377
$\Delta pCO_2/C_{a-v}O_2$	0.993 (0.423)	2.708	1.177-6.184	**0.019**
Systolic pressure	0.020 (0.014)	1.020	0.992-1.048	0.168
SpO_2	-0.040 (0.027)	0.961	0.911-1.014	0.143
BE	0.165 (0.102)	1.179	0.966-1.439	0.106
$PaCO_2$	-0.696 (0.576)	0.499	0.161-1.542	0.227
Lactate 12	0.953 (0.261)	2.593	1.555-4.325	**<0.001**
Systolic pressure 12	0.012 (0.020)	1.012	0.974-1.052	0.531
BE 12	-0.194 (0.085)	0.824	0.697-0.974	**0.024**
$S_{cv}O_2$ 12	-0.069 (0.047)	0.933	0.850-1.024	0.144
P_vCO_2 12	0.206 (0.846)	1.229	0.234-6.446	0.808
P_aCO_2 12	0.744 (0.985)	2.104	0.305-14.513	0.450
Vassopresor use	3.118 (1.121)	22.596	2.513-203.146	**0.005**
Transfusion	0.571 (0.609)	1.771	0.537-5.843	0.348

Lactate 12, Systolic pressure 12, BE 12, $S_{cv}O_2$ 12, P_vCO_2 12, P_aCO_2 12 represent the measurements 12 hours after ICU admission; significant p values are indicated in bold text

4.5. Development of model for prediction of complications after major abdominal surgery

The first step in model development was to select variables to predict complications as explained in the methodology chapter. We selected variables from the following groups: Preoperative, Intraoperative, Postoperative on ICU admission, Postoperative 12 hours after the ICU admission, and Postoperative Day 1. The procedure was the same for all groups of variables and consisted of three steps:

Step 1: Two group comparison to select covariates that are significantly different across groups (with and without complications)

Step 2: Checking the correlations of the covariates from step 1 and selecting among the highly correlated ones ($r \geq 0.6$) based on domain knowledge

Step 3: Among the covariates from step 2, further selection based on statistical algorithms (median imputation and lasso or stepwise regression)

4.5.1.Preoperative variables

Selected variables in step 1 (two-group comparison) among continuous variables were: Serum albumin, CRP, Haemoglobin, and Preoperative length of hospital stay.

Table 31. Two group comparison for continuous preoperative variables

Variable	***Complication = Yes***					***Complication = No***					***p. wilcox***	***p.t***
	count	mean	SD	median	IQR	count	mean	SD	median	IQR		
Age	125	64.62	11.16	65	15	81	62.78	12.81	65	18	0.2823	0.2921
Albumin 1	113	35.15	6.4	36	9	74	39.45	4.32	40	6	0.0000	0.0000
ALT1	102	36.6	57.67	19	19	65	30.83	44.25	16	14	0.4198	0.4676
AST1	102	38.77	50.44	20	11	65	31.28	35.34	20	17	0.5268	0.2608
Bilirubin1	115	41.82	96.98	12.6	11.25	79	32.68	73.19	13.1	8.65	0.5211	0.4557
BMI	122	25.35	5.08	24.55	5.48	78	24.13	3.87	24.29	5.12	0.1790	0.0551
Creatinin1	116	92.59	84.57	74	32.75	79	75.35	18.83	78	24	0.8931	0.0359
CRP1	68	41.22	76.2	11.2	36.13	42	12.09	18.51	5.95	10.13	0.0251	0.0035
Hgb1	116	119.17	21.51	119.5	37	79	130.2	17.83	132	18.5	0.0003	0.0001
Preoperative LOS (days)	125	13.62	11.94	9	10	81	9.32	8.49	5	10	0.0018	0.0028
WBC 1	116	6.67	3.23	6.11	2.13	79	6.58	2.01	6.17	2.6	0.3595	0.8044
Number of drugs	125	2.26	2.21	2	4	81	2.25	2.23	2	3	0.9844	0.9772
Platelets 1	116	259.47	152.86	222	128	75	243.32	75.44	244	99.5	0.3757	0.3336
Urea 1	116	6.64	5.91	5.35	2.33	79	5.89	2.2	5.7	3.25	0.6260	0.2132

ALT-alanin aminostransferase; AST- aspartate aminotransferase; BMI – Body Mass Index; CRP1- preoperative C-reactive protein: Hgb 1- preoperative haemoglobin, LOS-length of stay, WBC-white blood cells; p.wilcox – p value by Mann-Whitney-Wilcoxon test; p.t – p value by Student's t-test

The categorical covariates that were significantly associated with complications ($p<0.05$) were ASA, Diabetes, and Corticosteroids. However, we found that the variable „Corticosteroids" had zero 1's among patients without complications, and the Fisher's test might be inaccurate for case like this. It may also cause larger variance and instability in predictive model. Therefore, we excluded "corticosteroids", even though it had p value 0.044. At the end of step 1 the selected categorical variables were: **ASA and Diabetes**.

Table 32. Two-group comparison for categorical preoperative variables

Variable	Complication = Yes					Complication = No				p value
	value	n.obs	percent	CI.lower	CI.upper	n.obs	percent	CI.lower	CI.upper	
Gender	0	42	33.60%	25.32%	41.88%	31	38.27%	27.69%	48.86%	0.552
	1	83	66.40%	58.12%	74.68%	50	61.73%	51.14%	72.31%	
Functional status	0	105	84%	77.57%	90.43%	70	86.42%	78.96%	93.88%	0.694
	1	20	16%	9.57%	22.43%	11	13.58%	6.12%	21.04%	
Comorbidity	0	31	24.80%	17.23%	32.37%	21	25.93%	16.38%	35.47%	0.871
	1	94	75.20%	67.63%	82.77%	60	74.07%	64.53%	83.62%	
ASA>2	0	55	44%	35.30%	52.70%	48	59.26%	48.56%	69.96%	**0.045**
	1	70	56%	47.30%	64.70%	33	40.74%	30.04%	51.44%	
Respiratory	0	106	84.80%	78.51%	91.09%	70	86.42%	78.96%	93.88%	0.841
	1	19	15.20%	8.91%	21.49%	11	13.58%	6.12%	21.04%	
Diabetes	0	97	77.60%	70.29%	84.91%	76	93.83%	88.59%	99.07%	**0.002**
	1	28	22.40%	15.09%	29.71%	5	6.17%	0.93%	11.41%	
Renal	0	110	88%	82.30%	93.70%	74	91.36%	85.24%	97.48%	0.497
	1	15	12%	6.30%	17.70%	7	8.64%	2.52%	14.76%	
Hepatic	0	102	81.60%	74.81%	88.39%	68	83.95%	75.96%	91.94%	0.711
	1	23	18.40%	11.61%	25.19%	13	16.05%	8.06%	24.04%	
Neurologic	0	118	94.40%	90.37%	98.43%	77	95.06%	90.34%	99.78%	1
	1	7	5.60%	1.57%	9.63%	4	4.94%	0.22%	9.66%	
Psychiatric	0	124	99.20%	97.64%	100.76%	80	98.77%	96.36%	101.17%	1
	1	1	0.80%	-0.76%	2.36%	1	1.23%	-1.17%	3.64%	
Endocrine	0	112	89.60%	84.25%	94.95%	71	87.65%	80.49%	94.82%	0.658
	1	13	10.40%	5.05%	15.75%	10	12.35%	5.18%	19.51%	
Obesity	0	110	88%	82.30%	93.70%	77	95.06%	90.34%	99.78%	0.137
	1	15	12%	6.30%	17.70%	4	4.94%	0.22%	9.66%	
Malnutrition	0	115	92%	87.24%	96.76%	70	86.42%	78.96%	93.88%	0.240
	1	10	8%	3.24%	12.76%	11	13.58%	6.12%	21.04%	
Chronictherapy	0	45	36%	27.59%	44.41%	23	28.40%	18.58%	38.21%	0.290
	1	80	64%	55.59%	72.41%	58	71.60%	61.79%	81.42%	
Corticosteroids	0	118	94.40%	90.37%	98.43%	81	100%	100%	100%	**0.044**
	1	7	5.60%	1.57%	9.63%	0	0	0	0	
Chemotherapy	0	111	88.80%	83.27%	94.33%	77	95.06%	90.34%	99.78%	0.137
	1	14	11.20%	5.67%	16.73%	4	4.94%	0.22%	9.66%	
Antibiotic	0	106	84.80%	78.51%	91.09%	62	76.54%	67.32%	85.77%	0.145
	1	19	15.20%	8.91%	21.49%	19	23.46%	14.23%	32.68%	
Smoker	0	88	71.54%	63.57%	79.52%	59	72.84%	63.15%	82.53%	0.874
	1	35	28.46%	20.48%	36.43%	22	27.16%	17.47%	36.85%	

Table 32. Two-group comparison for categorical preoperative variables *(Continued)*

Variable		Complication=Yes				Complication=No				p value
	value	n.obs	percent	CI.lower	CI.upper	n.obs	percent	CI.upper	CI.lower	
Alcohol	0	73	59.35%	50.67%	68.03%	52	64.20%	53.76%	74.64%	0.557
	1	50	40.65%	31.97%	49.33%	29	35.80%	25.36%	46.24%	
Weight loss	0	79	64.23%	55.76%	72.70%	56	69.14%	59.08%	79.20%	0.546
	1	44	35.77%	27.30%	44.24%	25	30.86%	20.80%	40.92%	
Cardiovascular.no	0	83	66.40%	58.12%	74.68%	54	66.67%	56.40%	76.93%	1
	1	42	33.60%	25.32%	41.88%	27	33.33%	23.07%	43.60%	
Cardiovascular.HTA	0	84	67.20%	58.97%	75.43%	58	71.60%	61.79%	81.42%	0.540
	1	41	32.80%	24.57%	41.03%	23	28.40%	18.58%	38.21%	
Cardiovascular. Other	0	83	66.40%	58.12%	74.68%	50	61.73%	51.14%	72.31%	0.552
	1	42	33.60%	25.32%	41.88%	31	38.27%	27.69%	48.86%	

HTA-Hypertension;value 0-absent; value 1-present; n.obs-number of patients; CI-confidence interval; p values are obtained with Fisher's test if the variables were binary, and Chi-square test if they had three levels or more

Step 2

Covariates albumin, CRP, and haemoglobin had 2, 9, and 1 missing data respectively. We used the median imputation to fill in the missing data, and then calculated correlations. (Table 33) All of the covariates were not highly correlated, therefore, they were passed to step 3.

Table 33. Correlation table of preoperative variables selected at step 1

	Albumin1	CRP1	Hgb1	Preoperative LOS	ASA	Diabetes
Albumin1	1	-0.37	0.59	-0.14	-0.32	0.03
CRP1	-0.37	1	-0.22	0.13	0.22	-0.01
Hgb1	0.59	-0.22	1	-0.13	-0.09	-0.09
Preoperative LOS	-0.14	0.13	-0.13	1	0.17	0.04
ASA	-0.32	0.22	-0.09	0.17	1	0.25
Diabetes	0.03	-0.01	-0.09	0.04	0.25	1

LOS-length of stay; albumin1-preoperative concentration of albumin; CRP1-preoperative concentration of C-reactive protein; Data represent Pearson's r

Step 3

Selected variables in step 3 were (Lasso and stepwise regression):

Lasso : Albumin, CRP, Haemoglobin, Preoperative LOS, and Diabetes

Note: Cross validation has been used to determine the parameter „lambda“ in Lasso model that yields the maximal area under curve (AUC).

Stepwise logistic regression: Albumin, Preoperative LOS, and Diabetes.

4.5.2.Intraoperative variables

Step 1

Selected variables after two–group comparison between patients with and without complications among continuous variables were: Duration of surgery and Intraoperative fluids.(Table 34)

Table 34. Two group comparison of continuous intraoperative variables

Variable	***Complication = Yes***					***Complication = No***					*p.wilcox*	*p.t*
	count	mean	SD	median	IQR	count	mean	SD	median	IQR		
Duration (min)	125	290.9	142.5	260	170	81	228.6	93.7	210	160	**0.002**	**<0.001**
Intraoperative fluids (ml)	124	4246.1	2056.6	4000	3151.7	81	2901.5	1178.6	3000	1731	**<0.001**	**<0.001**

The significant categorical variables ($p<0.05$) were: Intraoperative warming, Multiorgan resection, and Minimally invasive or hybrid surgical approach. Two group comparison of categorical intraoperative variables are shown in table 35. The p values are obtained by Fisher’s test for binary variables and chi-square test for variables with 3 or more levels.

Step 2

Among the variables selected in step 1 (Duration of surgery, Intraoperative fluids, Intraoperative warming, Multiorgan resection, and Minimally invasive or hybrid approach), covariate Intraoperative fluids has one missing value. After filling in the missing with column median,the correlations were calculated. (Table 36)

Table 35. Two group comparison of categorical intraoperative variables

Variable	*value*	*Complication = Yes*				*Complication = No*				*p.value*
		n.obs	percent	CI.lower	CI.upper	n.obs	percent	CI.lower	CI.upper	
	0	13	10.40%	5.05%	15.75%	5	6.17%	0.93%	11.41%	
Disease	1	112	89.60%	84.25%	94.95%	76	93.83%	88.59%	99.07%	0.326
	0	118	95.16%	91.38%	98.94%	71	87.65%	80.49%	94.82%	
Anesthesia	1	6	4.84%	1.06%	8.62%	10	12.35%	5.18%	19.51%	0.063
	0	70	56%	47.30%	64.70%	32	39.51%	28.86%	50.15%	
Warming	1	55	44%	35.30%	52.70%	49	60.49%	49.85%	71.14%	**0.023**
	0	9	7.20%	2.67%	11.73%	4	4.94%	0.22%	9.66%	
Monitoring	1	116	92.80%	88.27%	97.33%	77	95.06%	90.34%	99.78%	0.573
	0	55	44%	35.30%	52.70%	46	56.79%	46%	67.58%	
Adverseevents	1	70	56%	47.30%	64.70%	35	43.21%	32.42%	54%	0.087
	0	98	78.40%	71.19%	85.61%	61	75.31%	65.92%	84.70%	
Colorectal surgery	1	27	21.60%	14.39%	28.81%	20	24.69%	15.30%	34.08%	0.614
	0	106	84.80%	78.51%	91.09%	70	86.42%	78.96%	93.88%	
Hepatic surgery	1	19	15.20%	8.91%	21.49%	11	13.58%	6.12%	21.04%	0.841
	0	121	96.80%	93.71%	99.89%	73	90.12%	83.63%	96.62%	
Other surgery	1	4	3.20%	0.11%	6.29%	8	9.88%	3.38%	16.37%	0.066
	0	98	78.40%	71.19%	85.61%	69	85.19%	77.45%	92.92%	
Pancreatico-biliary surgery	1	27	21.60%	14.39%	28.81%	12	14.81%	7.08%	22.55%	0.276
	0	94	75.20%	67.63%	82.77%	52	64.20%	53.76%	74.64%	
Oesophagogastric surgery	1	31	24.80%	17.23%	32.37%	29	35.80%	25.36%	46.24%	0.116
	0	108	86.40%	80.39%	92.41%	80	98.77%	96.36%	101.17%	
Multiorgan resection	1	17	13.60%	7.59%	19.61%	1	1.23%	-1.17%	3.64%	**0.002**
	0	13	10.40%	5.05%	15.75%	16	19.75%	11.08%	28.42%	
Midline, subcostal approach	1	112	89.60%	84.25%	94.95%	65	80.25%	71.58%	88.92%	0.067
	0	116	92.80%	88.27%	97.33%	74	91.36%	85.24%	97.48%	
Thoracoabdominal approach	1	9	7.20%	2.67%	11.73%	7	8.64%	2.52%	14.76%	0.792
	0	121	96.80%	93.71%	99.89%	72	88.89%	82.04%	95.73%	
Minimally invasive or hybrid approach	1	4	3.20%	0.11%	6.29%	9	11.11%	4.27%	17.96%	**0.037**

Value 0 – variable absent; 1- variable present

Variables „Duration of surgery“ and „Intraoperative fluids“ were strongly correlated (r=0.62). It is logical and expected that patients receive more fluids during the long operation. Even though the correlation was strong, we thought it was important to include both in the analysis.

Therefore, we combined them and calculated a new covariate to represent the amount of intraoperative fluids adjusted for the duration of surgery and body weight (ml/kg/h). Since there was no significant difference between patients with and without complications regarding the new variable (p=0.512, TABLE 14), we chose the Duration of surgery to be selected in step 1.

Table 36. Correlation table of intraoperative variables in step 1

	Duration	**Intraoperative fluids**	**Warming**	**Multiorgan resection**	**Minimally invasive or hybrid approach**
Duration	1	0.62	0.48	0.15	0.1
Intraoperative fluids	0.62	1	0.11	0.18	-0.02
Warming	0.48	0.11	1	0.1	0.02
Multiorgan resection	0.15	0.18	0.1	1	-0.08
Minimally invasive or hybrid approach	0.1	-0.02	0.02	-0.08	1

Numbers in the table represent correlation coefficients (Pearson's r)

Step 3

Selected variables in step 3 (Lasso and stepwise regression) were:

Lasso: Duration of surgery, Intraoperative warming, Multiorgan resection, and Minimally invasive or hybrid approach

Stepwise logistic regression: Duration of surgery, Multiorgan regression, and Minimally invasive or hybrid approach

4.5.3. Postoperative variables on admission to the ICU

Step 1

The comparison of patients who did and did not develop complications is shown in table 15, page 59. The selected variables were: Peripheral temperature, Delta T, Heart rate, pH, Base excess, Lactate, Systolic pressure, MAP, $PvCO_2$, $PaCO_2$, and Intubation.

Step 2

Among the variables selected in step 1, $PvCO_2$ had 4 missing values and $PaCO_2$ had 2 missing values. After median imputation, we performed the correlations. (Table 37)

Table 37. Correlation table of postoperative variables on ICU admission selected in step 1

	BE	Delta T	HR	Lactate	Peripheral temperature	pH	PvCO2	Systolic pressure	MAP	PaCO2	Airway
BE	**1**										
DeltaT	-0.22	1									
HR	-0.35	0.15	1								
Lactate	-0.54	0.23	0.40	1							
Peripheral temperature	0.24	**-0.95**	-0.08	-0.21	1						
pH	**0.74**	-0.18	-0.24	-0.35	0.19	1					
PvCO2	0.12	0.10	-0.10	-0.02	-0.10	-0.26	1				
Systolic pressure	0.35	-0.15	-0.24	-0.38	0.19	0.21	0.05	1			
MAP	0.38	-0.02	-0.12	-0.41	0.08	0.21	0.20	**0.68**	1		
PaCO2	0.30	-0.09	-0.06	-0.12	0.11	-0.13	0.70	0.21	0.25	1	
Airway	0.25	-0.12	-0.17	-0.17	0.16	0.30	-0.08	0.03	0.04	0.02	1

BE-base excess; Numbers are correlation coefficients (Pearson's r)

Peripheral temperature and Delta T have shown a strong negative correlation (r= -0.95), which is expected as Delta T is the gradient between Epitympanic and Peripheral temperature. Base excess and pH were also strongly correlated (r=0.74), as well as Systolic pressure and MAP (r=0.68). Therefore, we decided to choose Delta T, Base excess, and Systolic pressure for further analysis.

Step 3

Selected variables from this group using Lasso and stepwise regression are:

Lasso: Delta T, Heart rate, Base excess, and $PvCO_2$

Stepwise logistic regression: Delta T, Heart rate, Base excess, $PvCO_2$, and $PaCO_2$

4.5.4.Postoperative variables 12 hours after ICU admission

Step 1

Variables significantly different between patients with and without complications are shown in table 16, page 60. Selected variables according to the difference were: Heart rate, pH, Base excess, Anion gap, Capillary refill, Glycemia, Lactate, PaCO2, PvCO2, ScvO2, CO2 gap, Intubation, and Mechanical ventilation.

Step 2

The numbers of missing data for the variables from step 1 were:

Anion gap	**Base excess**	**Capillary refill**	**Glycemia**	**Heart rate**	**Lactate**	**PaCO2**
3	3	2	2	3	4	5
pH	**PvCO2**	**ScvO2**	**CO2 gap**	**Intubation**	**Ventilation**	
2	4	7	4	0	0	

Missing data were filled by column mean, and correlations were calculated subsequently. (Table 38)

Table 38. Correlation of postoperative variables 12 hours after admission selected in step 1

AG12	**1**												
BE12	-0.70	1											
CRT12	0.27	-0.25	1										
Glycemia12	-0.06	-0.16	0.01	1									
HR12	-0.17	0.06	-0.10	0.18	1								
Lactate12	0.82	-0.73	0.26	0	-0.19	1							
PaCO212	-0.38	0.57	-0.10	-0.12	-0.11	-0.39	1						
PH12	-0.72	0.74	-0.29	-0.02	0.22	-0.73	0.09	1					
PvCO212	-0.32	0.47	-0.08	-0.05	-0.14	-0.34	0.79	0.04	1				
ScvO212	-0.31	0.24	-0.13	-0.08	0.02	-0.36	0.31	0.22	0.12	1			
CO2gap12	0.08	-0.15	0.09	0.09	-0.08	0.10	-0.38	-0.07	0.24	-0.32	1		
Intubation 12	-0.29	0.28	-0.20	-0.02	-0.10	-0.37	0.38	0.13	0.35	0.21	-0.06	1	
Ventilation12	0.32	-0.26	0.19	0.02	0.04	0.43	-0.26	-0.19	-0.24	-0.15	0.04	-0.83	1
	AG12	BE12	CRT12	Glycemia 12	HR12	Lactate12	PaCO2 12	pH12	PvCO2 12	ScvO2 12	CO2 gap 12	Intubation 12	Venti-lation 12

AG 12-anjon gap 12 hours after ICU admission;BE 12-base excess; CRT12-capillary refill time;HR 12-heart rate; PaCO2-arterial partial pressure of carbon dioxide; PvCO2 12-central venous partial pressure of carbon dioxide; ScvO2 12-central venous oxygen saturation; numbers represent correlation coefficients

We found that Lactate 12, pH 12, Base excess 12, and Anion gap 12 are highly correlated with each other. Although representing a difference between PvCO2 and PaCO2, CO2 gap was not highly correlated to these variables. As expected, intubation was highly correlated to mechanical ventilation. We chose Lactate 12, CO2 gap 12, and Ventilation 12, and drop other highly correlated variables.

Step 3

Selected variables in step 3 after applying Lasso and stepwise regression were:

Lasso: Capillary refill 12, Lactate 12, $ScvO_2$ 12, CO_2 gap 12, Glycemia 12, Ventilation 12, and Heart rate 12

Stepwise logistic regression: Capillary refill 12, Lactate 12, and Heart rate 12

4.5.5.Postoperative variables on the first postoperative day

Step 1

After two group comparison, based on significant differences between patients with and without complications, the following variables were selected: Albumin 2, Creatinine 2, Drainage output, Fluid balance, Haemoglobin 2, Intravenous fluids, Urea 2, Bilirubin 2, SAPS II score, and Transfusion. (Table 17, page 61). The covariate Vasopressor was present only in patients with complications, therefore it was removed from further selection as it might cause instability in the prediction model.

Step 2

Some variables selected in step 1 had missing values, so we used median imputation to fill in the missing data. These are the numbers of missing data for the variables from step 1:

Albumin 2	Creatinine 2	Drainage output	Fluid balance	IV fluids
4	4	1	0	0
Urea 2	Bilirubun 2	Transfusion	Hemoglobin 2	SAPS II
3	4	0	4	0

The correlations of the selected variables are shown in table 39. SAPS II score, Creatinine 2, and Urea 2 were highly correlated with each other, as was Fluid balance with Intravenous fluids. Therefore, we chose SAPS II and Fluid balance and dropped other highly correlated ones.

Step 3

Selected variables in step 3 were:

Lasso: Albumin 2 and Transfusion

Stepwise logistic regression: Albumin 2, SAPS II, and Transfusion.

Table 39. Correlations of postoperative variables on day 1 selected in step 1

Albumin2	**1**									
Creatinine2	-0.22	1								
Drainage	-0.41	0.24	1							
Fluidbalance	-0.40	0.34	0.35	1						
Hgb2	0.24	-0.27	-0.17	-0.29	1					
IVfluids	-0.33	0.24	0.45	**0.86**	-0.32	1				
SAPSII	-0.30	**0.67**	0.32	0.32	-0.28	0.27	1			
Urea2	-0.21	**0.92**	0.26	0.34	-0.26	0.23	**0.71**	1		
Bilirubin2	-0.06	0.14	0.05	0.13	-0.10	0.12	0.24	0.21	1	
Transfusion	-0.32	0.20	0.33	0.38	-0.41	0.41	0.28	0.21	0.05	1
	Albumin2	Creatinine2	Drainage	Fluidbalance	Hgb2	IVfluids	SAPSII	Urea2	Bilirubin2	Transfusion

The highly significant correlations are highlighted and bolded

4.5.6.Building a model to predict the complications

Table 40 shows the variables selected following the above procedures. There is total of 22 predictors from all three groups.

Table 40. The variables selected by lasso regression from preoperative, intraoperative and postoperative group

	Preoperative	**Intraoperative**	**Postoperative**		
			On admission to ICU	12 hours after the admission	On day 1
Lasso-selected variables	"Albumin 1" "CRP 1" "Hgb 1" "Preoperative LOS" "Diabetes"	„Duration of surgery" „Warming" „Multiorgan resection" „Minimally invasive or hybrid approach"	„BE" „Delta T" „Heart rate" „$PvCO_2$"	„Capillary refill 12" „Lactate 12" „$ScvO_2$ 12" „CO2 gap" „Glycemia 12" „Ventilation 12" „Heart rate 12"	„Albumin 2" „Transfusion"
λ	0.016	0.001	0.037	0.003	0.071

We conducted a univariate analysis to fit the logistic regression model on each of the selected variables. A multivariable logistic regression was applied to build a model using all of the above 22 variables from the within-group selection. The results of the univariate and multivariate analysis are shown in the table 41**.**

Table 41**.** Logistic regression results: variables associated with the occurrence of postoperative complications

	Variable	***Univariate analysis***		***Multivariate analysis***			
		OR	95% CI	B (SE)	OR	95% CI	P value
	Intercept			18.66(8.05)			
	Albumin 1	0.86	0.81-0.92	0.01 (0.08)	1.01	0.86 - 1.19	0.899
A	CRP 1	1.02	1.01-1.05	-0.02 (0.01)	0.97	0.95-1.01	0.065
	Hgb 1	0.97	0.96-0.99	-0.03 (0.02)	0.97	0.93-1.01	0.144
	Preoperative LOS	1.04	1.01-1.08	0.06 (0.03)	1.06	0.99-1.13	0.076
	Diabetes	4.39	1.75-13.40	2.64 (1.08)	14.08	1.94-141.13	0.014
	Duration of surgery	1.00	1.00-1.01	0.00 (0.00)	1.000	0.998-1.002	0.956
	Warming	0.51	0.29-0.90	-2.09 (0.89)	0.12	0.02-0.63	0.019
B	Multiorgan resection	12.59	2.51-229.24	5.34 (1.67)	208.73	10.98-9394.84	0.001
	Minimally invasive or hybrid approach	0.26	0.07-0.84	0.29 (1.21)	1.34	0.11-14.34	0.809
	Base excess	0.80	0.73-0.87	-0.02 (0.11)	0.98	0.79-1.20	0.828
C	Delta T	1.25	1.11-1.42	0.04 (0.12)	1.04	0.82-1.32	0.724
	Heart rate	1.06	1.04-1.08	0.08 (0.03)	1.08	1.02-1.16	0.016
	$PvCO_2$	0.64	0.40-1.01	-1.18 (0.66)	0.31	0.08-1.11	0.075
	Capillary refill 12	1.56	1.15-2.14	0.69 (0.37)	2.00	1.00-4.28	0.058
	Lactate 12	3.34	2.16-5.55	0.85 (0.50)	2.35	0.94-6.80	0.087
	$ScvO_2$ 12	0.95	0.91-0.99	0.08 (0.05)	1.08	0.97-1.21	0.158
D	CO_2 gap 12	1.09	0.99-1.21	0.24 (0.12)	1.28	1.02-1.63	0.037
	Glycemia 12	1.17	1.06-1.31	-0.26 (0.14)	0.77	0.58-1.01	0.064
	Ventilation 12	5.85	1.60-37.69	0.45 (2.34)	1.57	0.02-153.76	0.847
	Heart rate 12	1.03	1.01-1.05	0.03 (0.03)	1.03	0.98-1.09	0.263
E	Albumin 2	0.59	0.50-0.68	-0.75 (0.16)	0.47	0.33-0.62	<0.001
	Transfusion	9.51	4.13-25.92	0.64 (0.93)	1.91	0.29-11.87	0.489

A-preoperative variables; B-Intraoperative variables; C-Postoperative on admission; D- Postoperative variables 12 hours after the admission; E-Postoperative variables on day 1; LOS –length of stay; Hgb-haemoglobin

When we applied the above model (with all variables selected from step 3 as predictors) on the training data, the predictive error statistics are shown below. (Table 42)

Table 42. Predictive error statistics of the model with all selected predictors

Error rate	**Sensitivity**	**Specificity**	**PPV**	**AUC**
0.097	0.92	0.88	0.92	0.96

PPV-positive predictive value; AUC-area under curve

The model performs well on the training data. However, we found it overfitting when testing it via cross validation (CV). We split the data into 5 equal folds, each time treating one fold

as the testing data. We built the model on the rest and then applied on the testing data to calculate the error statistics on one fold. The results of 5-fold CV are shown in table 43. Each row in the table represents the error statistics on one fold. The model does not perform consistently well on all folds, especially the third row, indicating that the model with whole 22 predictors has the overfitting problem. In other words it corresponds too closely to a given data set and may therefore fail to predict future observations reliably. Possible reason is because the variables entered in the model may somehow be correlated to each other. The other reason may be the limited number of data points.

Table 43. Predictive error statistics of the model with 22 predictors

Fold	*Error rate*	*Sensitivity*	*Specificity*	*PPV*	*AUC*
1	0.190	0.92	0.65	0.79	0.833
2	0.146	0.83	0.92	0.96	0.820
3	0.317	0.81	0.55	0.65	0.824
4	0.195	0.79	0.83	0.92	0.922
5	0.049	1.00	0.90	0.91	0.981

PPV – positive predictive value; AUC-area under curve

To solve the overfitting issue, and to create a model that is not cumbersome for clinical use, we decided to conduct further variable selection and fit the risk model using penalised lasso regression. We combined the selected covariates from each group in table 40, and repeated lasso procedures to select the final predictors. The extent of shrinkage of regression coefficients was controlled with the parameter lambda (λ). Different λ values select different set of predictors, and the corresponding results are shown in table 44.

Table 44. The final predictors selected by lasso regression from each group

		Preoperative	**Intraoperative**	**Postoperative**		
				On admission to ICU	12 hours after the admission	On day 1
λ	0.1	NA	NA	BE Heart rate	NA	Albumin 2 Transfusion
	0.06	Diabetes	Multiorgan resection	BE Heart rate	Heart rate 12	Albumin 2 Transfusion
	0.05	Hemoglobin 1 Diabetes	Multiorgan resection	BE Heart rate	Capillary refill 12 Heart rate 12	Albumin 2 Transfusion

ICU-intensive care unit; BE-base excess

The figures 28 and 29 show how the area under curve (AUC) changes as the lambda parameter changes. There is a sudden drop in AUC when lambda is beyond 0.3. However, the AUCs are similar (>0.8) when λ are less than 0.3. Figure 29 demonstrates what happens with AUC when the range of λ is narrowed down to 0-0.25. Although the AUC is still decreasing, the drop is very small. The final model is selected to have large AUC value but at the meantime have reasonable clinical explanations.

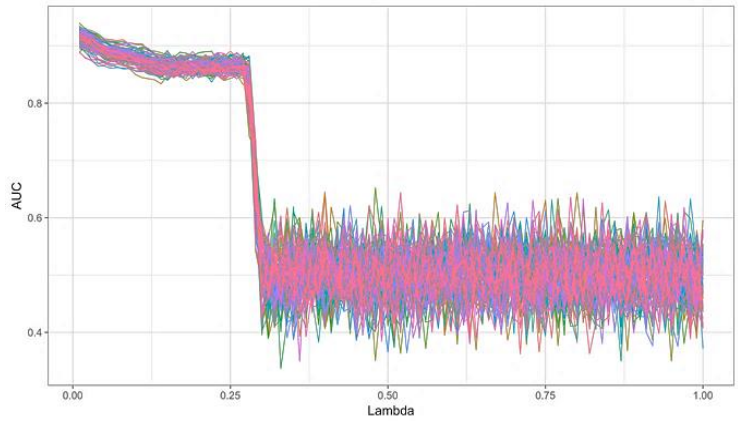

Figure 28. Change in area under curve (AUC) with changing value of lambda

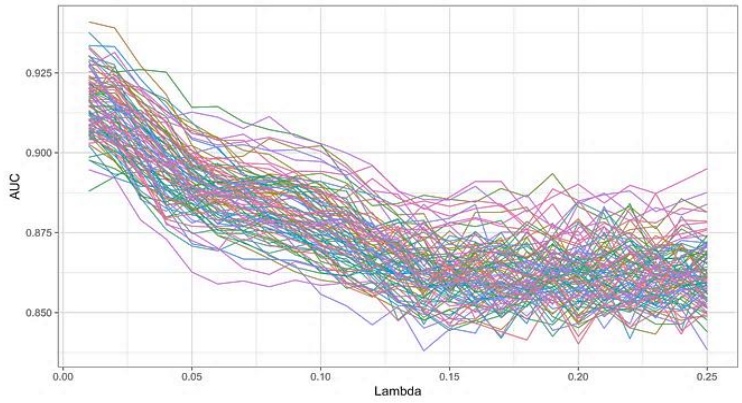

Figure 29. Change in area under curve (AUC) with change of lambda in the range of 0-0.25

Three different logistic models have been built on the three sets of predictors corresponding to different lambda values in Lasso. The models are summarized in table 45. The overall performances are very similar regarding to error rate, sensitivity, specificity, and AUC. The model corresponding to lambda 0.1 has fewer predictors. However, it only includes the postoperative covariates, while model corresponding to lambda 0.06 considered at least one covariate from each group. It may be unusual that some of predictors are insignificant since they are selected by Lasso algorithm. In fact, it could totally happen, since the significance of

each predictor in the model depends on other predictors. The removal of a predictor only because its coefficient is insignificant would cause the model to change totally with that predictor removed. The interaction between predictors is usually complicated, specially when the number of predictors is large and they are somehow correlated to each other. Lasso algorithm helps to select a subgroup of predictors that have good performance in predicting outcome, but it does not necessarily mean all the selected predictors have significant coefficients.

Since the model with lambda being 0.06 has a reasonable number of predictors (7 predictors), with at least one predictor from each group, and the model has satisfactory performance, we have decided the final lasso model to predict complications must include these predictors: Diabetes, Multiorgan resection, Base excess (ICU admission), Heart rate (ICU admission), Heart rate (12 hours after ICU admission), Albumin (on the first postoperative day), and Transfusion (within the last 24h hours).

Table 45. Logistic regression model fitted on the lasso selected variables to predict complications

λ	Predictor, coefficient, OR [95% CI]	Error rate	Sensitivity	Specificity	AUC
0.1	Intercept 11.92 **BE**, -0.14, 0.87 [0.77-0.97] **HR**, 0.05, 1.05 [1.08-1.02] **Albumin 2**, -0.51, 0.60 [0.51-0.71] **Transfusion,** 1.76, 5.81 [1.82-18.54]	0.16	0.87	0.78	0.894
0.06	Intercept 11.11 BE, -0.103, 0.902 [0.788-1.023] **HR**,0.044, 1.045 [1.006-1.087] HR12, 0.032, 1.032 [0.997-1.071] **Albumin 2**, -0.542, 0.582 [0.470-0.693] **Diabetes**, 2.039, 7.686 [1.939-36.598] **Multiorgan resection**, 2.611, 13.615 [1.497-338.413] **Transfusion**, 1.647, 5.190 [1.64-19.061]	0.17	0.89	0.78	0.903
0.05	Intercept 11.83 Hgb 1, -0.02, 0.98 [0.95-1.00] BE, -0.11, 0.90 [0.78-1.03] **HR**, 0.06, 1.06 [1.01-1.10] Capillary refill 12, 0.33, 1.39 [0.84-2.30] HR 12, 0.03, 1.03 [0.99-1.07] **Albumin 2**, -0.53, 0.59 [0.48-0.71] **Diabetes**, 1.80, 6.02 [1.44-25.27] **Multiorgan resection**, 3.01, 20.27 [1.66-248.03] Transfusion, 1.06, 2.89 [0.71-11.88]	0.16	0.88	0.77	0.901

BE-base excess on ICU admission; HR-heart rate on ICU admission; Albumin 2-albumin concentration on the first postoperative day; HR 12-heart rate 12 hours after ICU admission; Hgb 1-preoperative hemoglobin; Capillary refill 12 – capillary refill 12hours after ICU admission;AUC-area under curve; Predictors with significant coefficients are bolded; Error rate, Sensitivity, Specificity, AUC represent 10-fold cross validation average values

When we applied stepwise variable selection on the above logistic regression model (λ=0.06), the whole model was selected, which means predictors BE and HR 12 cannot be removed, even though with insignificant coefficients. The within sample error statistics is summarized below (Table 46, Figure 30):

Table 46. Error statistics of the logistic regression model fitted on the lasso selected predictors

Error rate	***Sensitivity***	***Specificity***	***PPV***	***AUC***
0.146	0.896	0.79	0.868	0.930

PPV-positive predictive value; AUC-area under curve

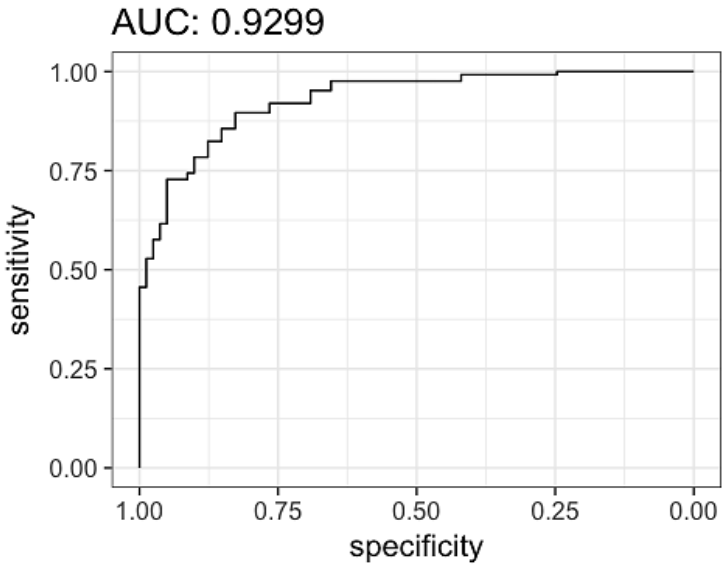

Figure 30. The within sample receiver operating characteristic (ROC) curve of the logistic regression model fitted on the lasso selected predictors (λ=0.06)

We performed 5-fold cross validation to compare the final model with the model with 22 predictors.(Table 47) Clearly, the final model performs consistently well on each fold, or at least better than the model with 22 predictors from step 3 (page 94). Besides, it avoids overfitting.

Table 47. Predictive error statistics for the model with 7 predictors

Fold	*Error rate*	*Sensitivity*	*Specificity*	*PPV*	*AUC*
1	0.143	0.92	0.76	0.85	0.946
2	0.195	0.76	0.92	0.96	0.882
3	0.219	0.95	0.60	0.71	0.876
4	0.146	0.86	0.83	0.92	0.917
5	0.097	0.95	0.85	0.87	0.967

PPV-positive predictive value; AUC-area under curve

4.5.7.Correlation of the predicted probability by lasso selected model with the CCI

There was a strong positive correlation of the probability of complications predicted by the model with the Comprehensive Complication Index (CCI) (r=0.73, p<0.001). Greater probability for complications (as predicted by the model) is associated with greater CCI. (Figure 31)

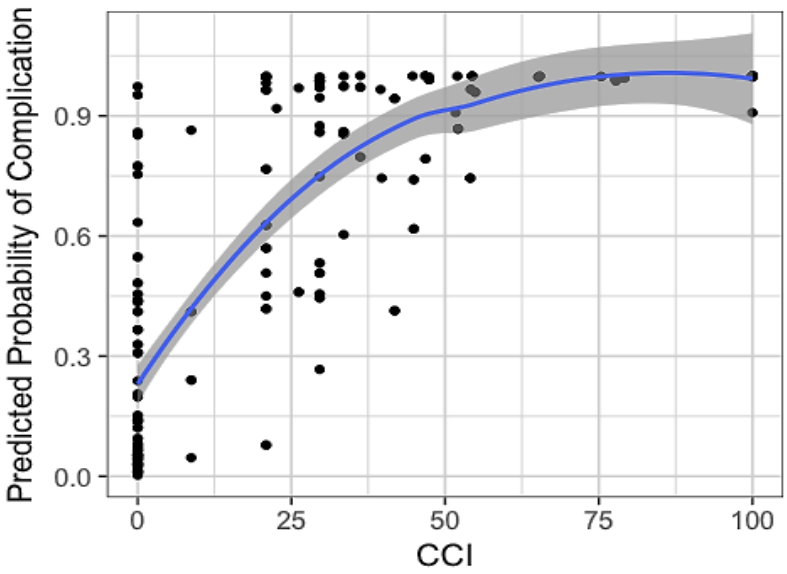

Figure 31. Scatter plot of lasso predicted probability of complications against CCI; Blue smooth line is generated by local regression (LOESS)

4.5.8.Rounding the coefficients

To simplify the model, we further rounded the coefficients to integers or some nicer numbers and than we did the validation on the whole data set. (Table 48)

Table 48. Original and new (rounded) regression coefficients of the model with 7 predictors

Variable	*Coefficient*	*New coefficient*
(Intercept)	10.603	11.00
BE	-0.103	-0.10
HR	0.044	0.04
HR 12	0.032	0.03
Albumin 2	-0.542	-0.55
Diabetes	2.039	2.00
Multiorgan resection	2.611	3.00
Transfusion	1.647	2.00

The error statistics based on the new coefficients are summarized in table 49. Compared with the original model, the overall error rate is similar (old vs new 0.146 vs 0.141), sensitivity is sacrificed a little (0.896 vs 0.848). However, specificity is increased from 0.790 to 0.877 and PPV is increased from 0.868 to 0.914. The AUC keeps the same.

Table 49. Error statistics of the model with 7 predictors and rounded coefficients

Error rate	*Sensitivity*	*Specificity*	*PPV*	*AUC*
0.141	0.848	0.877	0.914	0.934

This new model with rounded coefficients needs further testing on validation data set.

4.6. Model validation

Model validation was performed in a new set of patients operated at the Clinic for Digestive surgery from September 2018 to December 2018. The eligibility criteria, predictors, measurements and outcome definitions were identical to those in the development set. The validation cohort included 60 patients, and 37 of them developed complications in the postoperative period. The median CCI in the validation set was 20.9 [0.0-42.5]. Characteristics of patients in the development and validation set are shown in table 49. They didn't differ significantly regarding the parameters from the model except for the multiorgan resection which was more frequent in patients from the validation set.

Table 49. Characteristics of patients in the development and validation set

Variable	*Development set*	*Validation set*	*p value*
Diabetes	33 (16.0)	15 (25.0)	0.111
Multiorgan resection	18 (8.7)	11 (18.3)	0.036
Heart rate	80.2 ± 17.5	83.0 ± 17.9	0.262
BE	-6.2 ± 4.2	-6.05 ± 4.85	0.814
HR 12	80.8 ± 16.7	82.7 ± 17.8	0.445
Albumin 2	31.1 ± 4.0	30.2 ± 4.1	0.129
Transfusion	60 (29.1)	19 (31.7)	0.737
Complications	125 (60.7)	37 (61.6)	0.890
CCI	20.9 [0 – 44.9]	20.9 [0 – 42.5]	1.000

BE-base excess; HR 12 – heart rate 12hours after ICU admission; Albumin 2 – albumin concentration on the first postoperative day; CCI-The Comprehensive Complication Index

We calculated the probability of developing complications for each patient according to the formula derived from the model:

$$p = \frac{e^y}{1 + e^y}$$

Where p is the probability for developing complications and y is a linear combination of weighted predictors including the model's constant.

For the original model:

y = 10.60 – 0.103xBE + 0.044xHR + 0.032xHR 12 – 0.542x Albumin 2 + 2.039x Diabetes + 2.611x Multiorgan resection + 1.647xTransfusion

For the model with rounded coefficients:

y= 11.00 – 0.10xBE + 0.04xHR + 0.03xHR 12 – 0.55xAlbumin 2 + 2.0xDiabetes +3.0xMultiorgan resection + 2.0xTransfusion

(Diabetes, Multiorgan resection, and Transfusion = 0 if absent, and 1 if present)

The predictive performance of the original model and the model with rounded coefficients is shown in table 50 and figure 32.

Table 50. Predictive performance of the original model and model with rounded coefficients on validation data set

Model	*Error rate*	*Sensitivity*	*Specificity*	*PPV*	*AUC*
Original	0.167	0.919	0.696	0.829	0.913
Rounded coefficients	0.133	0.919	0.783	0.872	0.909

PPV-positive prediction value, AUC- area under curve

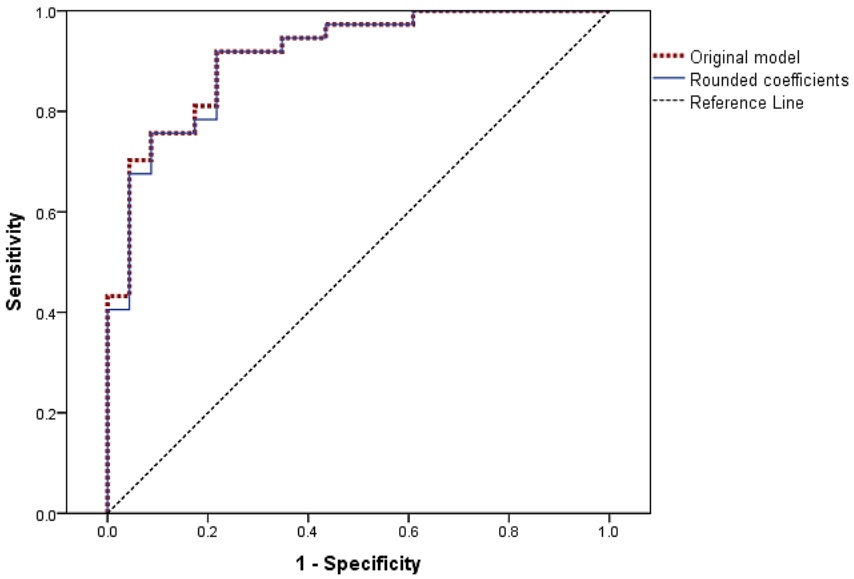

Figure 32. Receiver operating characteristic (ROC) curve for risk of occurrence of postoperative complications predicted with the original model and the model with rounded coefficients; The area under curve (AUC), (95% confidence interval) for the original model is 0.913 (0.841-0.985), p<0.001. AUC for model with rounded coefficients is 0.909 (0.835-0.984), p<0.001

The comparison of areas under curve of the original model and model with rounded coefficients showed no significant difference between them (z statistic 0.075, p=0.940). Both models predict complications pretty well on validation data, particularly the simplified model with rounded coefficients.

5.Discussion

Surgery can be considered safe nowadays since the majority of surgical procedures are associated with a mortality rate of less than 1%. Taking into account the huge global volume of surgery, it is still accompanied by more than 1.5 million of potentially preventable deaths, which almost equals the mortality attributed to road trauma. Postoperative complications are the leading cause of surgery-related mortality. Not only for that reason, postoperative morbidity represents a significant global health problem. Along with prolonged hospitalization and increased costs, it can be associated with some far-reaching consequences such as disability, diminished quality of life, and reduced long-term survival. Therefore, the identification of patients at high risk for developing postoperative complications is a challenging task for perioperative caregivers. Development of strategies aimed at reducing postoperative morbidity with outcome measures reported in a standardized fashion is equally important.

This prospective, observational study attempted to provide a multilayer overview of postoperative morbidity in high-risk patients undergoing major abdominal surgery. We addressed several questions: How frequent are complications in this population of patients? What is their impact on resource utilization? Which method for the assessment of postoperative morbidity is the most appropriate for this category of patients? Is the POSSUM scoring system an adequate tool for prediction of postoperative morbidity and mortality? We also explored whether monitoring of early postoperative perfusion indicators adds any value in the identification of patients with more complicated clinical course. Finally, we developed a statistical model to predict the occurrence of postoperative complications after a major abdominal surgery that included preoperative, intraoperative, and early postoperative risk factors

Incidence and type of postoperative complications; The association with length of stay and functional activity

Our study provided data for a cohort of 206 consecutive high-risk surgical patients admitted to the ICU following major or major + abdominal surgery. They made 4.6% (206/4458) of the total number of patients operated at our hospital during the study period. The proportion of ICU beds to hospital beds is 5.7% (14/245). However, these patients accounted for less than quarter (206/856; 24.1%) of all ICU admissions directly after surgery. In-hospital death

occurred in 14 (6.8%) patients. It is the expected mortality rate for procedures considered as high-risk.[8] The analysis of two large data sets in the United Kingdom revealed that the overall mortality after elective general surgery was 0.44%.[8] However, the mortality rate for complex procedures involving stomach or duodenum was 8.4% and 6.7% for esophagectomy. The European Surgical Outcomes Study (EUSOS) that assessed outcomes after non-cardiac surgery in Europe reported the overall mortality of 4%, which was higher than expected.[3] The mortality rate after upper gastrointestinal, lower gastrointestinal, and hepato-biliary surgery was 6.9%, 5.7%, and 5.0%, respectively. The findings of this study suggested that besides the country where surgery was done, surgery-specific and patient-specific risk factors act together to increase the mortality risk.[3] Three patient-related factors: ASA score, metastatic cancer, and liver cirrhosis acted independently in that direction. A recent study that obtained data from the NSQIP database and included only patients with an American Society of Anesthesiologists physical status (ASA-PS) class of 1 or 2 reported an overall 30-day mortality rate of 0.07% after elective non-cardiac surgery.[202] In this population of relatively healthy patients, male gender, duration of surgery, age, smoking, and hypertension were independently associated with mortality, while general surgery had the highest mortality rate.[202] Patients in our study were older (63.9 ± 11.8 years vs 49.7 ± 15.8), predominantly male (64.6% vs 39.1%), more frequently smokers (27.7% vs 17.8%), with a history of diabetes (16% vs 4.7%), and half of them had the ASA-PS class of 3 or 4. Moreover, they all underwent complex surgery, mainly for cancer (91.3%) or metastatic cancer (16.0%). It is therefore not surprising that patients in our cohort had a considerably higher mortality rate. On the other hand, our data originate from a high volume, university-affiliated center, specialized in digestive surgery which may explain the lower mortality than reported by some authors.[203]

The overall postoperative in-hospital morbidity in our cohort was high, as 125 (60.7%) patients developed at least one complication. It is usually reported that the incidence of complications following major gastrointestinal surgery is around 30%.[203–205] There are also reports that the occurrence of complications in unselected patients can even be higher than 70%.[31,206] The apparent heterogeneity may be in part explained by variation in criteria used to define a complication, and also by dissimilarities of studied populations and clinical setting.[41,207] In accordance with findings of previous investigations, the infectious complications (16.9%) were the most frequently encountered.[204,208] Infectious complications are found to be the main source of postoperative morbidity after abdominal surgery.[209] In a

multicenter study, Pessaux et al showed that the age, malnutrition or obesity, cirrhosis, a vertical abdominal incision, prolonged operative time, and anastomosis of the bowel represent the independent risk factors for infectious complications after abdominal operations.[210] Even the country's income according to the UN's Human Development Index (HDI) influence the burden of surgical site infections (SSI) after gastrointestinal surgery.[211] Our cohort consisted mainly of oncological patients whose immunological disturbances and susceptibility to infections are well known, particularly in the advanced disease or following adjuvant therapy.

Pulmonary complications were also common in our study, making 15.2% of all complications. The analysis of NSQIP database with more than 160000 patients who underwent major abdominal surgery demonstrated that among all patient-related and surgery-related variables, esophagectomy was the strongest predictor of postoperative pulmonary complications.[94] They were also more likely to occur after upper abdominal approach, being more common following open compared to laparoscopic surgery.[94,98]

Patients with complications were more likely to have preoperative anemia, hypoalbuminemia, and higher CRP levels. They were diabetics more frequently, had a higher ASA score and were more likely to receive chronic corticosteroid therapy. In contrast to many other studies, no particular comorbidity, except diabetes, was associated with the occurrence of complications in our study.[212,213] We believe that clinicians, aware of the risks inherent to complex cardiovascular or pulmonary comorbidities, undertook measures for optimization of patients' condition, thereby reducing the baseline risk. It is a common practice at our hospital to enable a prolonged preoperative hospitalization in order to complete necessary consultant investigations and to provide treatments prior to surgery so that chronic disorders can be stabilized. Patient preoperative management is individually tailored. Strategies for preoperative optimizations vary, and the choice is usually made on the discretion of the attending surgeon or anesthesiologist. These strategies were beyond the scope of our study, and preoperatively we recorded only the patient's medical history and the variables contained in the Physiological POSSUM score.

Length of hospital stay (LOS), commonly used as a measure of clinical outcome, is an indicator of perioperative resource consumption. It is easy to define and quantify and may serve as a suitable marker of resource utilization when detailed data on hospital costs are not available. When used to estimate hospitalization costs, level of care should be taken into

account, since the expenditures of the ICU stay are much higher than those of the ward hospitalization.

All indices of hospitalization, i.e. ICU LOS, postoperative LOS, and total LOS were significantly greater in patients with complications in our study. A considerably greater proportion of these patients had a prolonged hospital LOS. It is in agreement with previous studies that clearly demonstrated the association of postoperative complications with LOS.[214,215] The study that analyzed data on 11 elective major operations from the NSQIP database demonstrated that intraoperative factors along with the postoperative adverse events contributed more to the risk for prolonged LOS than preoperative characteristics, such as comorbidities or functional activity.[216]

However, there are some limitations that should be considered when using hospital LOS as the outcome. First, the level of fitness on discharge from the hospital may differ greatly between wards and institutions. It can be an important source of bias when comparing inter-institutional perioperative outcomes. All patients in our study were discharged without complications, and if the complication requiring readmission occurred within 30 days after discharge, it was recorded and the new LOS was added up to the previous. Still, not all of the patients were in the same state of well-being on discharge from hospital, since the over-all functional activity was significantly lower in patients with complications. Second, even in patients with the same level of fitness on discharge, the hospital LOS can vary markedly due to non-clinical, mainly socially influenced factors. The hospital LOS cannot be taken as a pure surrogate for postoperative morbidity, particularly in older patients in whom the accessibility of social service packages or rehabilitation facilities may influence the duration of postoperative hospitalization.[217] Similar can be applied to the ICU LOS, since the admission and discharge criteria differ between hospitals and the length of ICU stay can be influenced by the availability of critical care beds.

The evaluation of postoperative morbidity with the Clavien-Dindo Classification and the Comprehensive Complication Index

To the best of our knowledge, this study is the first to evaluate the CCI as a system for complication reporting and to compare it with the Clavien-Dindo classification in a relatively homogenous population of high-risk surgical patients undergoing major abdominal surgery. This is the population of patients in whom multiple postoperative complications are expected, not only as a result of complex surgery but also because of the patient-inherent risks. The rate

of multiple complications was high in the present study, as 98 patients (47.6%) developed more than one complication. The median CCI for the entire cohort was 20.9 [0-44.9], which is similar to other studies reporting results of specific types of major abdominal surgery.[31,32] The majority of patients with complications had the highest CD grade II (62/125 patients; 49.6%). However, their median CCI was 29.6, ranging from 20.9 to 47.4. The range of CCI values between the extremes further increased with the rising CD grade, with overlapping of lower CCI values of the higher CD grade with higher values of the lower CD grade. It is totally expected when multiple complications are being assessed. For example, a patient with one grade I complication (superficial wound infection) and one grade II complication (arrhythmia) would be reported as CD II with a CCI of 22.6. The other patient with one grade I complication (transient confusion) and four grade II complications (urinary tract infection, deep venous thrombosis, pneumonia, and *Cl.difficile* infection) would also be reported as a CD II, with a CCI value of 42.7. Conversely, according to the Clavien-Dindo classification, a patient with a single IVa grade complication (pulmonary embolism resulting in an acute respiratory failure) would be categorized as a more severely complicated than a patient who had reoperation due to an anastomotic breakdown (grade IIIb), complicated with pleural effusions (grade IIIa), anemia (grade II), tachyarrhythmia (grade II), and deep venous thrombosis (grade II). The CCI value of the first patient would be 42.4, while that of the latter would be 56.0. It has been demonstrated by Slankamenac and coworkers that a postoperative course with multiple complications is perceived by patients as a more severe.[28] Although the perceptions of patients, nurses, and physicians mainly matched with the assigned Clavien-Dindo grade, we believe that in the setting of high-risk surgical patients the therapy applied to treat the most severe complication cannot be used as the only method to describe reliably the entire postoperative course.

The number of postoperative complications in our study increased with the rising CD grade, as well as the proportion of patients with more than three complications. Clavien et al demonstrated similar findings in their study aiming to prospectively assess the value of the CCI compared with a standard classification of complications.[35] However, we found a significantly stronger correlation of the CCI with the number of complications than the association of the CDC with this parameter. It has been shown that the number of complications impacts not only the patients' safety and satisfaction, but is also strongly related to costs.[218,219] Moreover, a new cost prediction tool based on the CCI has been recently validated.[220]

The CCI values corresponded well with the CD grade in our study, reflected by the significant difference among each two grades, except the grades IVa and IVb. We assume that this can be attributed to the small number of patients in the IVb grade. Nevertheless, the two scales demonstrated a strong positive correlation.

Both systems for complication reporting showed strong correlations with hospitalization indices. The CCI was uniformly better correlated with all analyzed parameters, particularly with the ICU LOS and a prolonged ICU stay. Several authors were also able to show the stronger relation of the CCI with a hospital LOS.[28,31,92,218–220] However, there are some issues that need to be addressed regarding hospital LOS as an outcome measure. First, since the CCI and the CDC exhibit a strong correlation, with a correlation coefficient close to 1, it is possible to get inflation of t-statistics and clinically insignificant differences in correlations with LOS may be found statistically significant. Second, as previously said, there are many limitations of the length of stay as a clinical outcome, since discharge criteria may vary significantly between surgeons and institutions influenced by various nonclinical issues. Third, a longer postoperative course doesn't necessarily reflect the severity of the complication. There are severe complications that can resolve completely after a promptly indicated reoperation. On the other hand, some less severe complications might require long-term conservative treatment. Anyhow, length of hospital stay continues to be extensively used as an outcome measure, since it is commonly applied for cost assessments, and is easily accessible in medical records.

Our study demonstrated the association of the CCI as well as of the CD grade with functional activity on discharge. In a paper by Legner et al, it has been shown that postoperative complications significantly influenced a discharge location (home, home with assistance, or institutional care) after abdominopelvic surgery, but their severity has not been reported.[221] Although it is not easy, from a statistical point of view, to compare the effects of these two scales, we think that the impact of both of them on this patient-centered outcome is even more important finding than the effect on resource utilization.

The limitations of this study are common with those that originate from a single center. Local patterns of perioperative care may have influenced the treatment of complications. Personal practice of the attending surgeons and the available resources on wards most probably affected the length of preoperative and postoperative hospital stay. The fact that the study was conducted in the biggest tertiary care university hospital may in part explain the high

number of complications.

The strength of the study is that it was performed in a well-defined cohort of high-risk patients with a planned admission to the ICU, which reduced a bias coming from an early postoperative process of care. The prospective nature of the study allowed a meticulous recording of all postoperative complications, enabling a reliable CCI calculation.

The evaluation of the POSSUM and the P-POSSUM scoring system for complications and mortality after high-risk major abdominal surgery

A stone inscription of Hammurabi's law written almost 4000 years ago stated: „ If a doctor has treated a free man but caused a serious injury from which the man dies...the man is to cut off his hands".[222] It has been well recognized in the meantime that the outcomes of surgery measured by the mortality rate or long-term disability cannot be attributed exclusively to the surgeon's performance, but also to the patients' physical status and characteristics of the operation. Taking the mortality rate as the sole indicator would lead to the flawed conclusion that the units admitting only the low-risk patients perform better than the tertiary centers with high turn-over of more demanding cases. This observation was the basis for the development of methods for the surgical audit that rely on patient and operation risk-adjusted outcomes. The POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) scoring system was designed in 1991 for surgical audit across the wide surgical spectrum.[116] This system, as well as its related models (P-POSSUM, O-POSSUM, CR-POSSUM, E-POSSUM) modified in order to enchance predictive performance of the original score, have been also employed to determine an individual patient's risk for a specific planned or urgent operation.

Our study evaluated the predictive performance of the POSSUM and P-POSSUM score for postoperative morbidity and mortality. As far as we know, it was the first validation of the POSSUM scoring system in patients undergoing abdominal surgery in Serbia.

In the present study, the accuracy of POSSUM to predict postoperative morbidity was beyond optimal, since the underprediction of complications was found in all risk groups. It was particularly pronounced in the lowest risk band. Poor calibration of the score that we encountered confines its application for risk prediction in individual patients. In a systematic review of POSSUM and its related models as predictors of morbidity after surgery for

colorectal cancer, Richards et al showed considerable variations in the observed to expected morbidity (O:E) ratios between four analyzed studies.[223] It is also noteworthy that only 4 out of 10 studies evaluated POSSUM performance for prediction of complications, while all of them assessed the accuracy in prediction of mortality. The differences in O:E ratios for morbidity can be found across all studies regarding POSSUM (Table 5.1). It may be in part explained by arbitrary and non-uniform definitions of complications that differ from the original POSSUM descriptions. Our study defined complications according to the European Perioperative Clinical outcome (EPCO) definitions of perioperative outcome measures, issued by the European Society of Anaesthesiology – European Society of Intensive Care Medicine (ESA-ESICM) joint taskforce in 2015.[199] The list of suggested and defined complications is more comprehensive than the original Copeland's list.[116] It is therefore possible that that the underprediction of morbidity by the POSSUM score encountered in our study can be attributed to the more precise definitions of complications and a more detailed follow-up.

In terms of postoperative mortality, both POSSUM and P-POSSUM showed reasonable discrimination with similar area under ROC curves of 0.744 and 0.739, respectively. In other words, both scores had a good power to discriminate between patients by assigning the higher value to the patients who died. The results of our study suggest that POSSUM largely overpredicts mortality in our population (O:E ratio 0.38) and shows a lack of fit in all risk groups. Similar results can be found in many studies related to abdominal surgery. (Table 5.1) Wang et al. in a systematic review of 1734 pancreatic resections found a significant overprediction of mortality by POSSUM (O:E ratio, 0.35) and the underprediction by P-POSSUM (O:E ratio, 1.39) for this type of surgery.[126] Because the original POSSUM score was shown to overestimate mortality, particularly in low risk groups due to the nature of the logistic regression derived equation, the P-POSSUM was developed with the same predictors by adjusting the equation to overcome this shortcoming.[127] Poor calibration of POSSUM and P-POSSUM that doesn't allow a reliable individual risk prediction may be in part explained by the fact that these scores were developed in a population of general surgical patients. Therefore, the predictors proven to be of importance for the outcome of the specific type of surgery were not included in the model. In order to enhance the reliability of the prediction of postoperative mortality, several specialty-specific derivatives of POSSUM have been proposed, including CR-POSSUM for colorectal surgery, V-POSSUM for vascular surgery, O-POSSUM for oesophageal and gastric surgery, E-POSSUM for elderly.[122,128,129]

Table 5.1 Summary characteristics of studies of POSSUM and its derivatives for prediction of postoperative morbidity and mortality

Study	Year	Type of operation	Number of patients	Analyzed scoring system	Predicted mortality	O:E ratio for mortality	O:E ratio for morbidity	Comment
Lam[119]	2004	Hepatectomy	259	P-POSSUM	4.2%	1.4	-	Overprediction of mortality
Hariharan[229]	2009	Colorectal	232	CR-POSSUM	7.7%	0.9	-	Good calibration; AUC 0.69
Pinho[230]	2017	Bariatric	94	POSSUM P-POSSUM	1.05%	0 0	0.97	Overprediction by both scores; No deaths in the cohort
Pelavski[122]	2013	Emergency gastrointestinal	126	POSSUM P-POSSUM	34.9% 22.2%	1.07 1.57	-	AUC (POSSUM) 0.70 AUC (P-POSSUM) 0.70 Elderly patients
Valenti[118]	2009	Rectal cancer	273	POSSUM	6.6%	0.10	0.84	Significant overprediction of mortality
Zhong[231]	2013	Pancreaticoduodenectomy	396	POSSUM	5.31-8.82%	0.33	0.75	Better prediction in elderly
Carvalho[226]	2018	Colorectal	551	POSSUM P-POSSUM	11.3% 5.8%	0.5 0.97	 0.40	High-risk patients
Vishwani[120]	2014	Peritonitis	89	POSSUM	23.5%	0.28	0.71	Overprediction in low risk groups
Merad[232]	2012	Major gastrointestinal	3881	P-POSSUM	6.5%	1.00	-	AUC 0.87 Poor discrimination for liver surgery
Luna[36]	2009	Gastric cancer	106	POSSUM P-POSSUM O-POSSUM	13.0% 4.9% 12.1%	0.6 1.6 0.6	1.34 (total gastrectomy) 0.87(distal gastrectomy)	POSSUM and O-POSSUM overestimate mortality P-POSSUM underestimates
Tekkis[124]	2000	Gastrointestinal	505	POSSUM P-POSSUM	21.4% 11.3%	0.52 0.98	_	P-POSSUM better predictor of mortality
Tekkis[128]	2004	Gastric surgery	1042	P-POSSUM O-POSSUM	_	1.21 1.04	_	AUC (P-POSSUM) 0.746
Horzic[224]	2007	Colorectal	120	P-POSSUM CR-POSSUM	6.7% 7.5%	1.25 1.11	_	AUC (P-POSSUM) 0.70 AUC (CR-POSSUM) 0.59

For example, CR-POSSUM takes into account 6 physiological (age, cardiac failure, systolic blood pressure, heart rate, hemoglobin, urea) and 4 operative variables (complexity of the surgery, peritoneal soiling, Duke cancer stage, and urgency of surgery) in a logistic regression-derived formula.[129] These variables were shown to be specific for patients undergoing colorectal surgery. However, subsequent analyses of the CR-POSSUM didn't demonstrate superior performance in predicting mortality when compared to POSSUM and P-POSSUM. In a study of patients undergoing resection for colorectal cancer, the discriminatory power of CR-POSSUM was far below optimum (AUC=0.59) and inferior to that of the P-POSSUM score (AUC=0.70).[224] The systematic review that assessed the predictive value of POSSUM models for outcomes after colorectal surgery included ten studies on POSSUM, 17 studies on P-POSSUM, and 14 studies on CR-POSSUM, with more than 10000 patients.[223] The review clearly demonstrated that all models overestimate mortality after colorectal surgery, with O:E ratio for POSSUM, P-POSSUM, and CR-POSSUM of 0.31, 0.90, and 0.64, respectively.[223] The similar was shown in the analysis of POSSUM and O-POSSUM for mortality prediction after oesophageal and gastric surgery.[225] It appeared that surgery-specific O-POSSUM added no value since it overestimated mortality to a higher extent than POSSUM and P-POSSUM score.[225] We believe that the fact that POSSUM was developed more than 25 years ago may have influenced its low accuracy for mortality prediction in recent studies. The advent of minimally invasive surgery, fast track protocols, and improvement of perioperative care, contributed to the substantial drop in mortality in the past decades. The operative component of the POSSUM doesn't take into consideration any of these important parameters, therefore neglecting factors that positively influence the outcome.

In our study, the overall O:E ratio of the P-POSSUM score was 0.93, suggesting slight overestimation of mortality. However, the calibration (goodness-of-fit) was satisfactory. This finding is in accordance with other studies that showed P-POSSUM was able to accurately predict mortality, particularly in populations comprised of high-risk patients.[225,226]

The drawback of our study is a relatively small number of patients included in the analysis. It didn't allow for testing the calibration of the scores in deciles of risk. The study probably wasn't powered enough to assess the predictive performance of POSSUM and P-POSSUM given the low mortality rate after elective surgery. Usually, very large populations are needed to draw conclusions regarding the predictive accuracy of any model. Nevertheless, due to considerable overestimation of mortality that was encountered in our study, we think that the

POSSUM score cannot be used in our population of high-risk patients for individual risk prediction, particularly not when making decisions about potentially curative surgery. On the other hand, based on the results of previous studies, we don't believe that the accuracy for individual risk prediction can be improved by creating additional surgery-specific POSSUM derivatives, or by readjustments of POSSUM equation.[227,228] Furthermore, clinical utility and practical value of many different POSSUM predictive models is questionable.

Despite the limited usefulness for the assessment of individual risk, we believe that P-POSSUM score, due to non-significant O:E ratio for mortality found in our study, can be used for surgical inventory to compare the mortality of the populations after major abdominal surgery.

The association of disturbances of peripheral perfusion with postoperative complications

The principal finding of our study regarding the peripheral perfusion is that postoperative perfusion disturbances encountered early after major abdominal surgery were more pronounced in those patients whose postoperative course was burdened with more severe complications. Almost all indicators of peripheral perfusion were more markedly altered in patients who developed the more complicated postoperative course, as assessed with the CCI. This difference was already present on admission to the ICU and even more predictive than 12 hours later.

Perioperative hemodynamic optimization through goal-directed protocols has demonstrated efficacy in reducing complications and shortening the postoperative length of stay.[229,230] Goal-directed protocols suggest the use of manifold strategies such as fluid challenges, transfusion, and inotropes in a strictly protocolized manner aimed at achieving predefined hemodynamic targets. The idea around these protocols is to optimize oxygen delivery and keep the balance between oxygen delivery and consumption by maintaining global hemodynamic parameters such as stroke volume, mean arterial pressure, and central venous oxygen saturation ($ScvO_2$).[230] However, there is growing evidence that the normal range of $ScvO_2$ achieved during the implementation of goal-directed strategy in surgical patients may not reflect the optimal perfusion during the postoperative period.[197,198] Therefore, relying on $ScvO_2$ and other global hemodynamic parameters can produce a situation in which the true optimization of perfusion may be missed. Patients in our study were admitted to the ICU with

normal values of mean arterial pressure (MAP) and $ScvO_2$ and it was the same for patients with severe and non-severe complications. Different strategies and monitoring techniques (Esophageal Doppler, LidCo *Rapid*) were used intraoperatively to accomplish these values, on the discretion of the attending anesthesiologist. On the other hand, patients with severe complications presented on admission to the ICU, with the higher central-to-toe temperature gradient (Δ T), the higher CO_2 gap and $\Delta pCO_2/C_{a\text{-}v}O_2$ value, and the increased capillary refill time (CRT). None of these parameters were routinely monitored intraoperatively.

The events in the peripheral circulation during the immediate postoperative period resemble those of septic or hypovolaemic shock. The increased vascular tone as a consequence of increased sympathetic output and activated baroreceptor reflex is a compensatory mechanism with the aim to preserve the perfusion of vital organs.[231] It is usually achieved at the expense of reduced perfusion in splanchnic organs, skin, and kidneys. The physiological stress response that accompanies major surgery is characterized by inflammation mediated by cytokines released from the surgical site.[232] Inflammatory cascade along with the neural and endocrine mechanisms for volume conservation, such as the release of aldosterone and vasopressin, as well as catecholamine-induced vasoconstriction cause fluid shifts between compartments and affect the microcirculation.[231,232] Furthermore, stress-induced catabolism leads to increased oxygen demands. The extent of this stress response is largely dependent on the type of operation, but it has been demonstrated that it is associated with the development of postoperative organ dysfunction and impaired healing, thus strongly influencing the outcome.[233] Postoperative alterations of peripheral perfusion can occur even in the circumstances of maintained systemic hemodynamics.[143,173]

In our cohort, increased ΔT, enlarged CO_2 gap and $\Delta pCO_2/C_{a\text{-}v}O_2$, and delayed CRT that were encountered on admission to the ICU in patients who suffered a more complicated postoperative course may reflect the extent of these inflammatory changes and disturbances of peripheral perfusion.

Central-to-toe temperature gradient has been shown to correlate well with the extent of skin vasoconstriction, and that even its subjective evaluation may discriminate patients with abnormal perfusion and more severe organ dysfunction.[146] It was shown that mean ΔT was associated with ICU and hospital mortality in patients with septic shock while the mean $ScvO_2$ was not.[141] Our patient population had decreased both central and peripheral temperature on admission to the ICU, and we believe that it can partly be attributed to

inadvertent intraoperative hypothermia. However, Δ T was significantly greater in patients in whom more severe complications occurred postoperatively. Because of the observational nature of our study, we can't determine whether subsequent use of warming or the resuscitation measures that were undertaken influenced the decrease of ΔT after 12 hours in the ICU, making it insignificantly different between two groups of patients. Our results show that ΔT on admission to the ICU after the operation was the single most important perfusion parameter that could make good discrimination between patients with less and more severe complications. The fact that its prognostic value has not been found later during ICU stay points to the intraoperative period and the need for close monitoring of intraoperative temperature and prevention of hypothermia. The study of Kaplan et al demonstrated that surgical patients with cool extremities had lower cardiac output, cardiac index, pH, and SvO_2 compared to patients with warm extremities.[234] Despite no differences with regards to heart rate, systolic and diastolic blood pressure, arterial partial pressures of oxygen and carbon dioxide, patients with cold extremities had significantly higher lactate values.[234] A recent meta-analysis showed that perioperative hypothermia was not associated with surgical site infections.[235] The large cross-sectional study with 30-day follow up conducted in surgical patients in China revealed the same.[236] However, it was also able to demonstrate that hypothermia was associated with more postoperative shivering, longer PACU stay, more complications requiring ICU readmission, and longer hospitalization.[236]

Patients with more severe complications in our study had a delayed capillary refill time on admission from the operating room. Although the delayed CRT may have been influenced by the low peripheral temperature, this parameter remained a significant predictor of the CCI>50 in the multivariate analysis. Questions have been raised regarding the clinical reliability of CRT in the assessment of peripheral perfusion, due to its inherent subjectivity. In our study, CRT was measured by one investigator. However, good interobserver reliability between assessors was demonstrated.[142] Furthermore, it was shown that CRT correlates well with the sonographic pulsatility index, a validated measure of visceral blood flow.[237] The correlation of CRT with the intestinal flow was particularly strong.[237]

Patients in our study had normal values of central venous oxygen saturation ($ScvO_2$) on admission to the ICU. No differences were observed between patients with the less and more severe postoperative course. However, the difference became evident after 12 hours, since the $ScvO_2$ decreased in patients with CCI>50. Optimization of $ScvO_2$ (reaching target values >70%) is a standard component of goal-directed protocol that was proven beneficial in

improving outcomes of major abdominal surgery.[230] Since goal-directed therapy is aimed at optimizing tissue perfusion and oxygen delivery by the administration of fluids and vasoactive drugs, it should be underlined that none of the hemodynamic parameters stands out as its best endpoint during the perioperative period. The fact that systemic hemodynamic parameters cannot reveal alterations of tissue perfusion represents the rationale for the use of other indicators of tissue well-being, such as lactate and $ScvO_2$. The value of $ScvO_2$ is determined by global oxygen delivery (DO_2) and consumption (VO_2). Both DO_2 and VO_2 are subject to extensive changes during the perioperative period.[184] Pearse et al showed that $ScvO_2$ sharply decreases immediately after the end of surgery, despite unchanged DO_2 and cardiac index, suggesting the increased oxygen consumption after emergence from anesthesia.[184] On the other hand, the common practice of administering high FiO_2 during anesthesia may mask the detrimental intra-operative effects on tissues, if the monitoring was based on $ScvO_2$. The value of $ScvO_2$, as well as of other O_2-derived parameters should be interpreted cautiously when identifying tissue hypoxia during the perioperative period. Normal or even high $ScvO_2$ can be found despite severe tissue hypoxia if the tissue oxygen extraction has been impaired. The similar was shown for oxygen extraction ratio (O_2ER).[195] A randomized controlled trial by Jammer et al, conducted in patients undergoing colorectal surgery failed to prove the benefits of $ScvO_2$-guided goal-directed therapy in terms of reducing postoperative morbidity.[238] In the study of Robin et al, $ScvO_2$ couldn't discriminate between high-risk patients with and without postoperative complications.[197] Moreover, many of these patients, similarly to patients in our study were already "optimized" intraoperatively using $ScvO_2$ as the therapeutic endpoint. The main finding of that study was that an enlarged CO_2 gap was highly predictive for postoperative morbidity.[197]

These results match with those of previous studies demonstrating that the increased CO_2 gap was associated with worse outcomes in patients with septic shock or isovolemic anemia.[239,240] According to the Fick equation, CO_2 gap is directly related to CO_2 production (VCO_2) and inversely related to cardiac output (CO).[189] Therefore, an increase in CO_2 gap can be found during the low-flow state, even though no additional CO_2 has been generated. The stagnation phenomenon that lies behind the widening of CO_2 gap during the low-flow states may explain the situation in which a normal $ScvO_2$ is associated with the increased CO_2 gap. Futier et al in the study that included high-risk surgical patients undergoing major abdominal surgery demonstrated that postoperative complications occurred more frequently in patients with the increased CO_2 gap, despite the normal values of $ScvO_2$ and CI.[241] They proposed the use of

CO_2 gap as a complementary tool to $ScvO_2$ to detect the relative flow insufficiency when hemodynamics has been apparently optimized.[180] Patients in our study who developed more severe complications (CCI>50) had a significantly greater CO_2 gap on admission to the ICU compared to the patients with CCI<50. The value of CO_2 gap in both groups decreased thereafter,though significantly only in patients with less severe complications. We assume that the drop in this value occurred as a result of the therapy received during the first hours of ICU stay. Previous studies suggested that the physiological value of CO_2 gap is < 6mmHg.[179,197] Silva et al found even lower value (< 5mmHg) measured preoperatively in high-risk patients to be predictive for mortality.[242] Patients in our cohort exhibited higher median values of CO_2 gap than reported by previous studies.[195,197,241] It should be pointed out that CO_2 gap is determined by several factors besides cardiac output (CO): venoarterial CO_2 content difference, CO_2 dissociation curve, and minute ventilation.[243] It is noticeable that patients in our study who demonstrated wider CO_2 gap had lower arterial CO_2 partial pressure ($PaCO_2$). It can be ascribed to hyperventilation which may have happened at the start of postoperative mechanical ventilation, on admission to ICU. Besides, hypothermia which was common in our patients may have influenced the relationship between CO_2 content and CO_2 partial pressure.

It should be emphasized that CO_2 gap can be a marker of tissue hypoxia only when hypoxia ensues from the low flow.[189] Normal values of CO_2 gap can be found in the severely hypoxic conditions, i.e. in septic shock, if the hyperdynamic circulation is sufficient to wash out the excess carbon dioxide. It was shown in the animal model that an increase in CO_2 gap occurred only when hypoxic conditions were induced by a decrease in flow (ischemic hypoxia), and not when hypoxia was elicited by a decrease in FiO_2 with maintained blood flow (hypoxic hypoxia).[244] Therefore, a combination of venoarterial CO_2 difference and arteriovenous O_2 content difference ($\Delta pCO_2/C_{a\text{-}v}O_2$) was proposed as a better indicator of anaerobic CO_2 production and tissue hypoxia, regardless of the blood flow.[177,195] Patients with the more complicated postoperative course in our study were found to have significantly higher $\Delta pCO_2/C_{a\text{-}v}O_2$ ratio on admission to the ICU. The occult tissue hypoxia despite normal hemodynamic and oxygenation parameters may have been responsible for the later development of complications. Furthermore, in the multivariate analysis, $\Delta pCO_2/C_{a\text{-}v}O_2$ was identified as the independent predictor of severe postoperative complications, while CO_2 gap was not independently associated with CCI>50.

Serum lactate levels were similar on admission to the ICU in patients with and without severe complications. However, a significant difference in lactate levels between the two groups of patients was shown 12 hours after the admission. We demonstrated that the lactate levels assessed at 12 hours following the operation had the highest discriminative power to detect patients with a more complicated postoperative course. This is not surprising, knowing that hyperlactatemia is a relatively late phenomenon after the onset of hypoxia since the liver can increase the clearance of lactate produced during anaerobic metabolism.[245] The cut-off lactate value at 12 hours for CCI>50 was 1.65 mmol/l, which is the value commonly considered to be within the normal range in critically ill patients. However, a relative hyperlactatemia has already been identified as a bad prognostic factor in septic patients, suggesting that the serum lactate within the reference range should be interpreted cautiously.[246,247] A number of studies showed that hyperlactatemia (lactate levels between 2 and 4 mmol/l) is associated with a worse clinical outcome in patients with septic shock. The lower threshold has been proposed according to the new evidence.[248] Since the patients undergoing the elective abdominal surgery are considerably different compared to septic patients, in our opinion, the upper limit of lactate levels associated with worse outcomes in this population should be different as well. The results from this and other studies indicate the need for re-defining the cut-off values of serum lactate to predict outcomes in the perioperative setting.[171] Nevertheless, additional studies are required to elucidate which of lactate-guided therapies can improve perioperative outcomes. Overall clinical context should be considered when treating postoperative hyperlactatemia. For example, the attempts to normalize lactate levels through resuscitation with fluids or inotropes, in the absence of other signs of tissue hypoperfusion, may expose patients to overhydration and high doses of inotropes without any obvious benefit.[174] Thus, it is important to take into account other potential aerobic mechanisms of hyperlactatemia and to treat the underlying causes accordingly. With this regard, recognition of signs of hepatic dysfunction is essential as it is related to lactate clearance.[249] Moreover, reduction of increased muscle work arising from shivering, or increased work of breathing can decrease serum lactate levels. The study by Berg et al. demonstrated that the administration of thiamine may increase the aerobic metabolism in critically ill patients with stable hemodynamics, by enabling pyruvate to enter the Krebs cycle.[250] However, the role of thiamine in decreasing serum lactate and thus affecting the postoperative course remains unclear and requires additional studies.

The multivariate analysis of perfusion parameters adjusted for vasopressor use and transfusion showed that the independent predictors of the more complicated postoperative

course (CCI>50) were capillary refill, central-to-toe temperature gradient, and $\Delta pCO_2/C_{a\text{-}v}O_2$ on admission to the ICU and lactate level and base excess 12 hours after the admission. These results suggest that the key indicators of tissue hypoperfusion and hypoxia could be detected early after the operation. We believe that the increased lactate and base excess that were recorded later denote the expected after-effects of the deranged perfusion present immediately after the operation. In our study, indicators of peripheral perfusion were not monitored systematically during the operation. Therefore, the association of alterations of tissue perfusion that were present on admission to the ICU after surgery with severe postoperative complications should perhaps shift our focus to the intraoperative period. We hypothesize that the timely recognition of these derangements and the appropriate treatment could diminish postoperative morbidity to some extent.

To the best of our knowledge, no study to date has evaluated the specific perioperative goal-directed algorithm aimed to optimize the peripheral perfusion. The experimental animal study demonstrated favorable effects of restrictive fluid administration and permissive hypotension on microcirculation in a model of hemorrhagic shock.[251] Den Uil and colleagues showed dose-dependent beneficial effects of nitroglycerin on microcirculation, as measured with the decrease of central-to-peripheral temperature gradient and Side-stream Dark Field imaging, in patients with cardiogenic shock.[252] These effects were measurable before changes in systemic hemodynamics and were independent of cardiac index.[252] Clinical research during the past decade yielded many studies that suggested perioperative goal-directed protocols targeting macrohemodynamic parameters. These studies had conflicting results.[253] Further studies are needed to determine the effect of perioperative interventions based on the indicators of peripheral perfusion. Given the results we reported, we believe these indicators might be an important complementary tool for the assessment of hemodynamic status and patient management.

Our study has several limitations. First, the observational nature of the study didn't allow us to draw conclusions about the causality of the observed association between alterations of peripheral perfusion and the severity of complications. Second, we took the arbitrary cut-off value of the CCI of 50 to discriminate between more and less severe complications. This threshold was chosen because the results of our previous study showed that the CCI of around 50 corresponds to the Clavien-Dindo grade 3b (reoperation under general anesthesia) or multiple complications of lesser severity. Maybe the results of this study would have been different if the other cut-off was chosen. Third, we didn't collect data on preoperative and intraoperative parameters of tissue perfusion. It is possible that the duration of tissue

hypoperfusion and hypoxia had a significant effect on the occurrence of complications. However, many of the indicators of the tissue perfusion normalized during the first 12 hours in the ICU. The admission value was the one that independently predicted severe complications. Fourth, some of the possible confounding factors, such as the postoperative pain control or liver function that may have influenced the lactate values were not recorded. Finally, the drawback of our study is that we didn't collect the data on interventions and therapies that could have altered values of perfusion indicators. Nevertheless, all patients were treated according to the standards of local care and none of the variables that we analyzed were directly used to guide patient management in the ICU.

Development and validation of the new model for prediction of complications

George Box (1919-2013), one of the greatest statisticians of the 20th century stated: "All models are wrong, but some are useful".[254] Indeed, any model represents just a simplification or estimate of reality, and hence will never reflect the reality in its entirety. Models for risk prediction are widely used in medicine to predict the probability of the outcome of interest from a given set of risk factors selected on the basis of clinical experience and literature review.[255] According to the calculated probability of the event, patients can give informed consent for the planned treatment while physicians can be guided in decision making or planning of the process of care. A good model should be parsimonious, following the philosophy of William of Ockham, 14th-century Franciscan monk and philosopher, whose view at parsimony was also known as Occam's razors.[254] In other words, a model should be simple, with minimum assumptions and predictors but with the greatest explanatory power. In practice, regression methods are commonly used to develop prediction models from a specific dataset. If the model is not parsimonious, the problem of the model overfitting is frequently encountered. This happens with the use of standard regression methods since they capture in the model not only the association between the predictors and outcomes but also the noise coming from random variations in the dataset.[255] The overfitted model usually predicts well in the original dataset but fails to perform accurately in the new sets of data from other patient populations. Regularization is one of the common mechanisms to avoid overfitting and can be achieved by employing methods of penalized regression that apply constraints to the value of regression coefficients. Lasso (***L**east **A**bsolute **S**hrinkage and **S**election **O**perator*) regression is a popular statistical method and the machine learning algorithm, introduced in 1996 by Tibshirani, which reduces overfitting and automatically

performs variable selection.[256] By shrinking regression coefficients to zero following the predefined rule, Lasso effectively removes these predictors from the final model. Thereby, the final model gains higher prediction accuracy (by allowing a little bit bias to reduce the variance) and enhanced interpretability, since it includes the smaller number of predictors.[256]

Most of the commonly used scores for prediction of postoperative complications rely only on preoperative risk factors. Findings from our study demonstrate the significance of early postoperative predictors for the outcome of surgery. Besides, sometimes surgery represents the only acceptable treatment no matter how great is the predicted risk. Therefore, we thought that it was important to include all perioperative phases during the risk assessment. We needed a model able to early identify patients at risk for postoperative complications based on preoperative, intraoperative, and early postoperative risk factors. Early prediction of complications would allow for correction of modifiable conditions in order to decrease the risk. It would also help to plan postoperative monitoring and level of care, precluding unnecessary "preventive" ICU stay.

In this study, we used two different statistical methods to develop the model. We applied stepwise forward-backward algorithm and lasso algorithm to first select variables within each group (preoperative, intraoperative, postoperative). After within-group selection, we combined the selected covariates from each group and repeated the above-mentioned procedures to select the final predictors. Finally, we used these predictors to fit the logistic regression model. The final stepwise regression model was built with 11 predictors (1 preoperative, 3 intraoperative, and 7 postoperative) and it demonstrated a good within sample discrimination (AUC 0.95). However, the model with so many predictors can be cumbersome for the clinical application and it predominantly selected predictors from the postoperative period. It was shown that the inherent problem with the stepwise regression is that variables selected in later steps may represent noise, thereby causing the overfitted model, unable to perform well during external validation.[257] On the other hand, the final lasso model was built with 7 predictors: 1 from the preoperative period (history of diabetes), 1 from the intraoperative period (multiorgan resection), 2 from admission to the ICU (heart rate and base excess), 1 obtained 12 hours after ICU admission (heart rate), and 2 recorded on the first postoperative day (albumin concentration and transfusion within 24 hours). The model showed good performance, both within sample (AUC 0.93, PPV 0.87) and after 10-fold cross-validation (AUC 0.90, PPV 0.84).

It is estimated that around 20% of patients list diabetes as comorbidity when admitted for an operation.[258] The association of diabetes, short-term and long-term glycemic control with

adverse postoperative outcomes such as major adverse cardiac events, surgical site infections, pneumonia, and sepsis have been proven by many studies.[259,260] It has been shown that patients who develop diabetes-related complications have 13 times greater odds for 30-day mortality following colorectal surgery.[261] Diabetic patients also have a longer length of hospital stay irrespective of the type of surgical procedure and higher odds for late cardiovascular events.[262] In our study, history of diabetes was the single most important preoperative predictor of complications, as diabetic patients were 7.5 times more likely to develop at least one postoperative complication. To date, no studies have analyzed the impact of diabetes severity, associated comorbidity and short-term preoperative glycemic control taken together on the occurrence of complications after abdominal surgery. According to the American Diabetes Association perioperative hyperglycemia influences postoperative outcome more than the HbA_{1c}.[263] Further studies are needed to determine which of the optimization strategies can be safely implemented in diabetic patients and whether the postponement of the elective surgery to achieve better glycemic control or to optimize chronic diabetes-related conditions would yield any benefit.

The multiorgan resection was ascribed the highest regression coefficient in the model we developed, suggesting the greatest contribution to the overall risk for complications. It is not surprising given that only one patient with multiorgan resection in our study experienced no complications. The association of multiorgan resection with complications was addressed in previous studies, many of them asking whether it is worth the risk that it engenders. Martin et al in the large retrospective study of more than 1200 patients who underwent gastrectomy found that the resection of two or more organs was the single independent predictor of postoperative morbidity.[264] Similar conclusions were made by Ozer and associates.[265] Patients with multiorgan resection due to the advanced colorectal cancer were shown to have a good overall survival and long-term outcomes, despite a more complicated postoperative course.[266] Multivisceral resections in complex hepatic and pancreatic surgery were particularly burdened with postoperative morbidity.[267] All patients with multiorgan resection in our study were operated for cancer. We believe that the chronic inflammation already present in the locally advanced cancer was additionally amplified by the inflammation of surgical stress, which may explain the high rate of complications seen in this category of patients. Furthermore, many of them received blood transfusion which can also be the contributing factor for worsening prognosis, probably via immunosuppressive mechanisms and higher susceptibility to infections.[268]

Excessive sympathetic activity during systemic inflammatory response syndrome (SIRS) causing tachycardia was shown to be associated with worse prognosis in patients with sepsis or congestive heart failure.[269,270] The deleterious effect of catecholamines may be also attributed to immunosuppression and metabolic changes they produce. Postoperative tachycardia is generally considered to be a foreseeable consequence of the released catecholamines in response to surgical stress, usually of benign nature and transient. In non-cardiac surgery, it is commonly attributed to large volume shifts, mechanical stimulation during the operation, or postoperative pain and hence not taken seriously. However, it was shown that postoperative tachycardia within 4 days following non-cardiac surgery was the independent predictor of adverse outcomes, such as pulmonary embolism or elevated troponin.[271] Haskins et al reported that sustained tachycardia was associated with serious adverse events after ventral hernia repair.[272] Heart rate both on admission to ICU and 12h later was selected in the final model for prediction of complications in our study. Even though heart rate 12 hours following admission had non-significant regression coefficient, it couldn't be removed from the model, since the model's performance decreased consequently. Recent evidence suggest that beta-blockade could afford beneficial effects to patients in sepsis through suppression of inflammation, modification of metabolic status, improvement of glucose homeostasis, and control of tachycardia.[273] Similarly, the protective short-term effect of beta-blockers was demonstrated in patients after non-cardiac surgery.[274]

Base excess (BE) has been traditionally used to assess the metabolic status and is considered to be the most reliable indicator of the non-respiratory component of the acid-base balance.[275] It is a better indicator of clearance of metabolic acidosis than pH and is superior in the prediction of complications and mortality after trauma.[276] A recent systematic review concluded that a BE less than -6 mmol/l is predictive of mortality in trauma patients.[277] Base excess was found to correlate with fluid requirement and hypovolemic shock and this association was attributed to tissue hypoperfusion and hypoxia.[275] Abdominal surgery is accompanied with significant fluid losses, infusions of large volumes of saline, hypotension, hypothermia, and hypoxemia, and it is not surprising that the metabolic acidosis with decreased BE was found to be the most frequent acid-base disorder upon admission to ICU following surgery.[278] Our results confirm the findings of previous studies. Although with non-significant regression coefficient, BE on admission to ICU was selected by lasso regression and included in the final model as this improved the model's predictive characteristics. Prognostic value of BE for complications and mortality was previously

confirmed in populations of critically ill patients, after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, and cardiac surgery.[279–281] Davis et al in a study that included patients with ongoing resuscitation due to bleeding trauma, classified them into three groups according to the value of deranged BE : mild, 2 to -5 mmol/l; moderate, -6 to -14 mmol/l; and severe, < -15 mmol/l. These authors concluded that the increasing base deficit was associated with the increasing volume of fluid needed for resuscitation and that further decline of BE despite the resuscitation was suggestive of ongoing bleeding.[282] Several studies have shown that BE and lactate concentration can be used complementary to predict the outcome and to identify patients that would benefit from the admission to the ICU.[279,281] The improvement in BE upon resuscitation in the ICU was associated with improved prognosis.[281]

Stress response during critical illness and following surgery has been comprehensively studied in an attempt to find a suitable marker of its extent and severity. Some of the indicators are not easily measurable, like insulin resistance for instance, and some of them, like interleukin-6 have never become a part of routine clinical practice. The slow kinetics of CRP impacts the rise of its value only 2-3 days following surgical trauma. Albumin is the serum protein that normally makes near 60% of proteins in human plasma. It is also a negative acute phase protein since it is downregulated by inflammatory mechanisms during major stress.[283] In contrast to CRP, albumin concentration declines sharply immediately after trauma, making it a sensitive measure of surgical stress.[283] Mechanisms behind the sudden albumin drop after surgery are not completely understood. They involve the exaggerated catabolism, impaired hepatic synthesis, and displacement into the third space.[284] One of the most interesting recent explanations is the hypothesis of occult protein-losing enteropathy that arises from the stress-induced derangement of splanchnic circulation.[285] Serum albumin concentration on postoperative day 1 (POD 1) was shown to be strongly predictive of complications in our study. As shown by our data, a decrease in albumin concentration by 1g/l increases the probability of complications by around 40%. This finding is in accordance with previous studies in the field of major abdominal surgery. Labgaa et al found that the postoperative drop in albumin concentration on POD 1 by > 10g/l was associated with a threefold increase in the rate of complications.[286] Albumin decline after gastrectomy was shown to be more predictive for the outcome than the CRP value, while in the patients undergoing laparoscopic colorectal surgery for treatment of carcinoma it was the only independent factor associated with severe complications.[287,288] However, the common practice of endless infusions of human albumin to treat postoperative hypoalbuminemia seem

to be without evidence-based justification. Previous randomized controlled trials demonstrated that the postoperative albumin supplementation was not beneficial in correcting hypoalbuminemia, nor led to the improvement of postoperative outcome after gastrointestinal surgery.[289,290]

Allogenic blood transfusion still represents the cornerstone in the treatment of perioperative anemia. Anemia is a common condition in patients undergoing abdominal surgery, both preoperatively due to the nature of the underlying disease, and postoperatively as the consequence of perioperative bleeding. It was shown that anemia increases postoperative mortality and is associated with the increased needs for transfusion.[291] However, the associated adverse effects may overcome the benefits of allogenic blood transfusions, many of which are not easy to explain.[292] There are some possible pathways by which allogenic blood transfusion may worsen the outcome, and the most prominent is the transfusion-related immunomodulation and immunosuppression making patients more susceptible to infections or the development of distant metastases and cancer recurrence.[293] Storage of packed red blood cells contributes to changes that diminish the principal function of transfusion, which is the oxygen delivery to tissues.[294] Besides, storage lesions impair deformability of erythrocytes resulting in a reduced microvascular flow.[294] There are many studies that clearly demonstrate the detrimental effect of transfusion on short-term and long-term outcomes of patients undergoing major abdominal surgery.[203,295,296] The recent work by Veličković et al, conducted in a large cohort of patients operated for esophageal cancer showed that allogenic blood transfusion was not associated with long-term survival.[297] One of the determinants of survival in this study were major complications, and they were significantly more common among transfused patients. It is difficult, however, to undisputably claim that the association of blood transfusion and outcomes is a causal one. The aforementioned results come from the observational studies and the effect of potential confounders can't be ruled out. For example, it may be that the indication for transfusion, such as surgeon's inexperience or the locally advanced tumor that caused intraoperative bleeding were the real source of complications and not the transfusion itself.[298]

Transfusion within the day of surgery was selected in the final model for the prediction of complications in our study. We performed several selection procedures during our data analysis, and this predictor has always been selected regardless of the applied algorithm. It was shown that the problem of correlations in the design matrix doesn't affect lasso prediction if the appropriate selection of the tuning parameter lambda was performed.[299]

Lasso is known for its tendency to pick one while ignoring the rest among the very correlated predictors. It is interesting that blood transfusion in our study was not highly correlated with preoperative hemoglobin nor with the intraoperative bleeding, which features the liberal transfusion policy at our institution. Therefore, we believe that transfusion itself was the real predictor of complications.

The calculation of the probability for complications requires values of the seven selected predictors. For instance, 60-year old patient, without a history of diabetes, who underwent left hemicolectomy, whose heart rate on admission to ICU was 62/min and BE on admission -0.2 mmol/l, whereas heart rate 12 hours after admission to ICU was 63/min, who hadn't been transfused and whose albumin concentration on the first postoperative day was 36g/l, would have 4% chance of developing postoperative complication. On the other hand, 42-year old patient, without history of diabetes, who underwent multiorgan resection for locally advanced gastric cancer, whose heart rate and BE on ICU admission were 103/min and -3.1 mmol/l and heart rate after 12 hours was 105/min, who received transfusion and whose albumin level on the first day was 18g/l, would be predicted to have 100% chance for postoperative complications.

Our model has several limitations. First, we used dichotomized variables for some of the categorical predictors with more than 2 levels. It certainly made the analysis easier, but we maybe missed the chance to get more sophisticated information. Second, we didn't include in the analysis some of the variables that were previously described as predictors of postoperative morbidity, such as malnutrition or frailty. Instead, we used other surrogate indices such as body mass index, weight loss, functional activity, or the number of drugs as chronic therapy. Third, we tried to collect and analyze as much information as possible which resulted in more than a hundred variables that were finally analyzed. However, we didn't include data regarding the performance of the attending surgeon and the anesthesiologist, which are difficult to measure objectively. The literature suggests the use of some surrogate measures, such as the experience, the volume expressed in the number of specific procedures per year, or the position. We don't think that these substitutes accurately describe the performance in each situation. On the other hand, we intuitively feel that the occurrence of complications is not dependent solely on objective measures.

The strength of the model is that it includes information from the early postoperative period. To the best of our knowledge, there are no suggested risk scores for prediction of

complications to date that take into account the risk factors from the immediate postoperative period along with preoperative and intraoperative information. Lasso penalty was shown to correctly select the subset of important predictors. We demonstrated that the predicted probability for complications strongly correlates with the CCI. Therefore, the clinicians are given an opportunity to make decisions regarding the postoperative strategies and the process of care with more data than before the operation. This model was validated in an independent set of high-risk patients and it demonstrated excellent predictive performance.

6.Conclusions

1. The postoperative complication rate in high-risk patients after major abdominal surgery is high as the complications occur in more than half (60.7%) of the patients. Complications significantly increase ICU stay and postoperative length of hospital stay and are associated with lower functional activity on discharge from the hospital.

2. The Comprehensive Complication Index and the Clavien-Dindo classification are the effective methods for reporting of complications after major abdominal surgery. With equal or better correlation with hospital length of stay and the possibility to take into account the overall burden of complications, the CCI may be the more accurate scale in high-risk patients with a likelihood for multiple complications.

3. POSSUM score is inaccurate for morbidity prediction in high-risk surgical patients as it significantly under-predicts in low-risk groups. The use of the POSSUM score to predict mortality is inappropriate in our patient population because of the poor calibration and the huge over-prediction. P-POSSUM score is the accurate tool and its use can be suggested in high-risk patients undergoing major abdominal surgery for mortality prediction and for the comparative surgical audit.

4. Peripheral perfusion early after major abdominal operations was more markedly altered in patients who developed a more complicated postoperative course (CCI>50). Central-to-toe temperature gradient after surgery could best discriminate patients with the CCI > 50 on admission to ICU following surgery. Lactate concentration demonstrated the best discrimination of the CCI > 50 12 hours after the admission. Capillary refill time, central-to-toe temperature gradient, and venoarterial pCO_2 to arteriovenous oxygen content ratio on admission to ICU, as well as lactate concentration and base excess 12 hours after the admission were the independent predictors of the more complicated postoperative course.

5. We developed a risk score based on seven predictors (diabetes, multiorgan resection, heart rate and base excess on admission to ICU, heart rate 12 hours after admission to ICU,

albumin on the first postoperative day, and transfusion on the day of surgery) selected by lasso methodology to predict complications in high-risk patients after elective major abdominal surgery. The model was validated in the separate cohort of patients and it demonstrated excellent predictive performance.

7. References

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Biography

Jelena V. Veličković, MD, MSc, was born on March 10, 1975 in Kladovo, Serbia. She finished elementary and high school in Belgrade. In 2001, she obtained medical degree at Belgrade University School of Medicine. After completion of one-year internship, she started the residency in anesthesiology and reanimatology which she finished in 2006 with the highest grades. She obtained her Master of Science degree in 2010, after the public defence of the thesis entitled "Possibilities for the prevention of postoperative nausea and vomiting after thyroid surgery". In 2014 she was elected as clinical assistant in anesthesia at the School of Medicine, University of Belgrade. From 2002 she works at the Clinic for Digestive Surgery, Clinical Center of Serbia as the anesthesiologist, primarily at the intensive care unit. During her career she completed numerous trainings, such as the advanced course in mechanical ventilation (Porta del Hierro, Madrid) and advanced course in clinical nutrition (Krakow, Poland). She took part in the Italian-Serbian Collaboration on treatment of severe respiratory failure during 2014, taking part as a speaker at joint symposia and doing the fellowship at San Gerardo Hospital, University of Milan-Bicocca, in Monza, Italy. She was the secretary of the working group steered by prof.Bumbaširević for writing the national guidelines for prevention and treatment of severe sepsis and septic shock in 2013. Dr Veličković took part as the invited speaker at a lot of domestic and international conferences and wrote chapters for two textbooks in anesthesia. Her fields of professional and scientific interest are: perioperative medicine, clinical nutrition, sepsis, and antimicrobial stewardship.

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