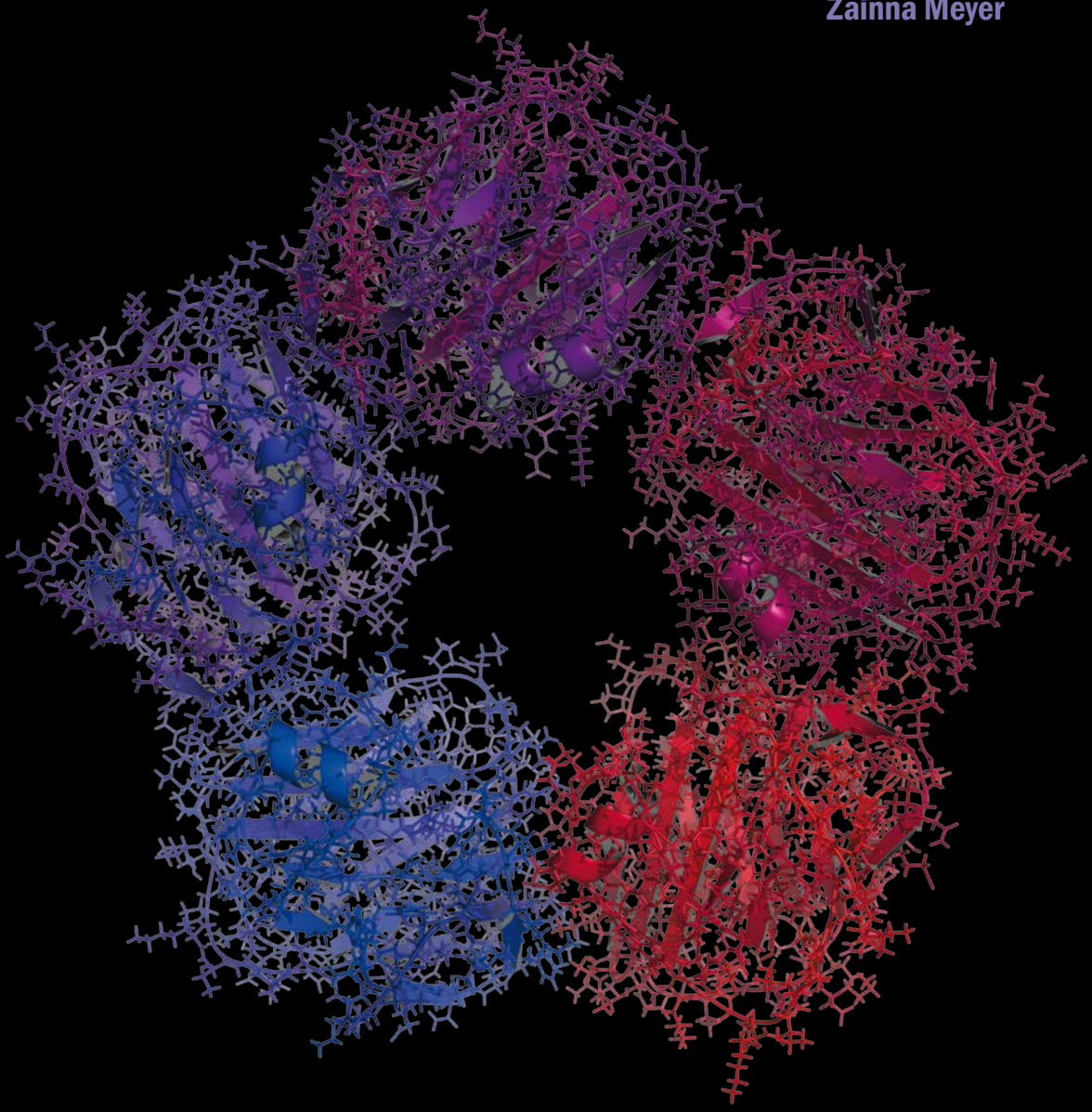
Biochemical markers in the surgical intensive care

Identifying critically ill surgical patients with complications

Zainna Meyer



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Biochemische markers op de chirurgische intensive care

Identificeren van kritiek zieke chirurgische patiënten
met complicaties

Proefschrift

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Aan mijn ouders en zus

CONTENTS

CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

Throughout the world over 230 million surgical procedures are performed yearly [1]. In the Netherlands an estimate of 1.4 million surgical procedures were performed in 2010 [2]. It should be realized that surgical procedures are not without risk. Most operations carry a relatively low risk for complications postoperatively and on the long term [3, 4]. However, more complex surgical procedures certainly when combined with co-morbidity, may result in a higher risk for complications leading to increased short and long term morbidity and even mortality [1].

A large Dutch population-based study of 3.7 million elective surgical procedures performed between 1991 and 2005 reported an estimated postoperative in-hospital mortality of 1.85% [5]. Postoperative mortality rate is found to be multi-factorial and most clearly correlated with the level of co-morbidity of the patient and the type of surgery performed. Major vascular and major abdominal surgery as well as neurological (cranial) surgery are associated with higher mortality rates compared to other procedures (incidence 6.0%, 2.7% and 3.4%, respectively) [5].

Patients who are at risk for serious complications or patients who actually develop serious complications may require admission to an intensive care unit (ICU). Thus, the ICU is the unit where focus on the prevention and treatment of surgical complications should be optimized to improve patient outcome. One may differentiate two groups of surgical patients admitted to the ICU: one for standard postsurgical care and one for additional critical care when perioperative complications developed. In 2011, a seven day cohort European multicenter study reported that a total of 7.7% of all surgical patients was admitted into an ICU after operation in the Netherlands [4]. During the postoperative period on the ICU these patients had an estimated mortality rate between 2%- 29%, depending on type of surgery and comorbidity the subpopulation [6-8].

A large population-based study in the United States showed that the occurrence of a complication within 30-days postoperatively reduces patient survival by 69%, independently of preoperative risks [9]. Also, patients with any type of complications within 30 days postoperatively were found to have an estimate 30-day mortality rate of 13.3% compared to 0.8% in patients who did not have postsurgical complications [9]. In patients who develop complications within 30 days of surgery the mortality rate is still increased at one and five years postoperatively compared to those without complications (28% and 58% at one year versus 7% and 40% at five years, respectively). The long term outcome has been found to be dependent on the type of perioperative complication [9].

It is argued that an early diagnosis of post-surgical complications (e.g. anastomotic leakage) and the start of early adequate therapy may decrease the severity of complications and thus the length of stay in the ICU. However, the identification of patients at risk for complications is not straightforward. Especially in the ICU, physicians are challenged to differentiate between patients who are vulnerable for major complications and those who will have an uneventful post-operative course. It can be difficult to detect early complications relying only on clinical symptoms (e.g. heart rate, respiratory rate and temperature) and conventional biomarkers, such as leucocytes or white blood cell count [10, 11]. To facilitate early diagnosis of complications during the ICU stay, biomarkers like lactate and C-reactive protein (CRP) are being used on a regular basis in addition to clinical signs and symptoms [12-19].

One of the most commonly used biomarker is serum lactate concentration. Lactate is a product of the anaerobic metabolism of glucose and is related to cellular hypoxia. An increased lactate level is associated with sepsis, hypoperfusion and specific organ failure, such as liver coma or renal insufficiency. Two types of serum lactate are being used in clinical practice, L-lactate and D-lactate. L-lactate is the lactate form that is most commonly measured by clinicians as a marker for hypoperfusion and hypoxemia. D-lactate on the other hand, is a product of bacterial fermentation, and its use is described more frequently in studies on diagnosing acute mesenterial ischemia [20-22]. Even though lactate is not a very reliable marker for this diagnosis, surgeons continue to utilize it for lack of better [23, 24]. It is known that baseline lactate levels are independently correlated to mortality in surgical patients with sepsis or septic shock [12, 25, 26]. Also, in patients after cardiac surgery, initial lactate levels at admission into the ICU and during ICU stay are related to postoperative complications [27]. Furthermore, a cut-off value of 1.46 mmol/L is described as the limit for the diagnosis of complications [16]. When adequate resuscitation is applied in patients with complications, this can result in a decrease of lactate levels, which reflects a reversal of hypoxia. This decrease in lactate levels is an indicator of improved survival [26]. Both the duration and area under the curve of increased lactate concentrations are related to morbidity and mortality [28].

Another widely used biochemical marker is C-reactive protein. It is a sensitive but unspecific acute phase protein synthesized by the liver. CRP is one of the parameters frequently measured after major surgery in the intensive care unit, as its level rises in response to systemic inflammation. While it has been reported that early CRP (within 48 hours) concentration is a poor predictor for survival in critically ill patients, late (more than 48 hours) CRP concentrations may help identify those patients who are at risk for complications [29]. To date, many studies have assessed the association between CRP levels and various post-operative complications. Most of these studies focused on CRP

following colorectal surgery. In 1987, a report showed that serial postoperative measurements predicted septic complications prior to clinical diagnosis in patients undergoing intra-abdominal or thoracic procedures [17]. More recent studies reported that prolonged increased CRP concentrations are correlated with infectious complications as anastomotic leakage [30-34].

A newer biomarker of interest is procalcitonin (PCT). It is synthesized physiologically in thyroid C cells, but in sepsis it has an extra-thyroidal origin [19]. PCT is released into the circulation 3-4 hours after an endotoxin injection and reaches its peak after 8-12 hours, while CRP peaks at 36-50 hours after such a stimulus [35, 36]. Plasma concentration of PCT is believed to be of value to evaluate the progression of infection towards sepsis in critically ill patients with greater diagnostic accuracy than CRP [10, 19, 37, 38]. It has also been shown that PCT may be useful as a diagnostic tool for surgical conditions, including acute pancreatitis and secondary peritonitis [39-41], bowel obstruction [42, 43], surgical site infection after colorectal surgery [44] and postoperative complications after esophageal surgery [45, 46]. After trauma, patients with initially high PCT concentrations developed complications more frequently and had a worse outcome during the ICU stay [38]. These complications included infection, sepsis and prolonged treatment courses [38]. PCT concentrations can be easily and accurately assessed, its concentrations are stable and not impaired by hepatic or renal dysfunction [40, 47]. Procalcitonin therefore meets the demands of an ideal marker for routine clinical applications, and it may be useful as a routine and emergency marker for the diagnosis of complications in critically ill surgical patients.

Besides these three biochemical markers for diagnosing complications, a daily clinical scoring system is commonly used in practice as well. This scoring system is the Sequential Organ Failure Assessment score (SOFA score), which was developed to determine a patient's organ function or rate of organ failure. Blood lactate concentrations were found to have a strong relationship with SOFA score as well as with the level of multi-organ failure. [48]. Furthermore, an increasing SOFA score, as a reflection of the severity of multi-organ failure, was associated with higher serum PCT and CRP concentrations [49, 50]. Consequently, the SOFA score can be used as a marker for clinical deterioration in the critically ill patient.

It is unclear what the diagnostic value of the above described markers is for diagnosing complications in critically ill surgical patients in the ICU. Contradicting evidence has been published in previous studies. A diversity of complications were compared in literature, both surgical and non-surgical, and found little to no significant prognostic value for postoperative complications during the ICU stay (review chapter 2). Still, physicians

and surgeons on the ICU tend to rely heavily on these parameters to identify patients with increased vulnerability for complications. We also observed that the use of these markers seems to lead to unnecessary diagnostic and/or therapeutic interventions and re-interventions. Therefore, we hypothesized that the use of these markers is not justified in high-risk critically ill general surgical patients at risk for developing complications. Additionally, we examined the value of the currently used markers (CRP, lactate, PCT) and scoring system (SOFA score) for the identification of surgical complications in critically ill surgical patients in the ICU.

THESIS OUTLINE

The aim of this thesis was to evaluate the use of biomarkers including lactate, C-reactive protein (CRP), procalcitonin (PCT), and the Sequential Organ Failure Assessment score (SOFA) for early identification of complications in critically ill surgical patients during the ICU stay.

Chapter 2 presents a literature review concerning the use of each of these parameters in diagnosing different types of complications in critically ill general surgical patients. Chapter 3 describes the presentation of three patients admitted to the emergency department with non-traumatic acute abdominal pain and increased concentrations of the biomarkers CRP and lactate. The outcome of these patients in relationship to these parameters is discussed. In addition, we present a short review of literature on the usefulness of these biomarkers in daily practice and their influence on establishing a diagnosis and decisions to perform an intervention.

To evaluate the clinical use of these markers in diagnosing surgical complications (abscesses, bleeding, perforation, ischemia and ileus), we conducted several studies in which these parameters were investigated for their use in general surgical patients admitted to a level three general intensive care unit between April 2010 and June 2012. The first of these studies is described in chapter 4. This chapter reports the role of C-reactive protein as a parameter for clinical deterioration and its value for clinical decision-making as compared to routinely used diagnostic tests. In addition, we evaluated the value of CRP in the early detection of surgical complications and its interpretation in combination with a clinical scoring system, the SOFA score.

Chapter 5 describes a study on the value of lactate in clinical practice in a heterogeneous group of general surgical patients admitted to the ICU. As contradicting results have been published on the utility of lactate as a parameter for diagnosing surgical complications the efficacy of this test is still open for discussion. We therefore per-

formed a study to assess the value of lactate concentrations in diagnosing surgical complications.

The final biomarker that we studied was procalcitonin, a biomarker introduced recently as a promising prognostic factor to predict infection. The design and results are described in chapter 6, in which we investigated the value of PCT concentrations to recognize (early) surgical complications in surgical patients in the ICU.

The last chapter, chapter 7, presents a study model for developing risk stratification using the three commonly used parameters (CRP, lactate and SOFA score) for the early prediction of severe postoperative complications in critically ill surgical patients in the ICU. In this model, we elaborate on the value of these markers separately as well as combined with each other.

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CHAPTER 2

Searching for predictors of surgical complications in critically ill surgery patients in the intensive care unit: a review

Surg Today. 2015 April

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ABSTRACT

We reviewed the use of the levels of C-reactive protein, lactate and procalcitonin and/or the Sequential Organ Failure Assessment score to determine their diagnostic accuracy for predicting surgical complications in critically ill general post-surgery patients.

Included were all studies published in Pubmed from inception to July 2013 that met the following inclusion criteria: evaluation of the above parameters, describing their diagnostic accuracy and the risk stratification for surgical complications in surgical patients admitted to an intensive care unit.

No difference in the Sequential Organ Failure Assessment scores was seen between patients with or without complications. The D-lactate levels were significantly higher in those who developed colonic ischemic complications after a ruptured abdominal aortic aneurysm. After gastro-intestinal surgery, contradictory data were reported, with both positive as negative use of C-reactive protein and procalcitonin in the diagnosis of septic complications. However, in trauma patients, the C-reactive protein levels may help to discriminate between those with and without infectious causes.

We conclude that the Sequential Organ Failure Assessment score, lactate concentration and C-reactive protein level have no significant predictive value for early postoperative complications in critically ill post-surgery patients. However, procalcitonin seems to be a useful parameter for diagnosing complications in specific patient populations after surgery and/or after trauma.

INTRODUCTION

Patients admitted to the intensive care unit (ICU) after gastrointestinal surgery, vascular surgery or trauma are more vulnerable to complications (for example, infections, bleeding, anastomotic leakage and ischemia) than patients in regular care units. Accurate and early identification of these vulnerable patients is crucial, as the risk of mortality is increased if the diagnosis of complications is delayed or if complications are misdiagnosed. To diagnose these complications, biochemical parameters like the levels of C-reactive protein (CRP), lactate and procalcitonin (PCT) and scoring systems such as the Sequential Organ Failure Assessment score (SOFA score) are frequently used as markers of clinical deterioration and/or for the diagnosis of postoperative complications.

An increase in serum CRP (reference range CRP: 0-10 mg/L in healthy individuals) during an ICU stay is associated with a poor outcome and a mortality rate up to 61% [1]. Furthermore, a prolonged rise in CRP levels is a strong indicator of infectious postoperative complications, such as anastomotic leakage after colorectal surgery [2-10]. Although the association of an increased CRP concentration with anastomotic leakage has been well studied, the serum CRP level is not specific for all particular type of inflammatory complication or for all types of surgery [11-13].

On the other hand, procalcitonin (reference range PCT: < 0.05 ng/mL in healthy individuals) is a newer widely reported biomarker used to indentify infection, and has a better accuracy than CRP for the diagnosis of infection or sepsis [14]. When prolonged high postoperative PCT levels are observed, they can be considered to predict severe infectious complications [15-18]. However, recent studies have concluded that after colorectal surgery, the postoperative PCT concentrations are not more accurate than the CRP levels for the diagnosis of anastomotic leakage [19-21].

The SOFA score is a scoring system (reference range: 4-24 points) describing multi-organ dysfunction [22]. An increased SOFA score, which is a reflection of the severity of multi-organ failure, is associated with higher serum PCT and CRP concentrations [1, 23]. Since this scoring system correlates with both the CRP and PCT levels, we can speculate that the SOFA score may also be used to predict or identify complications in patients postoperatively.

An older well-studied biomarker is lactate (reference values: 0.5-1.6 mmol/L in healthy individuals). Hyperlactemia is known to be an independent factor predicting mortality in postoperative patients [24-27]. A recent study in patients undergoing elective major abdominal surgery reported that the lactate levels and the lactate clearance are independent predictors of postoperative complications [28].

The main aim of this review was to evaluate the predictive value of the levels of CRP, lactate and PCT and/or the SOFA score for surgical complications in critically ill general post-surgery patients admitted to the intensive care unit.

METHODS

Studies were identified by an electronic search of the Pubmed and Cochrane Library databases from inception to July 2013. The literature search strategy used the title, text words or key words, including the following: "C-reactive protein", "lactate", "procalcitonin" and "Sequential Organ Failure Assessment score". Each key word was put together with the keywords "Surgery or postoperative" and "critically ill or Intensive Care Unit" (search 1). The other combinations of keywords which were used were "complications" and "Surgery or postoperative" (search 2). The limits used were the availability of an abstract and English language.

Inclusion criteria and exclusion criteria

We identified articles eligible for in-depth examination by applying the following inclusion criteria: evaluation of the target parameters (CRP, PCT, lactate and/or SOFA score) describing their diagnostic accuracy and risk stratification for surgical complications in critically ill general post-surgery patients admitted to an intensive care unit. The parameters mentioned above have been chosen for this review as they are the current biomarkers and scoring system most commonly used in the ICU. A surgical complication was defined as a complication related to prior surgery and requiring additional surgical treatment during the ICU stay. Examples included as complications were an intra-abdominal abscess, anastomotic leakage, mesenterial ischemia, peritonitis, ileus, perforations and non-acute bleeding.

Case reports, case series, review articles, editorial and clinical guidelines were excluded. Other exclusion criteria were pediatric patients, patients admitted to non-high care units or undergoing cardiopulmonary, orthopedic or transplantation surgery.

Subsequently, the articles were identified by the title (text words), and the abstract was screened for relevant information to ensure that the inclusion criteria were met. We also searched the reference lists of each primary study for additional publications relevant to this review.

RESULTS

The search yielded a total of 1,594 articles describing the use of the parameters CRP, lactate and/or PCT in critically ill general post-surgery patients during an ICU stay. On the basis of the title and abstract, with a focus on the inclusion criteria mentioned above, a total of 62 citations were deemed eligible for further full-text review. A total of 15 studies met all inclusion criteria and are summarized below (Fig. 1).

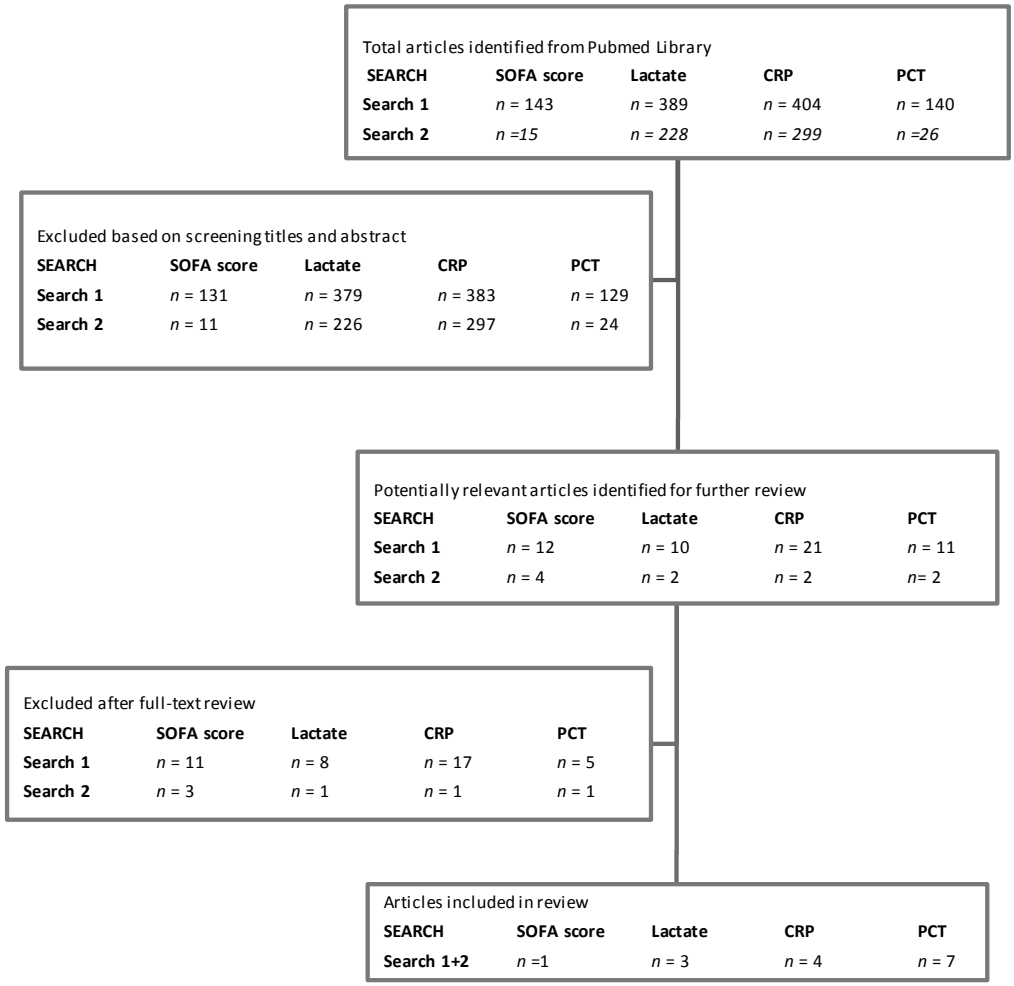

Figure 1: Search flow chart
SEARCH 1: keywords "Surgery or postoperative" and "critically ill or Intensive Care Unit".
SEARCH 2: keywords "complications" and "Surgery or postoperative".
LIMITS: Limits used were availability of abstract and English language.
EXCLUSIONS: Mortality, non-surgical patients, no intensive care admission, no surgical complications
SOFA score= Sequential Organ Failure Assessment score
CRP = C-reactive protein
PCT = procalcitonin

The sequential organ failure assessment score

The SOFA score has been used in many studies as a predictor for mortality in postoperative patients and trauma patients during the ICU stay. However, only one study was reported that used the SOFA score as a predictor for complications in a heterogeneous group of surgical patients during the ICU stay. No difference in SOFA scores was reported between patients with and without complications [29]. Even a one-point increase in the SOFA score showed no significant benefit for the diagnosis of surgical complications in surgery patients in the ICU [29] (Table 1).

Lactate

The use of lactate concentrations to predict post-surgical complications in critically ill postoperative patients has been described in the studies presented below. Watanabe et al. described that the lactate concentrations were significantly higher in patients who developed postoperative complications after hepatectomy ($p < 0.001$) [30]. In patients after a ruptured abdominal aortic aneurysm (rAAA) repair, the D-lactate levels were significantly higher those who developed colonic ischemic complications [31]. However, no significant difference was reported for using L-lactate to differentiate between those with and without intestinal complications following rAAA repair [31]. Likewise, our study in a group of general surgery patients admitted to the ICU after different types of surgery showed no significant effect of lactate changes on the probability of complications [32] (Table 2). Even when the lactate levels were above 2.5 mmol/L, there was no increase in the risk of surgical complications (Odds ratio 1.32; 95 % CI: 0.68-2.56; p= 0.41) [32].

C-reactive protein

Surgical complications could not be identified earlier in a heterogeneous group of surgical patients in the ICU based on an increase in the CRP concentration [29] (Table 3). In contrast, in one study, fewer complications were observed when the CRP levels increased [29].

Results are available in the literature for a few specific groups of patients. For example, after esophagectomy with gastric tube reconstruction, CRP levels above the cut-off values of 109 mg/L at 24 hours and 175 mg/L at 48 hours postoperatively were associated with the development of postoperative complications [33] (Table 3). In addition, that study reported that the CRP concentrations were independently associated with the development of complications during the ICU stay [33]. On the other hand, the CRP levels on postoperative day two had a poor predictive value for detecting respiratory insufficiency on day three after elective esophageal tumor resection [34].

Table 1: The studie on sequential organ failure assessment score identified by search (SOFA score)

Article	Number of patients	Age (mean)	Operation before admission	Length of stay in ICU (mean)	Mortality	Complications	Outcome	Conclusions
Meyer et.al. 2013	174	72 years	Heterogeneous group: elective and acute gastro-intestinal or thoracic, vascular surgery and trauma surgery	7 days	9.8%	intra-abdominal abscesses, anastomotic leakage, mesenterial ischemia, ileus, perforations, bleeding, diaphragm rupture or pneumothorax	SOFA score at T0= 5.2 SOFA score and risk complications: OR (-0.70 points; 95% CI: -1.58-0.19; p= 0.12)	No difference between complication or no-complication

Abbreviations: OR: Odds ratio CI: confidence interval T0 = at admission T: Time of measuring

Table 2. The studies onlactate identified by search

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (mean)	Mortality	Complications	Outcome	Conclusions
Watanabe et.al. 2007	151	-	Liver resection	-	5%		Lactate has an AUC predicting mortality of 0.86 (independent predictor)	Lactate levels are higher in non survivors and in those with complications (p <0.001)
Poeze et.al. 1998	24	71	Repair of ruptured abdominal aortic aneurysm (rAAA)	-	50%	Intestinal ischemia	D-Lactate > 0.20mmol/L has a prediction sensitivity of 82% for ischemic colitis and a specificity of 75%.	Only D-lactate levels are higher in patients with intestinal ischemia than in those without ischemia after rAAA. The L-lactate levels are not different.
Meyer at.al. 2013	174	72 years	Heterogeneous group: elective and acute gastro-intestinal or thoracic, vascular surgery and trauma surgery	8 days	9.8%	Intra-abdominal abscesses, anastomotic leakage, mesenterial ischemia, ileus, perforations, bleeding, diaphragm rupture or pneumothorax	Lactate (mmol/L) at T0= 3.4 Risk complications and lactate: 10% increase OR 0.968 95% CI: 0.875-1.070) Lactate > 2.5 OR 1.32; 95 % CI: 0.68-2.56)	Higher lactate levels are not correlated with surgical complications.

Abbreviations: CI: confidence interval OR: odds ratio AUC: area under the curve rAAA: ruptured abdominal aortic aneurysm T: time of measurement

Table 3. The studies on C-reactive protein (CRP) identified by search

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (mean)	Mortality	Complications	Outcome	Conclusions
Meyer et.al. 2013	174	72 years	Heterogeneous group: elective and acute gastro-intestinal or thoracic, vascular surgery and trauma surgery	7 days	9.8%	Intra-abdominal abscesses, anastomotic leakage, mesenterial ischemia, ileus, perforations, bleeding, diaphragm rupture or pneumothorax	CRP levels postop day 3: Mean ±SD 226 ± 114 mg/L CRP and risk complications -4.7 %; 95% CI: -26.8 % to +24.7%; *p*= 0.73)	No difference in CRP between surgical complications.
Van Genderen et.al. 2011	63	61 years	Esophagectomy with gastric tube reconstruction	6 days	55% of patients with complications	Pneumonia, pneumothorax, emphysema, arrhythmias, leakage, chylothorax, wound infection, pleural empyema	CRP complications vs no complications: p= 0.005 Mean CRP at 24h = 166 ± 87 mg/L vs 112 ± 34; 48h = 237 ±73 vs 173 ± 44 mg/L). AUC complications: 24h >109 mg/L, AUC 0.74 (95% CI 0.60 -0.88) p=0.004 48h > 175 mg/L, AUC 0.78 (95% CI 0.65 -0.92) p=0.0041	Higher CRP in patients with complications vs no complication. CRP levels are independently associated with the development of complications.

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (mean)	Mortality	Complications	Outcome	Conclusions
Chromik et.al. 2009	69	76	Secondary peritonitis (SP)	19 days	9.3% in SP and 60% in TP	Tertiairy peritonitis (TP)	CRP (mg/L) in TP vs SP on postoperative: Day 1 204 vs 166; p<0.05) Day 2 265 vs 217; p=0.05) Day 7 174 vs 119; p=0.03 AUC on postoperative day 2= 0.696 (95% CI 0.562-0.830; p=0.02)	In patients with tertiary peritonitis CRP is higher than in secondary peritonitis.
Miller wt.al. 1999	59	43 years	Blunt or penetrating trauma (directly or postoperative)	-	10%	SIRS with infectious cause (pneumonia, line sepsis, Blood infection, wound infection, intra-abdominal infection)	Tpeak 19.2 mg/dL High CRP with cut-off value of 17 mg/ dL has a sensitivity of 74% and specificity of 75% to differentiate between SIRS with infection or without infection. (AUC 0.81)	CRP above 17mg/dL may help to differentiate between SIRS or sepsis in trauma patients.
Steinbach et.al. 2006	84	7-89 years	Major abdominal surgery, vascular surgery, orthopedic surgery and trauma	Max 14 days	-	sepsis	Relationship CRP and sepsis: p= 0.09. mean AUC was 0.56 (SD ±0.02)	No strong correlation between CRP levels and sepsis was found with a weak prognostic value for sepsis

Abbreviations: CI: confidence interval OR: odds ratio AUC: area under the curve TP: tertiairy peritonitis
SIRS: systemic inflammatory response syndrome SD: standard deviation T: time of measurement

Another study reported that patients who developed tertiary peritonitis after adequate management of secondary peritonitis had higher CRP levels on the second postoperative day [35]. However, the predictive value of the postoperative CRP level was moderate. The area under the curve (AUC) for a CRP concentration over 215 mg/L on postoperative day two was 0.7 (95% CI 0.562-0.830; p=0.02) [35].

CRP has also been widely used as a marker for sepsis and septic complications. In trauma patients, the CRP levels may help to discriminate between those with infectious causes of systemic inflammatory response syndrome (SIRS) and those without infectious causes. One study in trauma patients admitted to the ICU reported that CRP values higher than 17 mg/L may help in determining the presence of infection in patients with SIRS after trauma, with an area under the curve of 0.81 (p=0.003) [36]. However, Castelli et al. observed no significant increase in the plasma concentrations of CRP in patients after trauma at the time when septic complications were diagnosed [37, 38]. In addition, the CPR level had a weak prognostic value for sepsis in postoperative patients with an AUC of only 0.56 [39].

In summary, in a heterogeneous group of surgical patients in the ICU, the C-reactive protein level is not a reliable predictor or marker of surgical complications. However, it may help with the identification of complications in specific homogeneous groups. For example, it was shown to be helpful in patients with complications after secondary peritonitis or elective esophageal resection. In trauma patients, the CRP level cannot be used as a marker for septic complications, as contradictory results have been reported.

Procalcitonin

As expected, the PCT level has also been used an independent predictor of the mortality of critically ill surgery patients, with an area under the curve of 0.73 [40, 41]. However, it does not have any early discriminative power after ICU admission compared to the SOFA score for the prediction of a lethal outcome [42].

The PCT concentrations showed a high AUC for predicting infection in a study of postoperative patients after acute traumatic spinal cord injury (0.82; 95% CI 0.74- 0.91) [43]. Moreover, a cut-off value of 0.1 ng/mL had a sensitivity of 92% to exclude an infection in these patients [43]. The PCT concentrations in trauma patients on admission were higher in those who developed a septic complication later on [37, 38]. In addition, an early and rapid significant increase in the PCT value was observed compared to one day prior to the diagnosis of a septic complication in trauma patients in the ICU [37, 38] (Table 4). Another study in multi-trauma patients and major abdominal surgery patients reported a trend towards a decrease in the severity of sepsis-related organ failure when using PCT-guided diagnostic and therapeutic strategies [44] (Table 4).

Table 4. the studies on Procalcitonin (PCT) identified by search

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (Mean)	Mortality	Complications	Outcome	Conclusions
Nie et.al. 2011	339	-	Surgery for acute spinal cord injury after trauma	-	-	Postoperative infection	Cut-off 0.1 ng/mL AUC for infection was 0.82 (95% CI 0.74- 0.91). Cut-off 0.1 ng/mL sensitivity of 92% to exclude infection	Higher PCT and CRP in those with postoperative complications.
Svoboda et. al 2007	289 and 164	43 years	Multi- trauma patients and major abdominal surgery	17 days	10-13 %	PCT-guided diagnostic and therapeutic strategy to find sepsis- related complications after trauma, mortality, LOS	Cut-off 2 ng/mL SOFA score on day 5 PCT groups vs no PCT group: 7.9 ± 2.8 vs 9.3 ±3.3; p=0.06	The PCT group showed a trend toward decreased severity of sepsis-related organ failure.
Al-Bahrani et.al. 2010	32 (18+14)	57 years	Severe acute pancreatitis and patients with intra-abdominal sepsis	12 days	28%	Diagnosing and treatment of intra-abdominal hypertension (IAH) and abdominal compartment syndrome(ACS)	PCT in patients with severe pancreatitis and abdominal sepsis vs healthy subjects (1.89 vs 0.01, p<0.001) PCT in IAH vs no IAH 1.53 vs 0.84; p=0.205 PCT in ACS vs no ACS 2.88 vs 1.1; p=0.056	Patients with severe pancreatitis and abdominal sepsis have higher PCT levels No difference in patients with or without IAH Difference between patients with and without ACS
Bogar et.al. 2006	33	61 years	Elective esophageal tumor resection via a thoracoscopic or transhiatal approach	6 days	15%	Prediction of third day arterial hypoxemia as the earliest sign of evolving respiratory dysfunction	PCT (ng/mL) on day 2 in patients with respiratory complications vs no respiratory complications on day 3: 2.8 vs 1.2; p< 0.01	The PCT levels on the second postoperative day can predict arterial hypoxemia as an early sign of threatening respiratory complication

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (Mean)	Mortality	Complications	Outcome	Conclusions
Castelli et.al. 2006	49 of 366	59 years	Trauma	-	-	Septic complications	PCT (ng/mL) in those with complications vs no complications at admission 3.4 vs 1.2; p<0.05	Higher PCT levels at admission in patients with septic complications than without complications
							PCT (ng/mL) in those with complications vs no complications on day before diagnosis 0.85 vs 2.1; p<0.05	Increase in PCT value one day prior to diagnosis of complication
Castelli et.al. 2009	94	59 years	Multitrauma and head injury only	-	5%	Septic complications	PCT (ng/mL) in complications vs no complications at admission 5.4 vs 1.6; p< 0.001	Higher PCT values at admission in patients who develop septic complications
							PCT (ng/mL) increase before diagnosis of complication 0.85 to 3.32; p< 0.001	Increase in PCT level one day before septic complication
							AUC 0.787 (p<0.001) for diagnosis of sepsis, cut-off value 1.09ng/mL	

Article	Number of patients	Age	Operation before admission	Length of stay in ICU (Mean)	Mortality	Complications	Outcome	Conclusions
Mokart et.al. 2005	50	58	Elective major abdominal surgical procedure for gastrointestinal or gynecological tumor resection	-	0%	Diagnosing sepsis and septic complications until five days after the operation	PCT (ng/mL) in sepsis vs no sepsis 2.1 vs 0.56, p=0.003 Higher PCT levels on postoperative Day 1 than Day 0 in septic and non-septic patients (p<0.001) Cut-off value of 1.1 ng/mL: sensitivity of 81% and specificity of 72% for septic complicationson the first five postoperative days (AUC 74.9, 60.2-89.6)	Higher PCT in septic patients compared to those with no complications Higher PCT levels in both septic and non-septic patients

Abbreviations: CI: confidence interval OR: odds ratio AUC: area under the curve T0 = at admission T: time of measurement; Tm = mean score/ concentration during ICU stay; Tc = score /concentration on complication day during ICU stay; in = increase in score / concentration on complication day during ICU stay

In critically ill patients with severe acute pancreatitis and intra-abdominal sepsis, the development of high intra-abdominal pressure was not correlated with a significant increase in the PCT concentrations [45]. On the other hand, when abdominal compartment syndrome was diagnosed, higher PCT levels were observed. These higher levels decreased again after the resolution of the abdominal compartment syndrome [45] (Table 4). It was also reported that PCT levels over 2.5 ng/mL on postoperative day two predict the development of respiratory complications on the third day after elective esophageal tumor resection [34] (Table 4). Mokart et al. noted that there were increased PCT concentrations on postoperative day 1 in septic patients after major elective oncological surgery [46]. In these patients, the PCT levels used to diagnose postoperative sepsis (1.1 ng/mL) showed good sensitivity (81%) and specificity (72%) [46].

Similar to the CRP level, the PCT concentrations are not reliable to predict complications for all surgical patients in the ICU. However, in trauma patients, the PCT level can be used as a marker for the early diagnosis of surgical complications.

DISCUSSION

The early identification of vulnerable critically ill surgery patients prone to develop complications during their intensive care stay is important in order to start adequate treatment. Many parameters and scoring systems have been developed to identify those with an increased risk of complications and for predicting a lethal outcome. Nonetheless, not all patients benefit from surgical therapy, as reoperations increase the inflammatory host response, which may contribute to a further impairment of organ function. It is therefore crucial to identify those critically ill patients who would benefit from a new surgical intervention from those who would not benefit [47, 48]. However, it is challenging to conduct homogeneous studies in surgery patients with sepsis, and many studies have compared a diversity of complications, both surgical and non-surgical. The pathogenesis of sepsis may differ between these patients due to the differences in infection, the pathogen spectrum, underlying morbidities or other patient characteristics, making such analyses of little value [40].

Major trauma patients present a challenge in terms of diagnosing early complications, as the trauma itself influences the septic parameters during the first few days after trauma. These complications are also difficult to distinguish from SIRS. Based on the present review, we concluded that an increase in PCT may be an early significant predictor of septic complications. In addition, the PCT level correlated with the SOFA scores and exhibited a good prognostic value for identifying those at risk for organ dysfunction, but not earlier than the SOFA score itself [38, 42]. Nevertheless, contradictory conclusions have been reported regarding the use of the CRP levels in diagnosing post-

traumatic complications. Positive and negative correlations with these septic complications have both been reported after trauma.

C-reactive protein

Both the plasma C-reactive protein concentrations and procalcitonin levels have been used as markers for SIRS, sepsis and septic complications. An increase in CRP levels has been described as a crucial indicator for the diagnosis of postoperative complications, such as infection, SIRS, sepsis, anastomotic leakage or mesenterial ischemia in patients after surgery [2, 4]. Although this correlation has been reported in all post-surgical patients, few studies have been published on the predictive value of these parameters in critically ill post-surgery patients. In addition, the kinetics of the induction and elimination of CRP suggest that it would not be useful as a diagnostic marker for surgical complications. This is because the CRP levels has a late reaction following infection, and it has no preferential induction for infection or other stresses. As its concentrations generally increase after the implementation of a therapeutic intervention, it also may not be useful for the diagnosis of complications. Contradictory results on the use of this parameter have been described, which indicates that CRP should not be used to diagnose surgical complications in critically ill general surgery patients or in trauma patients.

Procalcitonin

On the other hand, procalcitonin seems to have a better predictive value for identifying those with a higher risk of postoperative complications [15, 16]. When the PCT levels were being used as an additional marker for postoperative sepsis and making therapeutic decisions, the extent of multiple organ dysfunctions seemed to decrease [44]. The PCT concentrations may also reflect the effectiveness of a goal-directed therapeutic surgical procedure to eliminate a septic focus [17, 38, 49]. However, a recent meta-analysis concluded that the PCT concentrations in critically ill patients may not differ significantly between those with sepsis and other non-infectious causes of systemic inflammatory response syndrome [50]. However, that review estimated the diagnostic accuracy of procalcitonin for sepsis diagnosed in all critically ill patients in all clinical settings. In our review, we studied only general surgery patients admitted to an intensive care unit. Therefore, the value may be specific for certain patient population.

Further apparently contradictory data were reported, with some authors speculating that surgical trauma itself may explain the increased postoperative PCT levels, and therefore may not be used for diagnosing surgical complications or sepsis [15, 16, 49]. In addition, other mechanisms, such as transient bacterial contamination during the operation or cytokine release during wound healing may contribute to this increase [16, 51]. However, most of these increases in PCT concentrations may be explained by its

mechanism of induction and action. Only monocytes adherent to the trauma site produce a significant amount of PCT [52]. Once induced, PCT may act as a chemokine in the area and attract more monocytes or may lead to the production of more PCT by adherent monocytes [52]. However, this occurs only for a limited amount of time (hours), thus limiting the local action of PCT [52, 53].

During sepsis or infection there is a continuous and systemic stimulus leading to the increased and continuous production of PCT by parenchymatous cells, and probably the liver [49, 52]. Although there are clinical diagnoses where the PCT values may be falsely elevated in the absence of a bacterial infection, for example, in the case of acute respiratory distress syndrome (ARDS) or systemic candidiasis, under these conditions, the elevation of PCT is relatively limited, reaching only 1.5-2 ng/mL [16, 52, 54]. The reliable biological activity, stability in blood samples and the easy laboratory tests which provide quick information makes PCT a superior parameter to monitor the course of systemic inflammation than the conventional biomarkers that were previously discussed. Even in patients with non-specific induction of PCT, it may still be used as a diagnostic parameter, since its elimination kinetics and possible range can be predicted.

This review emphasizes that persistently high or increasing PCT levels suggest an ongoing systemic inflammatory response or a septic complication under specific conditions, such as acute pancreatitis, elective esophageal tumor resection and elective major oncological surgery.

The Sequential Organ Failure Assessment score

This review showed that there has been a lack of studies investigating the use of the SOFA score and lactate level for the prediction of postoperative complications in surgery patients during the ICU stay. Although a correlation between the SOFA score and higher serum PCT and CRP levels has been reported [1, 23], the SOFA score may not be used as a predictor of surgical complications in critically ill patients [29], at least based on the limited existing data.

Lactate

Numerous studies have assessed the use of lactate concentrations in critically-ill patients as a way to monitor the response to therapy and the prognosis. However, few studies have assessed the use of lactate for the prediction of postoperative complications. The use of the lactate levels to anticipate septic complications after hepatectomy has been evaluated in only one study available in the databases searched [30]. Other studies have concluded that the lactate level seems to be a very poor marker for the diagnosis of complications in surgical patients in the ICU [31, 32]. However, the D-

lactate level may be useful in diagnosing ischemic intestinal complications after a ruptured abdominal aortic aneurysm [31].

It is crucial to sort out which critically ill patients are going to deteriorate and would benefit from additional surgical therapy. The available parameters and scoring systems all suffer from similar drawbacks. First, they are all whole body measurements. Differences in which body site a blood samples is taken from may be interference with the change in the level of the biomarker. In addition, we can speculate that a fair degree of organ failure may be present before whole body measures of inflammatory mediators or lactate are elevated. Another problem is the lag time in these biomarkers. As stated throughout this review, the early detection of complications in frail and vulnerable patients is difficult, and only those markers that change rapidly and have a small half-life may be of importance.

However, the half-lives of these various inflammatory mediators are largely unknown. Clinical scoring systems are generally applicable only at admission or once daily. This means that in a rapidly deteriorating patient, the measurements may be in a steady state, and the actual concentrations are of little importance as the levels may still be rising.

Finally, it is necessary to assess the patient variability. In general surgery patients in the ICU, every subject is different, as each patient has undergone a different surgery based on their individual anatomy. Therefore, these variables may change differently in every patient. A common score that is applicable to all surgical patients may be unrealistic. New markers or panels of markers are needed that have rapid responses and are easy to sample and measure, with a short half-life.

CONCLUSIONS

Early identification of critically ill post-surgery patients at risk for surgical complications could allow for early goal-directed therapy in order to decrease lethal outcomes. The SOFA score and lactate level have little to no significant predictive value for postoperative complications. As contradicting data has been published regarding the use of C-reactive protein, this marker may not aid in the decision-making for starting therapeutic interventions. On the other hand, procalcitonin seems to be a useful parameter for diagnosing postoperative septic complications after general surgery and trauma. These factors can be of greater value in small homogeneous groups as opposed to a heterogeneous group, as all surgical patients in the ICU.

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CHAPTER 3

The value of C-reactive protein and lactate in the acute abdomen in the emergency department

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ABSTRACT

Case presentation This report describes the presentation of three critically ill patients with non-traumatic acute abdominal pain and increased concentrations of the biomarkers C-reactive protein (CRP) and lactate. In these three patients an exploratory laparotomy was carried out. Remarkably, the laparotomy showed no intra-abdominal abnormalities. We discuss the usefulness of these biomarkers in practice and their influence on establishing a diagnose and making a decision to perform an intervention.

Conclusions We conclude that biomarkers lactate and CRP in patients with acute abdominal pain should only be used in adjunct to the history and clinical findings, as they are not specific and can be misleading in establishing a diagnosis. In addition, relying on these biomarkers may contribute to more diagnostic examinations and/or unnecessary invasive interventions (for example laparotomy).

INTRODUCTION

Diagnosing patients who present in the emergency department with acute abdominal pain can be challenging. In addition to history taking and physical examination, clinicians often use laboratory tests and radiological examinations to exclude diagnoses that can mimic acute abdominal pain for example pneumonia. Physicians in the emergency department often base their decisions for consultation of the surgeon for a laparotomy on clinical presentation combined with biochemical abnormalities. Examples of those biochemical parameters are high concentrations of C-reactive protein (CRP) or lactate concentrations [1, 2]. The question remains if these parameters are reliable to diagnose an acute abdomen. The pitfall of relying on laboratory values could lead to over treatment or under treatment.

This report presents three patients with non-traumatic acute abdominal pain and abnormal C-reactive protein and /or lactate concentrations with a negative laparotomy. Furthermore, we discuss the usefulness of these markers in practice and their contribution to establish a diagnosis by means of interventions in the emergency department.

CASE PRESENTATION

First Case

Our first case was of a 65 years-old man who presented in the emergency department (ED) of our tertiary health care institute with acute abdominal pain which irradiated to the back in combination with hypotension. He was recently admitted into an orthopedic ward for two days with lumbar pain due to discopathy of all lumbar vertebrae with signs of spondylodicitis. Suspicion of an aneurysm of the abdominal aorta raised at presentation and a CT-scan was made. No acute pathology was seen except a dilatation of the stomach and small intestine. Laboratory results showed a leucocytes count of $8.4 \cdot 10^9$/L (normal reference value: 4-10 $\cdot 10^9$/L), CRP concentration of 661 mg/L (0.8-2 mg/L), creatinine level of 548 µmol/L (45-100 µmol/L) with a glomerular filtration rate of 9 mL/min/1.73m^2 and a lactate level of 3.9 mmol/L (<1.8 mmol/L). Additional conventional chest X-rays was also made without pathological findings. Based on the clinical presentation and laboratory results we performed a laparotomy, which showed no abnormalities. He was admitted into the Intensive Care Unit (ICU) for pulmonary and cardiovascular support.

During the first five days of admission he was septic and required cardiovascular and pulmonary support. Continuous Venovenous Hemofiltration (CVVH) for acute kidney failure was started. The first blood cultures showed a staphylococcus aureus. At that

time, the patient was treated with Tobramycine and Cefotaxim as prophylaxis for ventilator-associated pneumonia in combination with Orabase protective paste. A Positron Emission Tomography- Computed Tomography scan (PET-CT scan) and several CT-scans were performed, but did not show a focus.

After a stay on the ICU of one month with several complications he stabilized and was discharged. Complications included re-intubation, a central venous line infection with Enterococcus Faecium, an ischemic cerebrovascular accident in the left fronto-occipital region, an ileus and a segmental ischemic colitis with deep ulcers in the transverse colon. The lactate levels and CRP concentrations decreased to near normal values (Figure 1). Within a few days on the ward he developed a pneumosepsis, which was treated with Augmentin. When the patient deteriorated he was abstained from further treatment after consultation with patient and family. He deceased within 24 hours.

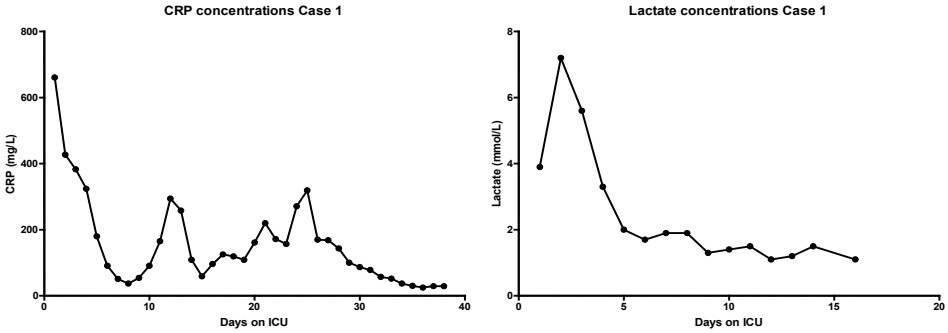

Figure 1. C-reactive protein and lactate concentrations over time of the first case.
Legend: *A* C-reactive protein concentrations and *B* Lactate concentrations. C-reactive protein levels and lactate concentrations decreased to near normal values during the ICU stay.

Second Case

The second patient was a 60 years-old woman. She presented in the ED with acute intense pain in the lower abdomen. One day earlier she started vomiting. Within the last six months she had several attacks of abdominal pain. The medical history included a laparoscopic cholecystectomy. On physical examination she had a tachycardia and was tachypnoeic. The lower abdomen was tender and a mass was palpated. A rectal and vaginal exam showed no abnormalities. Laboratory results demonstrated a leucocytes count of $18.1 \cdot 10^9$/L, CRP 4 mmol/L and no abnormal kidney or liver function parameters. Arterial gas showed a pH of 7.71 (normal ref. values: 7.35-7.45), pCO_2 of 1.7 kPa (4.7-6.4 kPa), pO_2 15.2 kPa (10.0-13.3 kPa), bicarbonate 4 mmol/L (22-29 mmol/L), base excess of -21.6 mmol/L (-3.0-3.0 mmol/L) and lactate level 6.7 mmol/L. Abdominal ultrasonography and conventional chest X-rays showed no abnormalities except a bladder retention which was treated.

Based on clinical and laboratory findings, a laparotomy was performed with the differential diagnosis of acute mesenterial ischemia. The laparotomy was negative for mesenterial ischemia, but bladder retention of more than one liter was found despite earlier treatment with an urinary catheter.

Postoperatively, the patient was admitted into the ICU and the lactate levels increased till 10 mmol/L and thereafter decreased to normal values (Figure 2). The CRP followed the same pattern (Figure 2). She was hemodynamically stable with low dosage of vasoactive medication and had mechanical ventilation support for a short period. Also, she developed acute kidney failure. Spontaneous mild correction of renal failure was seen within some days with a normal urine production of 60ml/ hour after administration of Furosemide. Abdominal pains in the right lower abdomen without a focus remained her main complain. After 3 days she was discharged from the ICU.

Complementary diagnostic examination by means of a gastroscopy showed a mild gastritis. A new abdominal ultrasonography showed no pathological findings.
During the stay on the internal medicine ward a spontaneous recovery of kidney failure was seen and constipation was successfully treated with Movicolon (a polyethylene glycol preparation; PEG 3350). Her abdominal pain decreased but was not totally over. After 11 days of admission, she was discharged.

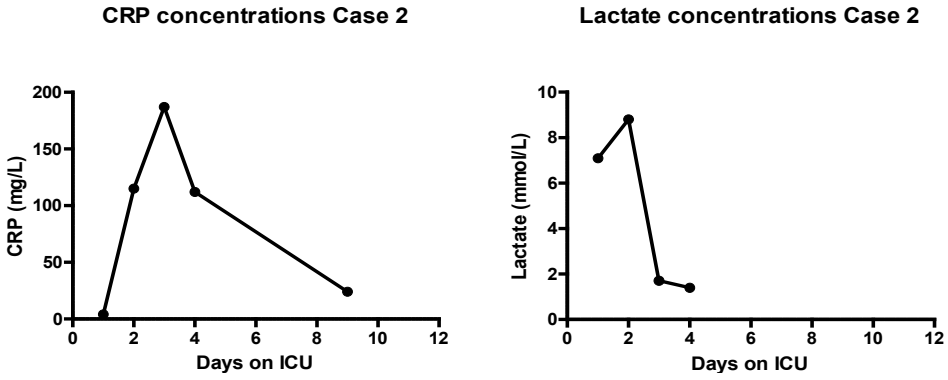

Figure 2. C-reactive protein and lactate concentrations over time of the second case.
Legend: *A* C-reactive protein concentrations and *B* Lactate concentrations. After admittance into the ICU, the lactate levels increased till 10mmol/L and thereafter decreased to normal values. The C-reactive protein levels follow the same pattern.

Third Case

The third patient was a 68 years-old male which presented in the ED with a productive cough, sore throat and perspiration at night without a fever. Furthermore he developed a generalized rash. He recently spent time abroad (Finland) for construction work. Clinical features at the ED showed petechial rash on the face, extremities and abdomen.

Furthermore, an enlarged submandibular lymph node was palpated. Examination of the abdomen was normal without tenderness. Laboratory results demonstrated a thrombocytes count of $20{\cdot}10^9$/L (normal ref. values: 150-400$10^9$/L), hemoglobin concentration of 9.1 mmol/L, leucocytes count of 6.6 mmol/L, CRP 9 mmol/L, bilirubine 24 µmol/L (0.0-20.0 µmol/L), alanine transaminase 212 U/L (0-45 U/L), aspartate transaminase 340 U/L (0-35 U/L), lactate dehydrogenase 677 U/L (,<248 U/L) alkaline phosphatase 684 U/L (0-115 U/L) and gamma-glutamyl transferase 265 U/L (0-55U/L). He was admitted into the internal medicine ward for further analysis of thrombocytopenia and liver failure.

Complementary diagnostic examination of the bone marrow demonstrated an increase in small lymfoide T-cells. Serology for viruses was negative. Conventional chest X-rays showed peribronchial changes like seen in COPD without other pathologic signs. Abdominal ultrasonography demonstrated a hepatomegaly, a small liver hemangioma and a thickened gallbladder wall without gallstones or signs of cholecystitis. Based on these findings the diagnosis for viral infection or auto-immune disease was made.

On the seventh day after admission he developed a fever of 38°C without any complaints. The same generalized petechial was observed without abdominal tenderness. Laboratory results showed further liver failure and no signs of infection. Because of a fever (>39°C), a CT-thorax and abdomen were made which showed a small consolidation in the right dorsal lung sinus, ascitis and infiltrative changes in mesenterium with air bubbles. It was suggested that these findings might indicate a bile-induced peritonitis. Antibiotics by means of Augmentin were started and a surgeon was consulted. Considering that the patient had no abdominal pain and no tenderness during physical examination, the team agreed to a conservative treatment. During the day and night the patient deteriorated with abnormal breathing, tachycardia of 110 beats per minute and jaundice without abdominal complaints or tenderness. New laboratory findings showed an increased lactate level with deterioration of liver tests (Figure 3). He was admitted into the ICU with the diagnosis abdominal sepsis with high lactate concentrations (lactate 15.1 mmol/L). The surgeon was consulted again based on a suspicion of intestinal pneumatosis due to acute mesenterial ischemia by means of high lactate levels, although no abdominal pain or abnormal physical examination was seen. A diagnostic laparotomy was performed. No pathological findings were observed except serosangulent fluids. He returned to the ICU.

On the ICU the patient remained hemodynamically unstable with high doses of inotropics and vasoactive medications. He had no abdominal pain and a normal physical examination. All cultures of blood, urine, sputum, ascitis and perioperative fluids were negative for infection. Nevertheless, broad spectrums of antibiotics were administered (Tobramycine, Augmentin and Doxycicline). CVVH was started due to acute kidney failure. During the next days the patient remained septic with high lactate concentrations,

liver failure and kidney failure, disseminated intravascular coagulation accompanied with bleeding of the eyes and mucous membranes. Based on all the clinical findings, multi organ failure and inability to stabilize him, further treatment was stopped. He died 13 days after admission.

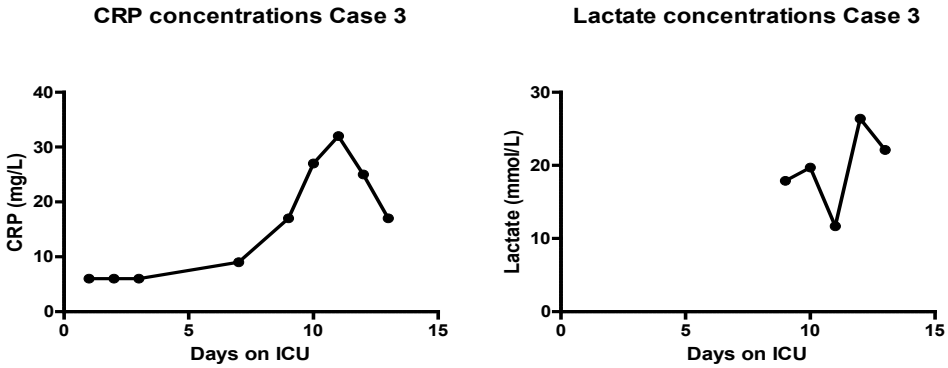

Figure 3. C-reactive protein and lactate concentrations over time of the third case.
Legend: *A* C-reactive protein concentrations and *B* Lactate concentrations. During admission both C-reactive protein as lactate levels increased over time.

DISCUSSION

Although some biomarkers like lactate and C-reactive protein can be useful in the diagnosis of an acute abdomen, these cases demonstrate that these parameters can mislead the physician and contribute to more diagnostic examinations or unnecessary invasive interventions like a laparotomy.

As described in all cases the main suspicion was acute mesenteric ischemia. This is a complex disease with a high mortality rate [3]. Until now, no reliable parameters to help diagnose such serious disease have been found and a search to identify this factor continues. One of the markers that are frequently used is plasma lactate concentration. An increase of lactate levels indicates an anaerobe glucogenesis and therefore it is a parameter for inadequate perfusion, oxygenation and an estimate of tissue oxygen deficiency. Increased plasma lactate concentrations were observed in patients with mesenteric ischemia with a sensitivity of 100% and a specificity of 42% [3]. Yet, another study on patient with an acute abdomen and increased lactate levels in the ED, showed a sensitivity of 75% and specificity 39% when using lactate concentrations for the diagnosis of acute mesenteric ischemia [4]. On the other hand the study of Lange et. al. [3] showed that elevation in lactate concentration can be due to other conditions as well. For example general bacterial peritonitis and in about 50% of the cases with strangulated intestinal obstructions [3].

Furthermore, other conditions correlated with high lactate concentrations are (septic) shock, diabetic ketoacidosis, liver coma, renal failure and acute pancreatitis. When other conditions have been excluded, an increased lactate level often may indicate an emergency abdominal condition. Some authors recommend an laparotomy in all patients with abdominal complaints and a raised plasma lactate level when other conditions correlated with increased lactate levels have been excluded [3]. However, we believe that this matter is more subtle as we observe that lactate levels are being used as a parameter only for acute mesenterial ischemia. Our third case is an example of a patient without abdominal pain but with high lactate levels, probably due to liver failure. Based on the lactate levels, an unnecessary invasive diagnostic intervention, a laparotomy was performed. As a study concluded, the determination of lactate concentrations has no better sensitivity in establishing the diagnosis of patient with acute abdomen compared to clinical findings and normal laboratory examination [4].

Another biomarker often used in the emergency department to aid in the diagnosis of an acute abdomen is the C-reactive protein (CRP). Most studies have focused mainly on the use of this parameter in establishing the diagnosis of appendicitis. Few studies have assessed its diagnostic role in the general conditions describing acute abdominal pain. The diagnostic value of CRP in the overall patient with acute abdominal pain showed a sensitivity of 79%, specificity of 64% and global accuracy of 73% for predicting subsequent hospitalization using a cut-off value for positive test of >5 mg/L [2]. More recently, Salem et. al. [5] reviewed the diagnostic value of CRP in true surgical patients with acute abdominal pain in the ED. They concluded that CRP alone is not useful in differentiating between surgical causes of acute abdomen or self-limiting condition [5]. In addition, CRP can neither differentiate between surgical conditions requiring intervention from those who can be treated non-operatively [5]. In conclusion, these studies confirm the difficulty to diagnose an acute abdomen and assessing the need for a laparotomy as in our cases. Although high CRP levels or increase in CRP concentrations are seen in combination with abdominal complaints, it does not directly mean that a surgical complication should be the problem.

When CRP is compared with lactate, one study concluded that CRP is as a poor marker for the diagnosis of an acute abdomen considering that its activation is later in the onset of the disease compared to lactate or Interleukin-6 (IL-6) [1, 5]. Patient with severe sepsis and those with sepsis on the ED with an acute abdomen can superiorly be differentiated by levels IL-6 and lactate [1]. But this study only included patients with sepsis or shock.

From our cases and a review of literature it is clear that we need more reliable markers to help establishing a fast and reliable diagnosis of patients with acute abdominal pain. Recently, the newer biomarker procalcitonin (PCT) showed to be a reliable marker to differentiate bacterial from nonbacterial infection or noninfectious in-

flammation with high accuracy [6]. Prospective studies on the use of PCT as screening test for appendicitis on the ED showed that this marker may only be useful in identifying patients with complicated (severe) appendicitis [7, 8]. Furthermore, procalcitonin has also been proven to be helpful during the diagnosis or exclusion of acute mesenterial ischemia, intestinal ischemia or necrosis in acute bowel obstruction and abdominal sepsis [9-11]. Its use may be considered as additional tool to improve clinical decision making and appropriate therapy.

Imaging modalities have proven to be valuable adjuncts in diagnosis patients with acute abdominal pain. In one patient the CT-scan revealed no abnormalities and neither did the following laparotomy. The third patient did not have abdominal pain and the CT-scan showed potential bile peritonitis. The critical illness of the patient with abnormal increase in CRP and lactate concentration pushed the surgeons to perform a laparotomy, again without abnormalities. Perhaps, it should be recommended that all patients with acute abdominal pain and increased CRP and/or lactate levels should additionally undergo a CT-scan [12]. Even though it is known that a CT-scan is not completely reliable, a biphasic CT angiography has been reported with a sensitivity of approximately 90% for the diagnosis of mesenteric ischemia independent of the underlying pathology [13, 14]. In addition, the CT scan can also provide alternative diagnoses for patients with an acute abdomen [13].

CONCLUSIONS

These cases demonstrate that although biomarkers CRP and lactate can be useful in the diagnosis of an acute abdomen, they are not specific and can be misleading in establishing a diagnosis. In addition, relying on these biomarkers may contribute to more diagnostic examinations and/or unnecessary invasive interventions (e.g. laparotomy). We conclude that lactate levels and CRP concentrations in patients with acute abdominal pain should only be used in adjunction to the history and clinical findings and perhaps to a CT-scan as well.

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CHAPTER 4

The role of C-reactive protein and SOFA score as parameter for clinical decision making in the surgical patient during the Intensive Care Unit course

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ABSTRACT

Introduction: C-reactive Protein (CRP) is used next to clinical scoring systems to recognize critically ill patients prone to develop complications on the Intensive Care Unit (ICU). The purpose of this study is to assess the predictive value of CRP as parameter for clinical deterioration and/ or clinical decision making as ordering diagnostic procedures or performing (re)interventions. Also, we wanted to determine the value of CRP in early detection of surgical complications in the critically ill general surgical patient in the ICU and its interpretation in adjunct to a clinical scoring system, the Sequential Organ Failure Assessment Score.

Methods: In our prospective observational study, 174 general surgical patients admitted into the Intensive Care Unit were included. We evaluated the Sequential Organ Failure Assessment Score (SOFA) and daily measured the C-reactive protein (CRP) concentrations. All events (diagnostic or therapeutic interventions) and surgical complications were registered. Then the relationship between SOFA score, CRP concentrations, events and complications were studied.

Results: Each 10% increase in CRP resulted in a 3.5 % increase in the odds of an event (odds ratio 1.035, 95% CI: 1.004-1.068; p= 0.028). However, an increase in CRP levels did not lead to a higher odds of complication (OR 0.983, 95% CI: 0.932-1.036; p= 0.52). When adjusting for the SOFA score the effect of CRP on the probability of a first event remained significant (OR 1.033, 95% CI: 1.001-1.065; p= 0.046), and again did not significantly affect the complication probability (OR 0.980, 95% CI: 0.929-1.035; p= 0.46).

Conclusions: An increase in C-reactive protein is a poor parameter for early detection of complications in the critically ill surgical patient in the ICU by means of diagnostic procedures or therapeutic (re)-interventions.

INTRODUCTION

C-reactive protein (CRP) is an acute phase protein synthesized by the liver, which levels raise in response to inflammation. It is a sensitive but non-specific inflammatory biomarker often used as an indicator for systemic inflammatory response syndrome (SIRS) [1, 2] secondary to surgery or early postoperative complications [3]. However, its role as predictor for clinical deterioration in the surgical critically ill patient in the intensive care unit (ICU) remains unspecific.

Many classification systems have been developed to recognize early deterioration in critically ill patients. An important scoring system is the Sequential Organ Failure Assessment Score (SOFA score) which describe the clinical course of the patient as marker for the degree of organ dysfunction and predictor for mortality [4].

Next to the clinical scoring systems, other conventional markers are used to recognize these specific patients who are prone to develop complications, for example CRP. Studies about the value of CRP in the critically ill patient on the ICU are contradictory. Increased CRP concentrations in a heterogeneous population on the ICU have been associated with organ failure, prolonged ICU stay, high infection rates and mortality rates [3, 5, 6]. On the contrary, a recent review on the predictive value of CRP concentrations for survival concluded that CRP is not a good predictor for survival in the critically ill patient during the early course. Yet it may help to identify patients who are at risk for death [7].

Despite contradictory studies, trends in CRP concentrations during the ICU admission are frequently used to determine whether or not further, more invasive, diagnostic procedures and/ or therapeutic interventions are required. An increase in CRP levels has been described as a crucial indicator for the diagnosis of postoperative complications in surgical patients such as infection, SIRS, sepsis, anastomotic leakage or mesenterial ischemia [8-10]. In addition, in patients with CRP levels > 140 mg/L on the 4th postoperative day after rectal surgery with primary anastomosis, a 90.5% positive predictive value for postoperative infection was measured [3, 9, 11]. However, CRP concentrations change throughout the postoperative course in both subjects with or without complications, and they are not specific for any kind of complications [9]. The question remains if this parameter is correctly interpreted in clinical decision making. To our knowledge, there is very little information available on the predictive value of changes in CRP concentrations in the critically ill general surgical population in the ICU with regards to diagnostic procedures or (re)interventions.

The purpose of this study is to assess the predictive value of CRP concentrations as parameter for clinical deterioration and/ or clinical decision making as ordering diagnostic and therapeutic (re)interventions in a heterogeneous group of surgical patient on the ICU. Furthermore, we wanted to determine the value of CRP in detection of surgical

complication in the critically ill surgical patient in the ICU and its interpretation in adjunct to a clinical scoring system, the SOFA score.

METHODS

All surgical patients, admitted to the level three general surgical Intensive Care Unit at the Amphia hospital Breda, a tertiary health care institute, were prospectively included into the study when inclusion and exclusion criteria were fulfilled. Data were collected from April 2010 until June 2011. Inclusion was regardless of the indication for admission. The study was approved by the Institutional Review Board of the Amphia Academy Breda and the need for informed consent was waived.

Exclusion criteria were defined as non-surgical patients or cardiac surgery patients, duration of stay shorter than two days and patients younger than 18 years of age at time of admission into the ICU. The duration of follow-up was until the day of discharge or set at a maximum of 28 days. In case that more than one ICU-episode was observed within the same patient, only the first episode was chosen in order to meet the assumption of independence of observations.

Patient characteristics, initial surgery type and diagnosis for admission into the ICU were collected. Definition for systemic inflammatory response syndrome (SIRS) and sepsis, as described by Bone [1, 2], were used for the determination of severity of infection at admission. Also, the Acute Physiology and Chronic Health Evaluation II (APACHE II) as score for morbidity was calculated. Laboratory findings for C-reactive protein concentrations were also recorded. Diagnostic and therapeutic interventions and their outcome, surgical complications, length of stay and death were recorded as well.

All patients admitted into the ICU underwent standard care, including daily routine laboratory tests (with CRP concentrations) and a plain chest X-ray. Prophylaxis for ventilator-associated pneumonia was started when a duration of stay of 72 hour or longer was expected and/or mechanical ventilation for more than 48 hours was started (SDD). This prophylaxis included Cefotaxim 1 gram 4 times daily continued for four days and Orabase protective paste 4 times daily applied in the mouth and administered through a nasogastric tube.

Sampling and laboratory analysis

Routine laboratory tests (hematology and biochemistry) were taken for all patients admitted into the ICU as part of the standard care. CRP concentrations were quantified using particle-enhanced immunologic turbimetric measurement for C-reactive protein Gen 3 in serum, as described by Roche (according to manufacturer's instructions, Cobas 6000).

Outcome variables

The Sequential Organ Failure Assessment Score (SOFA score) was used as a marker for organ dysfunction over time in patients on the Intensive Care Unit. This simple scoring system daily assigns 1 to 4 points to each of the six organ systems examined depending on the level of dysfunction. The tracts used in this scoring system are pulmonary, cardiovascular, coagulation function, hepatic, renal and neurological (Table 1)[4].

Table 1. The Sequential Organ Failure Assessment Score

SOFA score	1	2	3	4
Respiration	<400	<300	<200	<100
PaO_2/FiO_2mmHg			With respiratory support	With respiratory support
Coagulation	<150	<100	<50	<20
Platelets x $10^3/mm^3$				
Liver	20-32	33-100	101-203	>203
Bilirubin µmol/L				
Cardiovascular	MAP	Dopamine ≤ 5	Dopamine >5 or	Dopamine > 15
Hypotension[1]	<70mmHg	or Dobutamine (any dose)	epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	or epinephrine > 0.1 or norepinephrine > 0.1
Central Nervous System	13-14	10-12	6-9	<6
Glasgow Coma Score				
Renal	110-170	171-299	300-440 or <	>440 or <
Creatinine, µmol/L or urine output			500mL/day	200mL/day

To define the SOFA score, biochemistry data and clinical parameters of patients were collected at 5 o'clock a.m. during routine controls on the Intensive care unit.; [1]Adrenergic agents administered at least in hour (dose given are in µg/kg·min)

To calculate the value of CRP and SOFA score in clinical decision making, we defined the following interventions as events: CT-scan, ultrasonography (with or without punction), and flexible endoscopy or (re) laparotomy/thoracotomy. When surgical complications were found during these interventions, the events were defined as positive. Surgical complications were defined as intra-abdominal abscesses, anastomotic leakage, mesenterial ischemia, ileus, perforations, bleeding, diaphragm rupture or pneumothorax. Other non-surgical complications were also registered if present.

The treating physicians were not blinded for CRP nor SOFA score in order to reflect actual practice on the ICU. In addition, the majority of the treating physicians was not involved, nor participated in the design, purpose and methods of the study.

The number of historical ICU-episodes to be retrieved in this observational study is determined by the smallest group: the number of complication as proportion of the number of events to be predicted by two consecutive CRP measurement and SOFA measurements. Based on the rule of thumb that in logistic regression analysis the size of the smaller group should be at least ten times the number of variables in the model, the number of historical ICU episodes to be retrieved and the number of events should be large enough to yield at least 40 complications. We anticipated that 40 complications would result from 100 first events which in its turn would result from 200 ICU-episodes.

Statistical analysis

Results are presented as means ± standard deviation for continuous variables that have a Gaussian-shaped distribution and as (relative) frequencies for categorical nominal variables. When comparing two groups, the Chi-square test was used for categorical nominal variables and the unpaired T-test for continuous variables.

The relationship between the observation that an event had taken place and the preceding levels or changes of CRP was analyzed in a case-cohort design using conditional logistic regression analysis. Time was measured as days since admission to the ICU. For each day that an event occurred, the last and next to last CRP measurements were compared between patients with an event (the cases) and patients without an event on that same day (the remaining cohort). This comparison was made by using conditional logistic regression analysis. In this analysis the data were stratified by event-day, providing an optimal adjustment for day since admission when estimating the simultaneous effect of level and change of CRP on the event probability. Only the first occurring event within a patient was involved in this analysis so that events can be considered as mutual independent outcomes.

CRP-measurements were logarithmically transformed before analysis because of their positive skewness. The difference and sum of both measurements were entered in the model, respectively standing for the simultaneous effect of CRP-change and CRP-level on the event probability.

Directly after an event had taken place in a patient, additional investigations were done to confirm the event. So, in all ICU-patients in whom a first event had taken place a second outcome variable was observed: confirmation (yes or no). That outcome variable was analyzed using ordinary logistic regression analysis with the same explanatory CRP-variables as in the conditional regression analysis for explaining event (yes/no).

Prior to the above described (conditional) logistic regression analyses we analyzed the dependency of CRP on ICU-day (a maximum of 28 days) and event (yes/no) using linear mixed modelling. The first aim was to estimate the mean difference in CRP between events and no events across all 28 days (at maximum) and across all subjects in

the total ICU-cohort, while correcting for the categorical day-effect on CRP. In this analysis all events within a patient were taken into account by considering event (yes/no) a time-dependent within-patient explanatory factor equal to 1 at ICU-days that an event occurred and 0 at other ICU-days. The variance-covariance structure of the repeated CRP measurements across ICU-days was assumed to be first-order autoregressive with heterogeneous variances. A similar analysis was done for the effect on complication (yes/no). The second aim was to analyze the dependency of CRP levels on the SOFA score entered in the linear mixed model.

Statistical analysis was performed using SPSS 15.0, GraphPad Prism 5.0 for Windows and EGRET. A two sided *P*-value below 0.05 was considered to indicate statistical significance.

RESULTS

A total 174 patients were included in the study with 198 ICU-episodes. Four patients had three ICU-episodes, 16 patients had two ICU-episodes and 154 had one ICU episode. At time of admission into the ICU, the mean age of our patient population was 72 years (± 12 years, minimum 26 years and maximum 91 years). Postoperative SIRS and sepsis were the main indications for admission in 45% (n= 78) of all patients. Most patients admitted into the ICU had undergone an emergency laparotomy for an acute abdomen or a re-exploration for complication of previous surgery (18% and 14%, respectively). Further baseline characteristics between patients with and without events are showed in table 2. The groups were not overall similar, for example the operations before admission into the ICU and the APACHE II score differed between groups (Table 2).

The mean Acute Physiology and Chronic Health Evaluation II score on admission was 21 ± 9 points (min 8 - max 49 points). Patients with an event had significant higher scores than those without an event (23 ± 8 points versus 19 ± 7 points, respectively; p= 0.003). No significant difference in APACHE II score was seen between patients with and without complications (22 ± 8 and 24 ± 8, respectively; p= 0.22).

Overall in-hospital mortality on the ICU in our patient group was 9.8% (17/174). A higher mortality rate was observed in patients who underwent an event compared to those without an event (14.3% versus 6.2%, p= 0.07). Patients with and without complications had a small, non-significant difference in mortality (15% versus 13%, respectively; p= 1.00). The main cause of death was multi organ failure.

Seventy-seven patients (47%) of the 174 patients admitted into the ICU had an event of which twenty-four underwent more than one intervention. A total of 117 events were identified of which 50 (43%) were CT-scans in 30 patients and 32 (27%) re-operations in 23 patients (Table 3). In 48% of the CT-scans made, no complications were

found. In 61% of the ultrasonograms, no complications were found (Figure 1). If the event was an operation and the decision to perform surgery was based on the clinical parameters without radiological findings, in 72% of the cases an actual complication was found.

Table 2. Patients characteristics of patients with an event versus patients without an event (N=174)

	No event (N=97)	Event (N=77)[1]	P-value
Age mean *(SD)*	71.0 (12.3)	72.2 (11.1)	0.51
Male *N (%)*	61 (62.9)	53 (68.8)	0.41
Length of Stay on ICU *mean (±SD)*	5.0 (4.3)	9.9 (6.7)	<0.0005
Apache II score *mean (±SD)*	19.1 (6.5)	22.5 (8.0)	0.003
Indication for admission into ICU			0.40
Standard postoperative care after elective major surgery *N (%)*	16 (16.5)	9 (11.7)	
Postoperative with SIRS/sepsis *N (%)*	40 (41.2)	38 (49.4)	
Respiratory insufficiency *N (%)*	21 (21.6)	13 (16.9)	
Vascular operation *N (%)*	5 (5.2)	1 (1.3)	
Primary sepsis/ AKI/ MOF *N (%)*	8 (8.2)	11 (14.3)	
Others[2] *N (%)*	7 (7.2)	5 (6.5)	
Indication for operation before admission into ICU			0.047
No operation *N (%)*	15 (15.5)	16 (20.8)	
Elective colorectal operation *N (%)*	8 (8.2)	7 (9.1)	
Ileus *N (%)*	6 (6.2)	4 (5.2)	
Acute abdomen *N (%)*	21 (21.6)	11 (14.3)	
Epigastric region *N (%)*	6 (6.2)	2 (2.6)	
Complication of prior operation *N (%)*	10 (10.3)	14 (18.2)	
Embolectomy, bypass, amputation *N (%)*	8 (8.2)	1 (1.3)	
Elective correction AAA *N (%)*	3 (3.1)	12 (15.6)	
Ruptured AAA *N (%)*	9 (9.3)	5 (6.5)	
VATS or thoracotomy *N (%)*	2 (2.1)	1 (1.3)	
Others[3] *N (%)*	9 (9.3)	4 (5.2)	
Mortality *N (%)*	6 (6.2)	11 (14.3)	0.074

N =number SD = standard deviation %= percentage of total patients events or no events; [1)] The number of patients who had an event was lower than the total number of events; [2)] Others indication for admission are cardiovascular observation without prior operation; [3)] Others indication for operation are coiling, surgery after trauma or stabilization of fracture

SIRS= systemic inflammatory response syndrome ; AKI= acute kidney injury; MOF= multi organ failure; Acute abdomen= includes perforations, mesenterial ischemia, peritonitis; Epigastric region= Whipple, cholecystectomy, BII stomach resection, splenectomy; Complications= mesenterial ischemia, anastomotic leakage, platzbauch, intra-abdominal abscess; AAA= aneurysm of the abdominal aorta

Table 3. Description of event type

	Patients (N=174)	Total events (N=117)
No events N (%)	97 (55.7)	-
CT-scan N (%)	30 (17.2)	50 (42.7)
Laparotomy or operation N (%)	23 (13.2)	32 (27.4)
CT and operation N (%)	7 (4.0)	8 (6.8)
Ultrasonography N (%)	13 (7.5)	18 (15.4)
Flexible endoscopy N (%)	4 (2.3)	9 (7.7)

%= percentage of total N =number

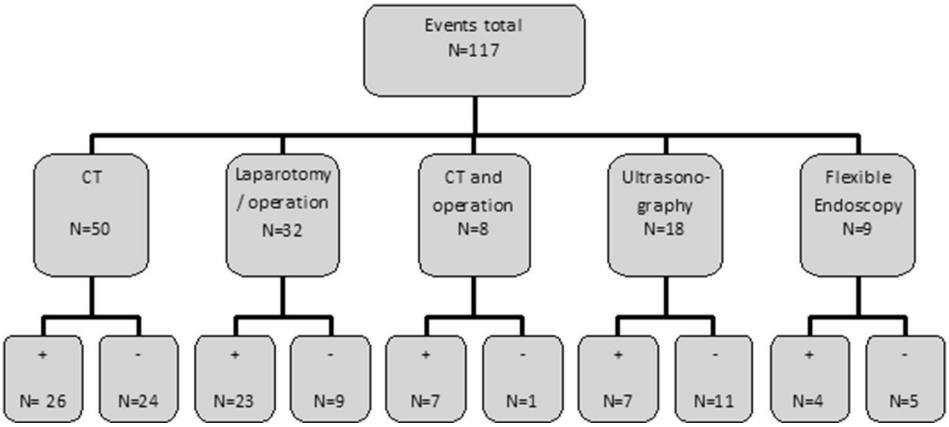

Figure 1. Events and outcome
Illustration of event type and its outcome, complication or not.
N= number += actual complication found -= no complication found

One-hundred and seventeen events occurred in 77 of the 174 patients admitted into the ICU. Of these 117 events, 67 (46/77 patients) were involved with a complication. The most common complications that we found were intra-abdominal abscesses (n= 31; 46%) followed by mesenterial ischemia (n= 15; 22%) (Figure 2). Non-surgical infectious complications found in this population were mainly pneumonias. An overview of non-surgical complications are shown in table 4

The Sequential Organ Failure Assessment Score varied between 0 and 16 points. At admission a mean SOFA score of 5.2 ± 2.6 points was found, which peaked at day two (5.6 ± 2.7 points). After this peak, the mean SOFA score decreased over time. No significantly different SOFA score was observed between patients with and without an event (mean difference -0.10 points; 95% CI: -0.32 to +0.13; *p*= 0.39). Furthermore, patients with and without complications had no difference in SOFA scores either (-0.70 points; 95% CI: -1.58 to +0.19; *p*= 0.12). On the other hand, a significant log-linear relationship

between SOFA score and CRP concentrations was found using linear mixes modeling. A one point increase in SOFA score corresponded with a 7.2% increase in CRP levels (95% CI: 5.3%-9.0% p<0.0005).

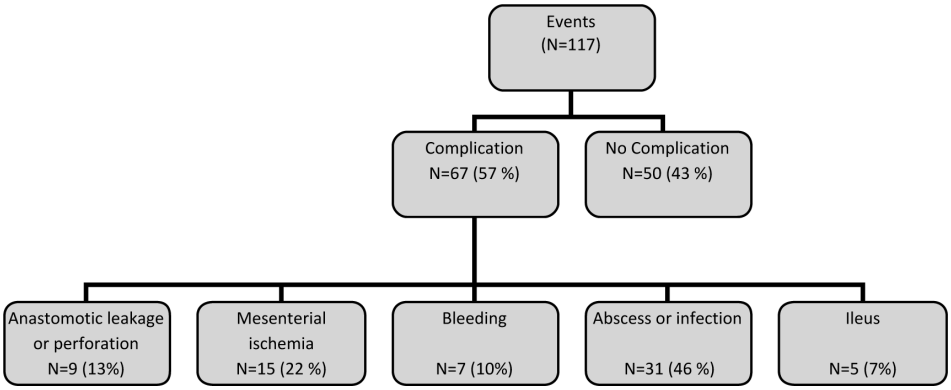

Figure 2. Event and complications
Description of complication type when found; N= number %= percentage of events/complications

Table 4. Description of non-surgical complications

	No event (N=67)	Event (N=77)
Pneumonia *N (%)*	22 (12.6)	18 (10.3)
Sepsis with infected central venous lines *N (%)*	3(1.7)	4 (2.3)
Wound infection *N (%)*	1 (0.5)	0 (0)
Positive cultures for ascites *N (%)*	0 (0)	1 (0.5)

%= percentage of total N =number

The overall mean CRP levels of patients included in the study peaked on day 3 of admission (mean 226 ± 114 mg/L). In patients with and without an event, CRP concentrations also peaked on day 3 (243 ± 116 mg/L and 212 ± 111mg/L, respectively; p= 0.080). After this peak the CRP concentrations started to decrease to normal levels (Figure 3). CRP concentrations in patients with an event showed a 7.5% higher CRP level compared to patients without an event on the same day (95% CI 0.3%-15.2%; p= 0.040). No significant difference in CRP levels was seen when comparing patients with a complications and without a complication on the same day (-4.7%; 95% CI: -26.8 %to +24.7%; p= 0.73). In these analyses linear mixed modeling accounted for all available daily repeated CRP measurements within patients during the ICU stay.

All 117 events contributed to the linear mixed model analyses, whereas in the (conditional) logistic regression analyses only the 77 first events were included. In the conditional logistic regression analysis we stratified on 10 different event days, with the number of events (cases) decreasing from 27 to 4 with increasing event day and the

number of patients in the remaining event-free cohort dropping off from 137 to 7 due to ending of ICU episodes. Meanwhile relatively small numbers of missings arose caused by incidentally missing last CRP changes or last SOFA score changes just before the event-day considered.

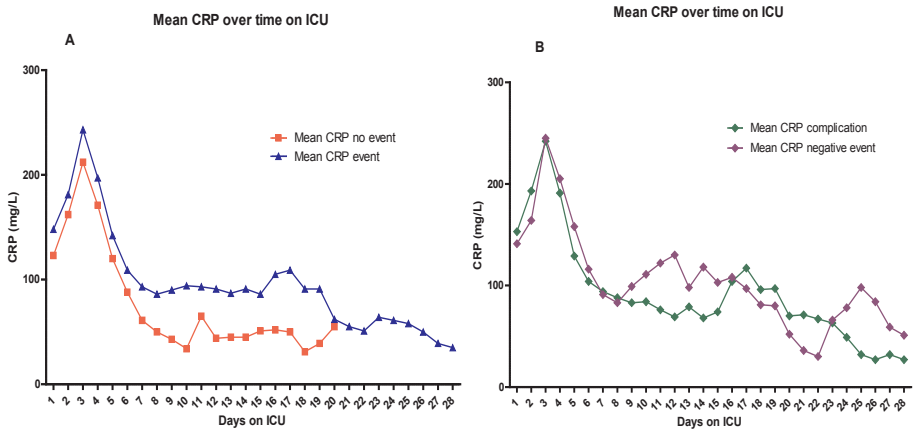

Figure 3. Mean C-reactive protein concentrations over time
A Mean C-reactive protein concentrations over time in surgical patients in the ICU with and without events. *B* Mean C-reactive protein concentrations of surgical patients with negative events and positive events (complications).

The effect on the odds of an event resulting from a relative increase in percent change of CRP, adjusting for ICU day and CRP level (and additionally for change and level of SOFA score) was estimated with the conditional logistic regression analysis. Effects of additive changes in SOFA score were estimated as SOFA score was not transformed in the analysis. Concerning CRP, effects of multiplicative (relative) changes were studied, as CRP was logarithmically transformed before analysis. From the analysis we found that each additional 10 % increase in percent change of CRP resulted in a 3.5 % increase in the odds of a first event (OR 1.035; 95% CI: 1.004-1.068, p= 0.028). A 10 % increase in CRP level resulted in a 2.6 % increase in the odds for an event (OR 1.026; 95 % CI: 0.997-1.055; p = 0.075). The p-value of the simultaneous effect of CRP change and level on the event odds is 0.059 (Table 5, Model 1).

A one point increase in SOFA score and an additional one point increase in SOFA score resulted respectively in a 5.5 % higher event odds (OR 1.055; 95 % CI: 0.925-1.204; p = 0.42) and a 7.3 higher event odds (OR 1.073; 95 % CI: 0.986-1.168; p = 0.10). The p-value of the simultaneous effect of SOFA change and level on the event odds was 0.18 (Table 5, Model 2). The effects of changes and levels of both CRP and SOFA scores

simultaneously, and hence adjusted for one another, are presented as model 3 in Table 5. The overall p-value of those four effects is 0.12.

Table 5. Effects of CRP and SOFA on the odds of an event or complications.

Model	Outcome events		Outcome complications	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*
model 1: CRP		0.059		0.39
10 % increase of change factor	1.035 (1.004-1.068)	0.028	0.983 (0.932-1.036)	0.52
10 % increase of level	1.026 (0.997-1.055)	0.075	1.009 (0.973-1.066)	0.44
model 2: SOFA		0.18		0.60
1 point larger increment	1.055 (0.925-1.204)	0.42	1.094 (0.876-1.366)	0.43
1 point larger level	1.073 (0.986-1.168)	0.10	0.932 (0.779-1.117)	0.45
model 3: CRP + SOFA		0.12		0.49
10 % increase of change factor in CRP	1.033 (1.001-1.065)	0.046	0.980 (0.929-1.034)	0.46
10 % increase of CRP level	1.022 (0.994-1.052)	0.13	1.021 (0.929-1.034)	0.40
1 point larger increment in SOFA score	1.037 (0.908-1.185)	0.59	1.156 (0.914-1.462)	0.23
1 point larger level of SOFA score	1.055 (0.966-1.151)	0.23	0.965 (0.799-1.164)	0.71

Using the data of the 77 first events, of which in 46 events a complication was confirmed, an ordinary logistic regression analysis was done in order to try to explain the probability of a complication from preceding CRP changes similar to the conditional logistic regression analysis described above. No significant effect of CRP change on the probability of a complication was found. Each additional 10 % increase in percent change of CRP resulted in a 1.7 % decrease in the odds of a complication (OR 0.983; 95% CI: 0.932-1.036, *p*= 0.52). Again after adjusting for SOFA a similar non-significant result was obtained (OR 0.980; 95 % CI: 0.929-1.034; *p* = 0.46) (Table 5). It can be concluded that the only significant effect found is that of CRP changes on the probability of an event. The decision of the treating clinicians to do an intervention is apparently partly based on the last observed CRP change.

DISCUSSION

To determine if a diagnostic and/or therapeutic (re)interventions are indicated in the critically ill surgical patient during the ICU stay, trends in CRP concentrations are often used. In this large prospective study with critically ill general surgical patients we found a significant relation between increase in CRP concentrations and events. However, no significant relation between increase in CRP levels and complications was found.

Although many studies showed that increasing CRP concentrations or persistently high CRP levels are suggestive for ongoing inflammation with multi organ failure and poor outcome, these studies mainly included a general ICU population [5, 6, 12]. In our study we evaluated the CRP levels and events of only critically ill surgical patients in the ICU.

C-reactive protein has been considered as an indicator for adverse postoperative course including both surgical and non-surgical complications as it responds to both infection and inflammation. Mustard et. al.[12] found in 1987 that a normal CRP response to surgery without a secondary rise can be used to exclude the possibility of a postoperative septic complication, due to its negative predictive value of 78%. In spite of the fact that this study included a small surgical population (n= 108), they concluded that CRP measurements should be used as adjunct to surgical care in patients at high risk for postoperative complications [12]. However, a negative predictive value of 78% is low. Further information on these complications is available from previous studies examining complications after colorectal surgery. Intra-abdominal infection caused by an anastomotic leak after colorectal surgery was correlated with prolonged CRP concentrations over 125- 190 mg/L or higher on the third postoperative day [10]. Similarly, this persistent CRP elevation and levels higher than 140mg/L on postoperative [9, 13-15] days 3 and 4 were predictive for infectious postoperative complications (86% and 91%)[9]. Despite of our large group of patients, we could not confirm this finding. In our study population, a value > 140 mg/L was not related to complications in the conditional logistic analysis. Yet, trends in CRP levels during the first 48 hours of ICU admission can be helpful in the decision whether or not further diagnostic procedures are needed in critically ill patients [5]. Our study showed a significant relation between 10% to 30% increase in CRP concentrations and events (diagnostic or therapeutic procedures). However, this increase in CRP levels showed no significant relation with surgical complications. Platt et.al. also confirmed higher CRP levels in patients with postoperative infectious complications compared to those without any complications [16]. Nevertheless, this large study could not differentiate between patients with surgical and non-surgical infectious complications as well.

Since it is difficult to diagnose early complications in critically ill patients, other parameters may also be used in the decision making for further diagnostic or therapeutic procedures. These may include the Sequential Organ Failure Assessment Score (SOFA) by means of clinical deterioration. The usefulness of SOFA score in critically ill patient has been validated in large cohorts demonstrating its prediction for mortality and outcome [17, 18]. With regards to our findings, an increase in mean SOFA score during the first 48-72 hours of admission was often seen. Nevertheless, no difference in SOFA score between patients with and without events and with or without complications was found during these 72 hours or rest of the stay in the ICU. Even when CRP was adjusted

for the SOFA score, only a significant relation with events was found, but none with complications.

It appears that an increase in CRP levels triggers physicians to perform additional interventions (events). As no relationship between an increase in CRP and postoperative complications is found, we can argue if CRP is a reliable marker. It is important to realize that changes in CRP concentrations should not be interpreted separately from clinical data in clinical decision making. Newer markers are needed and currently being studied as parameters for infection and sepsis and other complications.

There are several limitations to our study. The first is that the treating physicians were not blinded for CRP or the SOFA score. We realize that this is a risk for bias. The reason for not blinding the clinician is that we wanted to reflect practice as it is on the ICU. As the clinicians were not blinded for CRP concentrations or SOFA scores, it may have prompted the physicians to order diagnostic tests or perform interventions based on changes in CRP levels or SOFA scores. Yet, this is a reflection of actual practice in the ICU and clinicians should not make decisions based on isolated laboratory values or SOFA scores alone. Another downside of our study is that also non-infectious complications (surgical or non-surgical) were included in the analysis. For example patients with postoperative bleeding, ileus or mestenterial ischemia. These patients developed a complication which was not necessary accompanied by an increase in CRP. As this was only a small amount of patients, we can assume that they did not influence our data. Furthermore, as mentioned above our data provided us with more reliable information on the clinical course of the general surgical patients on the ICU. In addition, it might be that in different hospital region or countries, the threshold to perform a diagnostic or therapeutic intervention may differ from our hospital. Nevertheless, the patients included in our study were those admitted into a large level 3 ICU with a broad surgical population and different physicians. We therefore believe that this study is representative for a general critically ill surgical patients admitted into an ICU.

CONCLUSIONS

In this observational study we conclude that increase in C-reactive protein concentration is a poor parameter for detection of surgical complications in the critically ill surgical patient in the ICU by means of diagnostic procedures or therapeutic (re-)interventions. Yet, we found that when CRP increased, more diagnostic and therapeutic interventions were performed. In addition, we recommend that CRP should not be used by itself for clinical decision making but in adjunct to clinical parameters. Since a combination with the SOFA score does not seem to improve its value, more reliable clinical scoring systems and markers are needed.

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CHAPTER 5

Determining the clinical value of lactate in surgical patients on the Intensive Care Unit

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ABSTRACT

Introduction: The purpose of this study is first to assess the clinical value of lactate concentrations by comparison to clinical scoring systems and second to determine the value of lactate levels in clinical decisions as ordering diagnostic and therapeutic (re)interventions in the population of critically ill surgical patients on the Intensive Care Unit (ICU).

Methods: From April 2010 till June 2011 the L-lactate concentrations, Sequential Organ Failure Assessment Score (SOFA) and Acute Physiology and Chronic Health Evaluation II score (APACHE II) were prospectively collected in surgical patients (n=174) admitted into the Intensive Care Unit. The L-Lactate and scoring systems were related to events defined as performing CT-scans, laparotomy, ultrasonography and flexible endoscopy. Furthermore, all surgical complications were also registered.

Results: For SOFA scores above 4 points, mean lactate concentrations increased 4.5% for each point increase in SOFA score (p<0.0005). In APACHE II scores above 16 points, mean lactate concentrations increased 2.9% for each point increase in APACHE II score (p<0.0005). Each 10% increase in lactate concentration, showed a 3.3% higher odds for a first event (OR 1.033; p= 0.26). Lactate levels did not correspond with more complications (OR 0.968; p= 0.52).

Conclusions: There is a significant positive relationship between lactate concentrations, high SOFA scores and APACHE II scores. However, the important outcome is that lactateseems to be a poor predictor for surgical complications in the critically ill surgical patient in the ICU.

INTRODUCTION

Lactate is widely used in critically ill patients admitted into the Intensive Care Unit (ICU) as a parameter for severity of illness. It is a product of the anaerobic metabolism of glucose related to cellular hypoxia. Both its arterial and venous levels are a good indicator of the severity of metabolic acidosis secondary to tissue hypoperfusion[1]. Several studies have been published on the clinical use of lactate.

Lactate levels may aid in diagnosing critically ill patients. In acute mesenteric ischemia, which remains a difficult clinical diagnosis, lactate often contributes to diagnose these patients and thereby facilitates the start of adequate therapy. Increased plasma lactate concentrations in patients with acute mesenteric ischemia have a sensitivity of 75-100% and a specificity of 39-42%[2-4]. Furthermore, higher concentrations have been correlated with survival and outcome. Multiple studies have assessed the value of monitoring lactate levels in critically ill patients as a measure of severity of illness, response to therapy, and prognosis [1]. The risk of multi organ failure or death increases when lactate levels are higher for a longer period in patients admitted into the ICU[5]. These increased lactate levels are associated with worse clinical SOFA scores, a clinical scoring system for severity of disease in intensive care patients[5]. Also, in patients acutely admitted into the emergency department there is a significant correlation between increased lactate concentrations on admission and in-hospital mortality[1, 6-8]. In adult patients admitted into the ICU both a single measurement of lactate levels on admission ≥ 2.5 mmol/L and sustained concentrations > 2.0 mmol/L have been shown to be significant independent predictors of in-hospital mortality [1, 9-11].

Lactate levels are also used as guideline for response to therapy. Polonen et. al.[12] described that cardiac patients who were treated guided by lactate levels were administrated with more fluids and inotropes than patients who were treated without the guidance of lactate levels.

As lactate is often used for prediction of outcome and therapy monitoring, the question remains if it is correctly interpreted in clinical decision making on the ICU in general surgical patients. To our knowledge, there is very little information available on lactate levels in the clinical status of the surgical patients and the value of lactate concentrations in clinical decision making.

Moreover, the use of lactate is still controversial due to discrepancies regarding reference intervals, cut-off points and the interpretation of single or multiple lactate measurements [1].

The purpose of this study is first to assess the clinical value of lactate concentrations by comparison to clinical scoring systems (Sequential Organ Failure Assessment Score or Acute Physiological and Chronic Health Evaluation II). Second, we wanted to determine

the value of lactate levels in clinical decisions as ordering diagnostic and therapeutic (re)interventions in a heterogeneous group of surgical patient on the ICU.

METHODS

We included all general surgical patients admitted to the level three Intensive Care Unit at the Amphia Hospital Breda. This ICU is an tertiary referral center for patients in need for intensive care services and is capable of providing complex multisystem life support for indefinite period for all patients admitted into our hospital. Mostly general surgical patients and cardiovascular surgical patients were admitted in our ICU.

Exclusion criteria were defined as non-surgical patients or cardiac surgery patients, duration of stay shorter than two days and patients younger than 18 years. The maximum duration of follow-up was 28 days or until the day of discharge. Data were collected prospectively from April 2010 until June 2011. The study was approved by the Institutional Review Board and the need for informed consent was waived.

We collected patient characteristics, initial type of surgery and indication for admission into the ICU. The Acute Physiology and Chronic Health Evaluation II (APACHE II) as a score for morbidity at time of admission was also calculated. Laboratory findings and further data to calculate the Sequential Organ Failure Assessment Score (SOFA score) were recorded to describe the clinical course of patients over time as degree for organ dysfunction [13]. Diagnostic and therapeutic interventions and their outcome were also registered. Furthermore, (surgical) complications, length of stay and death were recorded as well. Surgical complications were defined as an intra-abdominal abscess, anastomotic leakage, mesenterial ischemia, ileus, perforations and bleeding. Other non-surgical complications were also registered if present. The non-surgical complications that were included to try to explain hyperlactatemia were other septic complications e.g. pneumonia, positive ascites cultures, infection of central venous lines and wound infections. We also included conditions that may induce hyperlactatemia like diabetic ketoacidosis, liver coma, renal failure and acute pancreatitis .

In the ICU all patients underwent the standard protocol of care, which included routine laboratory tests on a daily basis, a plain chest X-ray and SDD prophylaxis for ventilator-associated pneumonia.

Routine laboratory tests (hematology and biochemistry) were taken from all patients on a daily basis. Arterial (L-) lactate concentrations were measured only on indication. That usually means that if a patient deteriorates during the ICU stay lactate levels were measured. Lactate was quantified on a RAPID Point 500-analyser (Siemens, Breda, the Netherlands) using a sensor which lactate of the sample interacts with lactase oxidase on the membrane of the measuring electrode.

Outcome variables

Lactate levels, SOFA scores and APACHE II scores were compared to determine the clinical value of lactate concentrations. Additionally, the relationship between lactate concentrations and events was studied. We defined events as the following interventions: CT-scan (with or without punction/drainage of fluids), ultrasonography (with or without punction/ drainage of fluids), and flexible endoscopy or (re) laparotomy/thoracotomy. When surgical complications were found during these interventions, the events were defined as positive. The following were defined as surgical complications: an intra-abdominal abscess, anastomotic leakage, mesenterial ischemia, ileus, perforations, bleeding, diaphragm rupture or pneumothorax. These diagnoses were considered as surgical complications because most of them may be treated with surgical care and most commonly occur postoperatively. In addition, these complications may be the first presentation of more complex complications. No complications that occurred within 24 hours after surgery were included as complications as we regarded these as a direct technical complication of prior surgery.

In this observational intention-to-treat study we determined the number of patients to be included in our study. This was based on the number of complication as proportion to the number of events predicted by two consecutive lactate values. Based on the rule of thumb that in logistic regression analysis the size of the smaller group should be at least ten times the number of variables in the model, the number of historical ICU episodes to be retrieved and the number of events should be large enough to yield at least 40 complications. We anticipated that 40 complications would result from 100 first events which in its turn would result from at least 200 ICU episodes.

Statistical analysis

The results are presented as mean ± standard deviation for continuous variables and as (relative) frequencies for categorical variables. The two groups (with and without events or complications) were compared using the Chi-square or T-test as appropriate.

The occurrence of an event depending on preceding lactate concentrations was analyzed in a case-cohort design. Cases were defined as ICU-patients experiencing a first event immediately after at least two consecutive valid lacate measurements. Cases derived from the cohort remaining event-free at the day of the event. The probability of an event was analyzed using conditional logistic regression. Of interest was the effect of the two preceding lactate levels on the event probability, adjusted for day of the event by stratification.

Lactate measurements were logarithmically transformed before analysis. The two lactate levels were entered in the model through their two orthogonal contrasts: difference and sum, respectively representing change and level.

Confirmation (yes/no) of the event was analyzed similarly using ordinary logistic regression analysis.

Lactate was also analyzed as dependent variable in a linear mixed model with ICU-day (maximally 28 days) and event (yes/no) as independent variables. The first aim was to estimate the mean difference in lactate between events and no events across the maximally 28 ICU-days while correcting for the categorical day-effect. A similar analysis was done for the effect on complication (yes/no). The second aim was to analyse the dependence of lactate levels on the SOFA and APACHE II scores when separately entering these variables in the linear mixed model.

Statistical analysis was performed using SPSS 15.0, GraphPad Prism 5.0 for Windows and EGRET. A two sided *P*-value <0.05 was considered to indicate statistical significance.

RESULTS

One hundred and seventy-four patients were included in our study with a total data set of 198 ICU episodes with a maximum follow-up of 28 days. Some patients were admitted more than once (4 patients had 3 ICU-episodes, 16 patients had 2 ICU-episodes). Only the first episode of a patient was involved in the statistical analyses.

The mean age of our patients was 72 years (± 12 years, range 26-91 years). Most were admitted into the ICU because of postoperative SIRS and sepsis. Emergency laparotomy for an acute abdomen or a re-exploration for complication of previous surgery were the most common surgery prior to admission (n=32 and n=24, respectively). Other operations prior to admission into the ICU were elective colorectal operations, adhesiolysis in patients with an ileus, hepatobiliary surgery, vascular surgery, thoracothomy and trauma surgery. Both elective as emergency surgeries were included, but more emergency surgeries were observed. Twenty-five patients were admitted into the ICU as part of standard postoperative care after elective major surgery. Further baseline characteristics are showed in table 1.

One hundred and seventeen events occurred in 77 patients (47% of all patients). Of these patients, 24 patients underwent more than one intervention. An overview of the events and their outcome are shown in table 2.

In 46 of the 77 patients with a first event and in 67 of all 117 events a complication was confirmed. The most common complications that we found were intra-abdominal abscesses (n= 31; 46%) followed by mesenterial ischemia (n= 15; 22%). Non-surgical infectious complications in this population were mainly pneumonias. An overview of all complications is shown in table 3.

Overall in-hospital mortality on the ICU in our patient group was 9.8% (n=17). A higher mortality was observed in patients who underwent an event compared to those

without an event (14.3% versus 6.2%, *p*= 0.074). Patients with and without complications had a small, not significant difference in mortality (15% versus 13%, respectively *p*= 1.00). The main cause of death was multi organ failure.

Table 1. Patients characteristics (N=174)

Age mean *(SD)*	71.6 (11.8)
Male *N (%)*	114 (65.5)
Length of Stay on ICU of first ICU episode mean *(±SD)*	8.0 (5.6)
Apache II score *mean (±SD) at admission*	20.6 (7.4)
In event group	23 (8)
In non event group	19 (7)
SOFA score *at admission*	5.2 (2.6)
In event group	5.8 (2.7)
In non event group	4.6 (2.5)
Indication for admission into ICU	
Standard postoperative care after elective major surgery *N (%)*	25 (14.4)
Postoperative SIRS/sepsis *N (%)*	78 (44.8)
Respiratory insufficiency *N (%)*	34 (19.5)
Vascular operation *N (%))*	6 (3.4)
Primary sepsis/ AKI/ MOF *N (%)*	19 (10.9)
Others[1] *N (%)*	12 (6.9)
Mortality *N (%)*	17 (9.8)

N =number SD = standard deviation %= percentage of total patients events or no events;
1) Others indication for admission are cardiovascular observation without prior operation; SIRS= systemic inflammatory response syndrome; AKI= acute kidney injury; MOF= multi organ failure

Table 2. Description of event type

	Patients (N=174)	Total events (N=117) + complication - no complication
No events *N (%)*	97 (55.7)	–
CT-scan *N (%)*	30 (17.2)	+ 26 (22.2) – 24 (20.5)
Laparotomy or operation *N (%)*	23 (13.2)	+23 (19.7) – 9 (7.7)
CT and operation *N (%)*	7 (4.0)	+ 7 (6.0) – 1 (0.9)
Ultrasonography *N (%)*	13 (7.5)	+ 7 (6.0) – 11 (9.4)
Flexible endoscopy *N (%)*	4 (2.3)	+ 4 (3.4) – 5 (4.2)

%= percentage of total N =number

Table 3. Description of complications

	No event (N=67 patients)	Event (N=77 patients)
Surgical complications		
Anastomotic leakage or perforation *N (%)*		9 (11.7)
Mesenterial ischemia *N (%)*		15 (19.5)
Bleeding *N (%)*		7 (9.1)
Abscess or infection *N (%)*		31 (40.3)
Ileus *N (%)*		5 (6.5)
Non-surgical complications		
Pneumonia *N (%)*	22 (12.6)	18 (10.3)
Sepsis with infected central venous lines *N (%)*	3(1.7)	4 (2.3)
Wound infection *N (%)*	1 (0.5)	0 (0)
Positive cultures for ascitis *N (%)*	0 (0)	1 (0.5)

%= percentage of total N =number

A mean APACHE II score of 21 ± 7 points (range 8 - 49 points) was observed at admission. We compared patients who had an event/complication and without event/-complication. Patients with an event had significant higher scores than those without an event (23 ± 8 points versus 19 ± 7 points, respectively; p= 0.003). No significant difference in APACHE II score was seen between patients with and without complications (22 ± 8 and 24 ± 8, respectively; p= 0.22).

The Sequential Organ Failure Assessment Score varied between 0 and 16 points. At admission a mean SOFA score of 5.2 ± 2.6 points was found, which peaked at day two (5.6 ± 2.7 points). After this peak, the mean SOFA score decreased over time. No significantly different SOFA score was observed between patients with and without an event (mean difference -0.10 points; 95% CI: -0.32 to +0.13; p= 0.39). Furthermore, patients with and without complications had no significant difference in SOFA scores either (-0.70 points; 95% CI: -1.58 to +0.19; p= 0.12).

Lactate concentrations were available for maximally 23 days of follow-up. Lactate was only collected on indication when patient deteriorated. When all events were analyzed a total number of 81 events (81/117) with 46 complications were preceded by a lactate measurement and contributed to the linear mixed model analyses. In the (conditional) logistic regression analyses only the 59 first events (57/77) were involved with 33 a total of complications.

Overall mean lactate levels of patients included in the study peaked on the first day of admission (mean 3.4; range 0.6-18.3 mmol/L). In patients with and without an event, lactate had the highest concentrations on admission into the ICU in patients with an

event (3.9 mmol/L versus 2.9 mmol/L, respectively). After this peak the lactate concentrations started to decrease to almost normal levels (Figure 1).

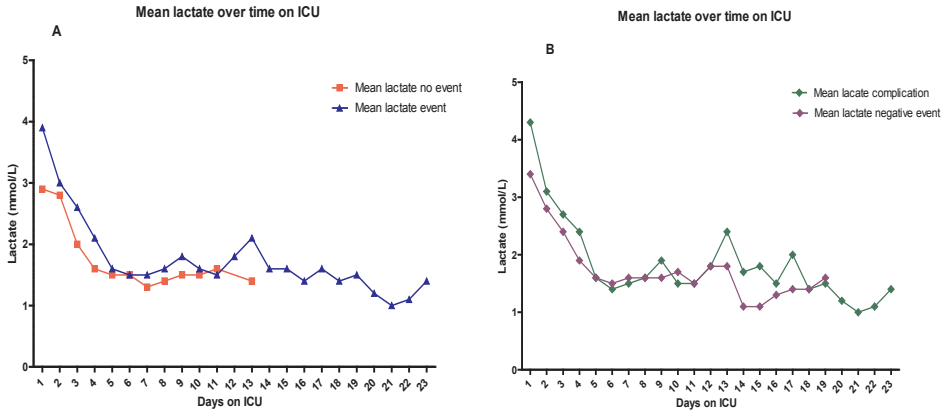

Figure 1. Mean lactate concentrations over time
A Mean lactate n concentrations over time in surgical patients in the ICU with and without events. *B* Mean lactate concentrations of surgical patients with negative events and positive events (complications).

The association of lactate levels with SOFA score as well as with APACHE II score showed a significant positive quadratic component. The resulting trough-parabolas had minimum lactate levels at a SOFA score of 4 points and at an APACHE II score of 16 points. For ease of interpretation we remodeled this parabolic relationships by piecewise linear ("broken stick") models with the just mentioned minimum SOFA and APACHE II scores as break points. For SOFA scores below 4 points geometric mean lactate concentrations decreased significantly with 3.7% for each point increase in SOFA score (95% CI: - 7.1% to -0.2%, p= 0.038). For SOFA scores above 4 points, a significant increase in geometric mean lactate concentrations of 4.5% for each point increase in SOFA score was found (95% CI: 2.8% to 6.2%, p<0.0005). APACHE II scores below 16 points showed a decrease in geometric mean lactate levels of 3.3% for each point increase in APACHE II score was estimated (95% CI: -8.3% to + 1.4%, p= 0.17). For APACHE II scores above 16 points, a significant increase in geometric mean lactate concentrations of 2.9% for each point increase in APACHE II score was found (95% CI: 1.8% to 4.0%, p<0.0005). While daily measurements of the SOFA score were available, there was only one measurement (at admission) of the APACHE II score. The effect of this single APACHE II score on the daily lactate measurements did not appear to be significantly modified by day since admission.

The 174 patients with 81 events preceded by a lactate measurement contributed to the linear mixed model analyses, whereas in the conditional logistic regression analyses and the ordinary logistic regression analyses the 174 patients with 59 first events were

included. We estimated the effect on the odds of an event resulting from a certain percentage change in lactate, adjusting for ICU-day and lactate levels (and additionally for change and level of SOFA score). Each 10% increase in lactate concentration, relatively to no change, showed a 3.3% higher odds of a first event (OR 1.033; 95% CI: 0.0976-1.094, *p*= 0.26), which was not significant. On days that an event took place a 0.4% higher geometric mean lactate concentration was found compared to lactate concentrations measured on days without an event (95% CI: -5.8% to + 7.1%; *p*= 0.90), which again was not significant, corroborating the previous result through this inverse relationship.

Using the data of the 59 first event patients, of which in 33 events a complication was confirmed, an ordinary logistic regression analysis was done in order to try to explain the probability of a complication from preceding lactate changes similar to the conditional logistic regression analysis described above. No significant effect of lactate changes on the probability of a complication was found: per 10% increase in lactate level, a 3.2% lower odds of a complication was found (OR 0.968 95% CI: 0.875-1.070; *p*= 0.52). Also, the effect on the probability of a complication of a lactate level above 2.5 mmol/L relatively to a lactate level below 2.5 mmol/L entered as a single explanatory variable in the logistic regression model was not significant (OR 1.32; 95 % CI: 0.68-2.56; *p*= 0.41).

DISCUSSION

Lactate measurements on the ICU have been widely correlated with in-hospital mortality. Its concentrations > 2.0-2.5 mmol/L seems to correlate with higher in-hospital mortality and more adverse outcome[1, 6-9]. A new point of view on the use of lactate in the ICU is the clinical value of lactate in surgical patients admitted into the ICU. We found a significant positive relationship of lactate concentrations with SOFA scores and APACHE II scores when considering SOFA scores above 4 points and APACHE II scores above 16 points. These findings confirm a previous report by Jansen et. al.[5] who found an association between SOFA score and increased lactate levels in all patients admitted into the ICU as well. An overall relationship between the two variables was an increase of 0.62 SOFA points per 1 day·mmol/L of lactate levels (represented as area under the lactate curve > 2 mmol/L)[5]. These findings indicate that lactate can be used in combination with other scoring systems (for example the SOFA score) as marker for clinical deterioration in both general critically ill patients as in critically ill surgical patients in the ICU.

However, we found that lactate levels should not be used as a predictor for (surgical) complications in surgical patients in the ICU. In our study population, a value ≥ 2.5

mmol/L was not significantly related to more events or complications in the (conditional) logistic regression analyses. Moreover, even changes in lactate levels on the continuous scale did not bear significant effects on the probability of events or surgical complications. Although we did not show a significant increase in events with high lactate levels, we observed that higher lactate concentrations appear to trigger the physician to perform more diagnostic and/ or therapeutic interventions. During our analysis in patients with high lactate levels and without a complication we also tried to find other causes to explain the hyperlactatemia besides sepsis with hypoperfusion, inadequate oxygenation and tissue oxygen deficiency. Other causes that we searched for were conditions inducing hyperlactatemia like diabetic ketoacidosis, liver coma, renal failure and acute pancreatitis. Patients in our study population with liver coma had a prior septic complication with liver failure as a secondary complication. Subjects with the diagnosis of renal failure were mostly also due to a septic complication. The patients with the diagnosis pancreatitis had no high lactate concentrations during the ICU admittance.

Both L-lactate as D-lactate are being used in studies as parameters for the diagnosis of acute mesenterial ischemia [3, 14-17]. D-lactate from bacterial fermentation in the gastrointestinal tract has been proven to have a sensitivity of 90% and a specificity of 87% in diagnosing acute mesenteric ischemia in patients undergoing emergency laparotomy [18]. Another study on L-lactate in pigs showed that both L-lactate as D-lactate were good markers for diagnosis of venous-induced intestinal ischemia, with D-lactate being more used in search of an anaerobic focus [14]. L-lactate is more commonly used by clinicians as indicator for hypoperfusion and hypoxemia. Yet, the use of L-lactate concentrations as diagnostic aid for acute mesenteric ischemia is arguable as it reflects late stage of the disease[2, 3]. Furthermore, a recent study in an minimally invasive porcine model of intestinal ischemia with an endovascular approach demonstrated no relation between intestinal ischemia and plasma L-lactate values[16]. In our study we measured L-lactate in order to find surgical complications in critically ill surgical patients in the ICU. As L-lactate is the current marker being used by most clinicians as guideline for diagnostic or therapeutic intervention, we conclude that L-lactate is a poor marker for detection of surgical complications including acute mesenteric ischemia.

Some studies showed that hyperlactatemia to be interpreted as a result of anaerobic conditions due to systemic oxygen imbalance which triggered the physician to increase oxygen supply or decrease oxygen demand [12, 19-21]. In addition, studies suggest the use of high lactate concentrations to assess resolution of hypoperfusion. As described earlier, Polonen et. al.[12] showed more fluids and inotropes administration in the cardiac surgical patient group treated by means of lactate measurements compared to patients treated without the measurements of lactate levels. Yet, published data contradict with the origin of hyperlactatemia as some authors proposed that in-

crease lactate levels often reflects increased aerobic glycolysis in skeletal muscle secondary to epinephrine-stimulated Na^+, K^+-ATPASE activity and not anaerobic glycolysis due to hypoperfusion [22, 23]. This may explain why hyperlactatemia sometimes neither correlates with indicators of perfusion nor diminish with increased oxygen delivery during resuscitation [22, 23]. However, the rapidity at which lactate is cleared from the blood during resuscitation also correlates with mortality and organ failure [11, 24]. It may also be usefull as end-parameter of resuscitation. Jansen et.al.[25] aimed to reduce lactate by 20% per 2 hours, and managed to reduce mortality significantly in the intervention group. Despite of the well documented use of lactate to predict mortality in the critically ill patients on the ICU, this study is the first to our knowledge which describes the use of lactate in clinical decision making in critically ill general surgical patients on the ICU.

The downside of our study is that we used a heterogeneous surgical patient population in the ICU. Yet, our data provide more reliable information in an overall large group of surgical patient on the ICU than data from a general ICU population. As the lactate levels were not daily measured, we may have missed the overall trend of lactate before the event. Furthermore, smaller numbers were involved in the statistical analyses concerning the relationship between lactate change and events (complications). The smallest number that we had to deal with in the logistic regression analysis was 26 (no complications). Inclusion of four explanatory variables as we did in the logistic model might theoretically blow up the estimated coefficient in the analysis. However, the estimated effects were found to be not significant and our conclusion was sustained. We therefore believe that data analyzed in this study was sufficient to make conclusions on the use of lactate for clinical decision making in general critically ill surgical patients admitted into an ICU.

We conclude that there is a significant positive relationship between lactate concentrations, high SOFA score and APACHE II score. However, lactate seems to be a poor predictor for surgical complications in the critically ill surgical patient in the ICU and should not be used as a guide to perform diagnostic and or therapeutic interventions. Decision making to perform diagnostic tests or (therapeutic) interventions based on increased lactate levels alone seems not justifiable.

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CHAPTER 6

Procalcitonin in the recognition of complications in critically ill surgical patients

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ABSTRACT

Introduction: Procalcitonin (PCT) is a relatively new, promising indirect parameter for infection. In the intensive care unit (ICU) it can be used as a marker for sepsis. However, in the ICU there is a need for reliable markers for clinical deterioration in the critically patient. This study determines the clinical value of procalcitonin concentrations in recognizing surgical complications in a heterogeneous group of general surgical patient in the intensive care unit.

Methods: We prospectively collected PCT concentrations from April 2010 until June 2012 in all general surgical patients admitted into the ICU. Both the relationship between PCT levels and events (diagnostic and therapeutic interventions) as the relationship between PCT levels and surgical complications (abscesses, bleeding, perforation, ischemia and ileus) were studied.

Results: PCT concentrations were lower in patients who develop a complication than those not developing complications on the same day, though not significant (p= 0.27). A 10% increase in PCT levels resulted in a 2% higher complication odds, but again this was not significant (OR 1.020; 95% CI 0.961- 1.083, p= 0.51). Even a 20 or 30 % increases in PCT concentrations resulted in no higher complication probability (OR=1.039; 95 % CI 0.927-1.165 and OR 1.057; 95% CI 0.897-1.246). Furthermore, an increase in PCT levels did not show an increase or a reduction in the number of diagnostic and therapeutic interventions.

Conclusion: An increase in procalcitonin levels does not help to predict surgical complications in critically ill surgical patients.

INTRODUCTION

Critically ill (surgical) patients admitted into the intensive care unit (ICU) are prone to infections and complications. Since prompt and adequate therapy of these complications contributes to decreased mortality and morbidity in patients postoperatively, early and reliable diagnosis is a compelling issue for clinicians. Therefore newer scorings systems and biomarkers are being studied to recognize complications in an early phase.

Procalcitonin (PCT) is a relatively new biomarker that is used as a prognostic marker for systemic inflammatory response, infection and to evaluate antibiotic treatment during sepsis. It is synthesized physiologically in the thyroid C cells. However, in an inflammatory process or sepsis it has an extra-thyroidal origin [1]. Increased PCT concentrations have been found to be an independent predictor for survival in postoperative patients with severe sepsis on the ICU[2]. In addition, PCT has been correlated with a high diagnostic efficiency for the need of renal replacement therapy, presence of organ failure and presence for multi-organ failure during the ICU stay [3]. It has also been demonstrated that a PCT measurement is a superior marker to differentiate between sepsis and infection from other non-infections systemic inflammatory response compared to C-reactive protein (CRP) [1]. As PCT is an indirect parameter for infection, it is believed that it may also be used as a marker for clinical deterioration in the critically ill patients. Non-survivors with a ventilator-associated pneumonia (VAP) and sepsis have a higher PCT concentration on the day of VAP occurence and diagnosis than survivals (AUC 0.752) [4].

PCT may also help in the decision making for additional interventions and in the recognition of surgical complications [5-7]. When using PCT levels as an additional marker for postoperative sepsis and making therapeutic decisions, the extent of multiple organ dysfunctions seems to decrease [8]. This could mean that infection and sepsis are recognized earlier. Reith et. al. found that patients with complications after an elective aortic or elective colonic surgery have a statistical significant higher course of PCT concentrations compared to those without infective complications such as pneumonia, ischemia, anastomotic leakage, sepsis or shock [6]. Another article studying the use of PCT concentrations after major abdominal surgery concluded that PCT with an cut-off value of 1 ng/ml may aid in the early identification of those with postoperative infectious complications[7]. Also, PCT may be used as marker for the prognosis of postoperative complications after orthotopic liver transplantation (AUC 0.657, 95% CI 0.474 – 0.819)[9]. On the other hand, PCT concentrations did not show any prognostic value in patients admitted into a emergency department high dependency unit with severe sepsis or shock [10]. A recent study comparing C-reactive protein (CRP) concentrations and PCT levels following colorectal surgery found that PCT levels was not useful in the diagnosis of infectious complications [11].

In perspective of the arguments mentioned above the question remains if PCT can also be used for the detection of surgical complications in critically ill general surgical patients admitted into the ICU. For this reason the aim of this study is to determine the clinical value of procalcitonin levels in recognizing surgical complications in a heterogeneous group of general surgical patient on the ICU.

METHODS

In a blinded cohort study we included all general surgical patients admitted into the level three interdisciplinary intensive care unit at the Amphia Hospital Breda. Data were collected prospectively from April 2010 until June 2012. The maximum duration of follow-up was 28 days, death or until the day of discharge. We excluded non-surgical patients or patients following cardiac surgery, patients having duration of stay shorter than two days and patients younger than 18 years. The investigation was approved by the Institutional Review Board of the Amphia Academy Breda and the need for informed consent was waived.

At the time of enrolment patient characteristics, initial type of surgery and indication for admission into the ICU were collected. The Acute Physiology and Chronic Health Evaluation II (APACHE II) was measured on admission into the ICU and the Sequential Organ Failure Assessment Score (SOFA score) was calculated at daily during the stay on the ICU [12]. The APACHE II score was used as score for morbidity at time of admission. The SOFA score on the other hand was calculated to describe the clinical course of patients over time as degree for organ dysfunction. Diagnostic and therapeutic interventions (events) defined as performing CT-scan (with or without intervention), ultrasonography (with or without intervention), flexible endoscopy or (re) operation (laparotomy) and their outcomes were also registered. Furthermore, complications, length of stay and death were recorded. Complications requiring surgical treatment were described as surgical complications. These were defined as an intra-abdominal abscess, anastomotic leakage, mesenterial ischemia, ileus, perforations and bleeding. Other complications related to the operation but without requirement of surgical treatment were described as non-surgical complication and were also registered if present.

During the ICU stay all patients underwent the standard protocol of care where multisystem life support was given when needed and clinical deterioration or complications were treated as well during. This protocol included routine laboratory tests on a daily basis, standard surveillance cultures twice a week, a plain chest X-ray every day and Selective Digestive Decontamination (SDD) prophylaxis for ventilator-associated pneumonia (VAP). The SDD prophylaxis consisted of Cefotaxim 1 gram 4 times daily continued for four days, Orabase protective paste 500mg 4 times daily applied in the

mouth and 10 mLOrabase suspension once daily administered through the nasogastric tube if present. The Orabase mouth paste consist of 20mg Amfotericine B (Fugizone), 20mg Tobramycin and 20mg Colistin Sulfate. The suspension consists of 5mL Amfotericine B (500mg suspension), 5mL Colistin Sulfate (100mg) with Tobramycin (80mg).

Peri-operative patients received cefazoline (Kefzol) 2g, amoxicillin clavulanic acid (augmentin) 2200mg or erythromycin 1g. In the ICU patients were treated with broad-spectrum antibiotics based on the surveillance or additional cultures according to local protocols. Clinicians responsible for the care of the patients were blinded for the PCT concentrations as they were determined afterwards.

Routine laboratory tests (hematology and biochemistry) were taken from all patients on a daily basis at the same time in morning. Plasma was stored at 20°C until further analysis for procalcitonin concentrations. Plasma procalcitonin levels were measured as recommended by the manufacturer using a time-resolved amplified crypt emission technology assay. This "sandwich "type luminescence immunoassay and a coated-tube technique, the LUMItest® PCT assay (BRAHMS Diagnostics, Berlin, Germany) has an analytical sensitivity of 0.01 ng/mL, also levels seen in healthy control groups.

Statistical analysis

Both the relationship between PCT levels and events (diagnostic and therapeutic interventions) as the relationship between PCT levels and surgical complications (abscesses, bleeding, perforation, ischemia and ileus) were studied.

We present the results as mean ± standard deviation for continuous variables that have a Gaussian-shaped distribution and as (relative) frequencies for categorical variables. The two groups (with and without events or complications) were compared by using the Chi-square test for categorical nominal variables and the unpaired T-test for continuous variables.

We analyzed the relationship between PCT and complications by using linear mixed modeling and logistic regression analysis. Because of its highly positive skewness PCT was logarithmically transformed before the analyses. The aim of linear mixed modeling was to estimate the mean difference in PCT at a given ICU-day between patients who will develop a complication later that day and the total cohort of patients without complications during all 28 days (at maximum), while correcting for the categorical day-effect on PCT. Also the difference of two consecutive PCT-levels directly preceding the complication was similarly analyzed. For the logistic regression analysis on the effect of procalcitonin on the probability of surgical complications, only the first event that was directly preceded by two consecutive PCT concentrations was involved in the analysis. The data were stratified by ICU day (potential range 2-28) that a complication occurred and consequently analyzed in a case-cohort setting. At that ICU day the cases were the

observed number of patients with a first complication as defined above; the cohort was the total number of patients still in the ICU at that day without former complications and with two directly preceding consecutive valid PCT concentrations. The explanatory variables entering the logistic regression model were: sum and difference of both log-transformed PCT-measurements as continuous variables and the counted event-number within a subject as categorical variable. The stratification has caused the estimated results to be optimally adjusted for the potentially confounding effect of ICU-day.

Statistical analysis was performed using SPSS 15.0 and GraphPad Prism 5.0 for Windows. A two sided *P*-value below 0.05 was considered to indicate statistical significance.

RESULTS

A total of one hundred and sixty-four patients were included in the study. The mean age of our population was 70 ± 13 years. Most patients were admitted to the ICU for post-operative SIRS reaction or sepsis. Most of them underwent an emergency laparotomy for an acute abdomen or a re-exploration for complications of previous surgery. Further baseline characteristics are shown in table 1.

Interventions (events) were performed in 82 patients. Of these patients, 29 underwent more than one intervention which resulted in a total of 134 events. Eighty-two patients had an uneventful course during the ICU stay. An overview is given in table 2. Most often CT-scans (n=61) were performed followed by (re) operations (n=42).

Of the 134 events, 77 were confirmed as a complication. These complications were found in 49 patients, as some patients experienced more than one complication. The most common complications that we observed were intra-abdominal abscesses followed by mesenterial ischemia. A total of 66 non-surgical complications were found. Most of the complications in this population were pneumonias. An overview of all complications is shown in table 3. First events peaked between the second and fourth day postoperative (52 of 82 first events) which was mainly CT scans or surgery. In 29 of these 52 events performed between days 2-4 a complication was found.

Antibiotics were administered at different time throughout the ICU in all patients except 12. The overall in-hospital mortality was 12% with the main cause of death described as multi organ failure.

Across all 1,178 patient-days of follow-up PCT ranged from 0.01 to 179.4 ng/mL with a median of 1.70 ng/mL. The logarithmic transformation of PCT turned its highly positively skewed distribution into a neat symmetric bell-shaped one, enhancing the asymptotic properties of the estimated results. The number of patients in ICU with a valid PCT

measurement by ICU day and by complication (yes/no) is presented in Figure 1 as a stacked bars chart.

Table 1. Patients characteristics (N=164)

Age mean (±SD)	70 (12.6)
Male N (%)	103 (62.8)
Length of Stay on ICU *mean (±SD)*	9.3 (6.1)
Apache II score at admission *mean (±SD)*	21.3 (8.0)
SOFA score at admission *(±SD)*	5.6 (2.7)
Indication for admission into ICU	
Standard postoperative care after elective major surgery *N (%)*	31 (18.9)
Postoperative SIRS/sepsis *N (%)*	82 (50.0)
Respiratory insufficiency *N (%)*	22 (13.4)
Vascular operation *N (%)*	1 (0.6)
Primary sepsis/ AKI/ MOF *N (%)*	16 (9.8)
Others *N (%)*	12 (7.3)
Indication for operation	
No operation *N (%)*	20 (12.2)
Elective colorectal operation *N (%)*	11 (6.7)
Ileus *N (%)*	10 (6.1)
Acute abdomen *N (%)*	35 (21.3)
Operation in epigastric region *N (%)*	4 (2.4)
Complication of prior operation *N (%)*	37 (22.6)
Embolectomy, bypass, amputation *N (%)*	4 (2.4)
Carotid endarteriectomy *N (%)*	1 (0.6)
Elective repair of aneurysm of the abdominal aorta *N (%)*	18 (11.0)
Rupture of aneurysm of the abdominal aorta *N (%)*	13 (7.9)
Others *N (%)*	11 (6.7)
CVVH *N* (%)	55 (33.7)
Mortality *N (%)*	19 (11.6)

N =number SD = standard deviation %= percentage of total patients; SIRS= systemic inflammatory response syndrome; AKI= acute kidney injury; MOF= multi organ failure; CVVH= continuous veno-veneouos hemofiltration

Table 2. Overview of event type

	Patients (N=164)	Total events N=134)
No events *N (%)*	82 (50.0)	-
CT-scan *N (%)*	34 (20.7)	61 (45.6)
Laparotomy or surgery *N (%)*	27 (16.5)	42 (31.3)
CT and operation *N (%)*	10 (6.1)	12 (9.0)
Ultrasonography *N (%)*	7 (4.3)	12 (9.0)
Flexible endoscopy *N (%)*	4 (2.4)	7 (5.2)

%= percentage of total N =number

Table 3. Surgical and non-surgical infectious complications

Surgical complications	Complications (n=77)	Patients (n=164)
Anastomotic leakage *N (%)*	10 (13.0)	6 (3.6)
Mesenterial ischemia *N (%)*	19 (24.7)	12 (7.3)
Bleeding *N (%)*	9 (11.7)	6 (3.6)
Abscess or infection *N (%)*	26 (33.8)	15 (9.1)
Perforation *N (%)*	3 (3.9)	3 (1.8)
Ileus *N (%)*	10 (13.0)	7 (4.3)
Non-surgical complications (*n* = 66)		
Pneumonia *N (%)*	26 (39.4)	
Positive blood cultures *N (%)*	9 (13.6)	
Sepsis with infected central venous lines *N (%)*	9 (13.6)	
Wound infection *N (%)*	5 (7.6)	
Infected prosthesis	2 (3.0)	
Positive cultures for ascites *N (%)*	15 (22.7)	

%= percentage of total N =number

Linear mixed modeling showed that patients who developed a complication had an estimated 5.9 % lower preceding procalcitonin concentration compared to those without a complication (95 % CI: 15.7 % lower to 5.0 % higher; p = 0.27), adjusted for number of days stayed in ICU so far as categorical variable. The preceding change factor in PCT levels was 11.2 % larger (or a factor 1.112 higher) with a complication than without a complication (95 % CI: 4.4 % smaller to 29.3 % larger; p = 0.17). For the conditional logistic regression analysis 39 first complications with two valid consecutive preceding PCT-measurements were available. Because many plasma samples were lacking at the first ICU day, the cohort size at the second ICU day with two preceding valid PCT measurements was only 15 out of the total of 164 admitted patients. The effects of a higher

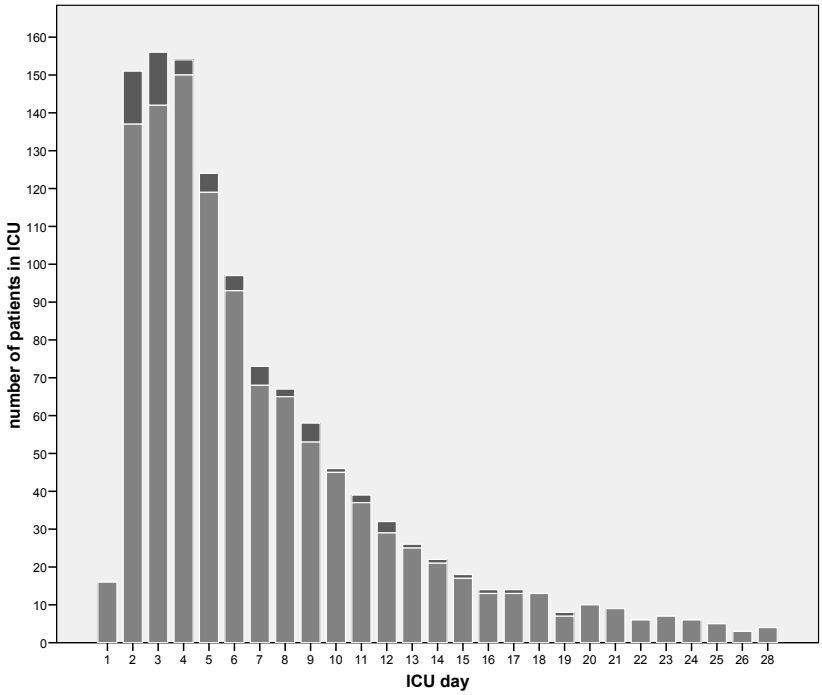

Figure 1. Number of patients in ICU with a valid PCT measurement by ICU day (lower stack = no surgical complication; upper stack = yes surgical complication; no valid PCT measurements at day 27)

PCT level and of a higher PCT change on the complication outcome are expressed by means of odds ratios. As the PCT levels enter the model after logarithmic transformation, higher PCT levels and changes have to be specified in a multiplicative way. For example, if before the complication PCT has increased by say 20 % (factor 1.2) and this change become twice as large, then the change factor becomes 1.2 x 2 = 2.4, an increase of 140 % in this example. Such a two times higher change factor in PCT concentrations resulted in a 1.21 times higher complication odds and was not significant ($p = 0.16$). The estimated effect of a twofold PCT level was a 1.17 times higher complication odds and was not significant either ($p = 0.078$). So, both these effects were small and also their simultaneous effect on complication was not significant ($p = 0.11$); see Table 4. These results were optimally adjusted for the possibly confounding day effect on the complication outcome.

Table 4. Results of conditional logistic regression analysis with complication at outcome

variable	estimated β- coefficient	p-value	estimated OR	95 % CI of OR	
PCT: twofold higher change factor	0.2775	0.16	1.21	0.93	1.58
PCT: twofold higher level	0.2206	0.078	1.17	0.98	1.38

The overall p-value of the fitted model is 0.11 (chi-squared = 4.423; df = 2).
Results of a conditional logistic regression analysis with complication as outcome, stratified by ICU-day at which the complication was observed. The estimated odds ratios (OR) for the twofold higher PCT level and change factor are calculated as 2^{β}.

DISCUSSION

Newer biomarkers are needed to improve prompt diagnosis of critically ill surgical patients in the intensive care unit. Procalcitonin seems a promising marker for the early diagnosis of infection and sepsis during the ICU stay and seems to be superior to C-reactive protein for this matter [1]. PCT is useful to identify those critically ill patients at risk for septic complications [1, 5-7, 13, 14]. We studied the clinical value of procalcitonin levels in recognizing surgical complications in a heterogeneous group of general surgical patients in the ICU. Despite the results of previous studies, our results showed that PCT does not help to predict surgical complications in a heterogeneous group of critically ill surgical patients during the ICU admission.

Previous studies showed that PCT levels only rise above the upper reference range of 0.5 ng/mL if a systemic host response to bacterial or fungal stimuli is present [13, 15]. PCT concentrations over 2ng/mL have been used as a cut-off point for generalized infection or localized infection (< 2ng/mL). In surgical patients, when this cut-off point was used to differentiate between a diagnostic or therapeutic approach in patients with multiple trauma or major abdominal surgery, adequate therapy for infections led to a reduction of SOFA scores, duration of stay in ICU and number of ventilated days [8].

Reports have also showed that PCT may help identify postoperative patients at risk for these septic complications. Following elective abdominal aortic surgery or elective colonic resection surgery concentrations of PCT were significantly elevated in patients suffering from pneumonia, ischemia and anastomotic leakage during the early postoperative period [6]. In another study, Di Fillipo et. al also found that PCT cut-off value levels of 1 ng/ml has a sensibility of 70% and a specificity of 81% in identifying those patients with postoperative infectious complications after major abdominal surgery [7]. Also, an increase in PCT levels over 3.9ng/mL 24 hours after orthotopic liver transplantation corresponded with a 16-fold increase in the risk for severe complications [9]. PCT levels can also reflect the effectiveness of the therapeutic surgical procedure to eliminate the septic intra-abdominal focus during the postoperative course [14, 16, 17]. A

decrease in 50-75% of baseline PCT levels on day 7 after surgery in patients with severe sepsis revealed a favorable outcome in terms of mortality with a positive predictive value and sensitivity of 75% and 97%, respectively [2].

On contrast to the favorable results of PCT as a reliable marker for septic complications, others have found that PCT is not as reliable in all clinical situations. A meta-analysis showed that PCT concentrations in critically ill patients may not differentiate between sepsis and other non-infectious causes of systemic inflammatory response syndrome [18]. Renal replacement therapy (RRT) as a surrogate for acute kidney injury is known to interfere with the diagnostic accuracy of PCT [19, 20]. Higher PCT concentrations are measured in patients with renal dysfunction [21]. Then again, PCT is cleared by different techniques of RRT [19]. However, patients needing RRT are often more critically ill with multi-organ failure. In our study we also included patients requiring RRT (33%) which might indicate why patients with low serum PCT levels still developed complications.

In this series, PCT levels peaked between the 2nd and 3rd postoperative day. This is in consistent with previous studies describing patients after abdominal surgery [6, 7, 11, 14]. As most events and complications in our patients' population were seen between postoperative day 2 and 4, we can concluded that the peak in the first days postoperative are not only due to surgical trauma. Others have also described PCT cut-off levels of 1.1-1.3ng/mL on postoperative day 1 or 2 as useful for the diagnostic accuracy of early postoperative septic complications [11, 22].

As our results indicate, increased PCT levels are also not always specific for surgical (septic) complications. Meisner et. al. described increased PCT concentrations as result to surgical trauma, mainly after intestinal surgery and major operations [5]. Specifically, increased PCT levels has been observed in patients without postoperative (septic) complications during the first week after gastro-intestinal surgery [5, 6, 23]. Other studies showed that PCT concentrations can also show falsely elevated levels in the absence of a bacterial infection in situations like mechanical major trauma or burns, following surgery, after therapeutic or diagnostic interventions, during circulatory failure or ARDS [5, 13, 24-28]. Furthermore, in patients with normal postoperative course the high PCT levels were not limited to the first three postoperative days, suggesting that other stimuli like transient bacterial contamination during operation or cytokines release during wound healing probably may also contribute to this increase [5, 29]. Although the elevation of PCT levels has been objected in these specific situations, its increase reaches up to 1.5-2ng/mL [24].

Our heterogeneous group of surgical patients in the ICU may be an explanation why we did not found a relationship between increased PCT levels and surgical complications. However we used a heterogeneous group to mimic general practice, standard care and decision making in the ICU with patient after different surgery type. Therefore,

we can conclude that PCT levels may not be used as overall biomarker to identify postoperative complications. Even reports on the use of PCT in homogeneous groups of patients after elective colorectal surgery showed that PCT may not always identify those at risk. PCT may not be more accurate than CRP in the diagnosis of anastomotic leakage after elective colorectal surgery [11, 30]. As the majority of our population admitted in the ICU was patients after abdominal operation and gastro-intestinal surgery, these data support our conclusion that PCT is not useful in the diagnosis of surgical complications in the critically ill postoperative patient. On the other hand, it is known that other stimuli can be responsible for increased PCT levels as well. Especially, in surgical patients in the ICU many complex stimuli may contribute to these increased levels. These patients in general are critically ill and many organ systems may be involved. Recently, we also concluded in a prior study that an increase in C-reactive protein is a poor parameter for early detection of surgical complications in the critically ill surgical patient in the ICU [31]. So both CRP and PCT are not specific parameters to be used in this population in the ICU to recognize those complications that need surgical treatment.

In conclusion, we agree with other authors that increased PCT levels postoperatively may help identify septic complications. However, PCT appears not to be suitable to identify surgical complications in a heterogeneous critically ill surgical population with very complex clinical situations. In addition we believe that this marker should not be used to diagnose surgical complications but more as a marker for overall septic/ infectious complications.

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CHAPTER 7

The evaluation of a prediction model for severe complications in surgical patients in the ICU based on the parameters CRP, lactate and SOFA score

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ABSTRACT

Introduction: Surgical procedures can lead to serious complications with increased morbidity and even mortality. When admitted to the intensive care unit (ICU), these surgical patients are prone to secondary complications. The purpose of this study was to develop risk stratification with three commonly used parameters for the predictions of surgical complications in the critically ill surgical patient on the ICU.

Methods: The relationship between daily measured Sequential Organ Failure Assessment Score (SOFA), C-reactive protein (CRP) concentrations, lactate levels and surgical complications in all surgical patients in the ICU were studied in a conditional logistic regression model.

Results: Linear mixed model analyses showed that only the change in log-transformed CRP was significantly associated with complications. The change factor in CRP immediately preceding an event with complication was 31 % lower ($p = 0.004$; 95 % CI: 46 % lower to 11 % lower) than that preceding an event without complication. The fitted conditional logistic regression model containing four independent variables was significant ($p = 0.014$). The only significant variable ($p = 0.011$) was the change in log CRP. However, the effect of this variable was negative in contrast to what was expected.

Conclusions: We conclude that the combination of three parameters (CRP, lactate and SOFA score) as risk stratification can not accurately predict surgical complications in surgical patients on the Intensive Care Unit.

INTRODUCTION

Surgical procedures can lead to serious complications with increased morbidity and even mortality. In severe cases surgical patients require treatment on the Intensive Care Unit (ICU). When admitted to the ICU, patients are prone to secondary complications. During ICU stay it is important to diagnose and treat postoperative complications early, because this may improve outcome[1].

As the early recognition of complications can be challenging, clinical studies on sensitive and specific markers or scoring systems are needed in order to help establish an early diagnosis and start adequate therapy. In daily practice, parameters such as C-reactive protein (CRP) and lactate or scoring systems like the Sequential Organ Failure Assessment Score (SOFA score) are used for clinical decision-making or diagnosing early deterioration in critically ill patients on the ICU [2-5]. On admission to the ICU, high levels of the parameter CRP have been associated with a negative outcome[4, 6-8]. Furthermore, an increase in CRP concentrations has been described as a crucial indicator for the diagnosis of postoperative complications in surgical patients[9-11]. Recently we reported that an increase in CRP is not correlated to the early detection of complications in the critically ill surgical patient in the ICU[12, 13].

A second parameter commonly used in the ICU for the evaluation of clinical deterioration of patients is lactate. Multiple studies evaluated the increase in lactate levels as a measure of severity of illness, response to therapy, and prognosis[5, 14-17]. Lactate has a clear association with the SOFA score[3, 5]. An increase in lactate concentrations corresponds with high SOFA scores.

In addition, in our ICU population we measured a significant positive relation between lactate concentrations, high SOFA scores and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores[13]. However, a positive correlation between lactate and the occurring of surgical complications could not be estimated in this study [13].

So, at the moment there are no sufficient studies on the utilization of these clinical parameters in relation to the recognition of severe complications during the ICU stay. Our previous research studies concluded that neither CRP nor lactate as individual were useful in the prediction of surgical complications[12, 13]. Hence, we wanted to evaluate the predictive value of the combination of the three most commonly used parameters (CRP, lactate and SOFA score) for the diagnosis of postoperative severe complications in critically ill surgical patients in the ICU.

METHODS

All general surgical patients admitted to the ICU of our hospital during the period of April 2010 to June 2012 were followed up to 28 days. Surgical critically ill patients included were those admitted into the ICU after emergency surgery, elective surgery or non-operative patients for observation after acute injury or trauma. For inclusion into the study, duration of stay of more than 3 days was required. If a patient had more than one ICU-episode, only the first episode was included in order to meet the independence assumption. All patients younger than 18 years at admission and cardiac surgery patients were excluded. The investigation was approved by the Institutional Review Board and the need for informed consent was waived.

Before enrollment patient characteristics, indication for admission and type of surgery prior to admission were collected. On admission the Acute Physiology and Chronic Health Evaluation II (APACHE II) was scored. Each day the Sequential Organ Failure Assessment Score (SOFA score) was calculated. Moreover, the CRP concentrations and lactate levels were measured routinely daily.

During the ICU stay all patients underwent standard protocol of care and adequate resuscitation therapy when needed. This protocol included routine laboratory tests on a daily basis, standard cultures twice a week, a plain chest X-ray every day, selective digestive decontamination (SDD) prophylaxis for ventilator-associated pneumonia and broad-spectrum antibiotics when an infection was diagnosed.

Diagnostic or therapeutic interventions performed in the critically ill surgical patients in order to find/treat a surgical complication were defined as events. Surgical complications were specified as those complications needing surgery as treatment. Interventions included in the analysis were CT-scan, ultrasonography, flexible endoscopy or (re-)operation[12, 13, 18]. The following complications were defined as surgical complications if found during the intervention, for example intra-abdominal abscess, anastomotic leakage, mesenterial ischemia, ileus, perforations or non-acute bleeding[12, 13].

The relationship between the occurrence of an event with or without a complication, and the change in CRP, lactate and SOFA-score was studied. Of these three variables the value observed at the very day of the event (and so immediately preceding it) was taken into account as well as the value observed at the previous day. This way we included the last observed changes in these variables before the event. To take the change in CRP, lactate and SOFA into account, only events that occurred from the second day of admission and later were included.

As a first step linear mixed modeling was used to get insight into statistical associations by analyzing the dependence of (change in) CRP, lactate or SOFA on ICU-day (maximally 28 categories) and on events (yes/no). The purpose was to estimate the mean

difference in (changes in) CRP, lactate or SOFA between an event (yes) or no event (no) across all days (maximum of 28 days) and across all patients in the remaining total ICU-cohort. This was estimated while correcting for the day-effect on (changes in) CRP, lactate or SOFA. The residual (co)variance structure in the linear mixed model was assumed to be first-order autoregressive. Similar analyses were performed in the subset of event-days in order to estimate the mean difference in (changes in) CRP, lactate or SOFA between yes-complication and no-complication across event-days, while correcting for the event-day-effect on (changes in) CRP, lactate or SOFA.

In terms of cause-effect we analyzed the predictability of an event (and subsequent complication) based on changes in CRP, lactate and SOFA score simultaneously. As event and complication rates as well as CRP, lactate and SOFA score appeared to depend on ICU-day, there was a confounding day-effect that had to be taken into account in these analyses. For this reason a conditional logistic regression model was used with the data stratified by event-day and with only taking the first occurring event within a patient.

For analyzing the probability of an event at a certain ICU-day the conditional logistic regression analysis was applied in a case-cohort setting. Each event-day represents a stratum. In each stratum the cohort is the remaining group of patients still in the ICU who were event-free before at the event-day considered. The cases are the patients with a first event at the event-day considered, a subset of this cohort. The conditional logistic regression analysis was performed across all event-days, with the data stratified by event-day. Only strata can be taken into account with the number of cases larger than zero and smaller than the size of the cohort from which the cases derived in the stratum considered.

When analyzing the probability of a complication at a certain event-day, the conditional logistic regression analysis was performed only in the group of patients having a first event with the data stratified by event-day again. What was considered the cohort in the event-analysis became the group of patients with a first event in the stratum considered. As for events, only strata can be taken into account with the number of complications larger than zero and smaller than the number of patients with a first event from which the complications derived in the stratum considered.

Explanatory variables in the conditional logistic regression analyses were the two consecutive measurements of CRP, lactate and SOFA-score just before the event. As two consecutive measurement of the same variable within a patient may be highly correlated, entering both these measurements simultaneously in the model as such would not be very informative about their effect on the outcome (event and complication). Therefore, instead of the two measurements as such, their orthogonal contrasts were used: their sum and their difference. These two contrasts are under certain conditions not correlated, and respectively stand for the effect of level and change of the

underlying explanatory variable on the outcome considered. By the conditioning on event-day, these effects were optimally adjusted for the confounding day-effect. The variables CRP and lactate were logarithmically transformed before analysis because of their positive skewness.

As in the conditional logistic regression analyses the effects of six independent variables on event and subsequent complication were to be simultaneously estimated, the number of events with as well as without a complication should not be much smaller than 60 following a well-known rule of thumb.

For the statistical analyses the statistical software packages SPSS (version 15) and EGRET (version 2.0.3) were used.

RESULTS

Two-hundred and twenty-eight different surgical patients (150 males) with a mean age of 70 (range 26-91) were included in the study. The mean length of stay was 8.48 days (range 3-28 days). Further patient characteristics are shown in Table 1. Distribution of the variables CRP, lactate and SOFA score are presented in the form of Box plots in the respective figures 1 to 3 by ICU-day. For the analysis, there were 1736 person-days of follow-up in the ICU. In this time-frame there were 167 events of which 94 complications observed in 106 patients with at least one event. The types of complication are listed in Table 2.

In the conditional logistic regression analyses with event or complication as dependent variable only a first event with two immediately preceding valid observations of CRP, lactate and SOFA-score as independent variables in a patient was included. This yielded 84 events of which 47 were complications with complete scores of the explanatory variables in a cohort of initially 162 patients. As in this analysis the data was stratified by day at which the event (or complication) occurred the results of the conditional logistic regression analyses are optimally corrected for a potentially confounding day-effect.

With event as outcome and with differences and sums of both measurements of SOFA, CRP (log-transformed) and lactate (log-transformed) as independent variables, the fitted total conditional logistic regression model containing six variables was not significant ($p = 0.671$), nor so was the effect of each variable in this model (Table 3). All six p-values exceeded 0.200. The estimated effects in terms of event odds ratios are very small. If a CRP change factor of e.g., 1.2 (or a 20 % CRP increase just before the event) becomes twice as large, then the change factor becomes $2 \times 1.2 = 2.4$ (or a 140 % increase just before the event). The resulting event odds ratio is estimated as only 1.055 (or 5.5% higher odds of an event). If the CRP-level becomes twice as large, then

the estimated odds ratio is 0.971 (or a 2.9 % lower odds of an event). A one point higher change in SOFA-score just before the event results in an estimated event odds ratio of 1.090. A SOFA-score increase by one point just before the event results in an estimated event odds ratio of 0.971. These far from significant results are adjusted for the other variables in the model and, because of the conditioning, optimally adjusted for day of the event.

Table 1. Patients characteristics (N= 228)

Age mean *(SD)*	70 (12)
Male *N (%)*	150 (65.8)
Length of Stay on ICU mean *(±SD)*	8 (6)
Apache II score mean *(±SD) at admission*	21,3 (8.1)
Indication for admission into ICU	
Standard postoperative care after elective major surgery *N (%)*	39 (17.1)
Postoperative SIRS/sepsis *N (%)*	102 (44.7)
Respiratory insufficiency *N (%)*	39 (17.1)
Vascular operation *N (%)*	6 (2.6)
Primary sepsis/ acute kidney injury/ Multi organ failure *N (%)*	27 (11.8)
Others *N (%)*	15 (6.6)
Indication for operation	
No operation *N (%)*	39 (17.1)
Elective colorectal operation *N (%)*	17 (7.5)
Ileus *N (%)*	11 (4.8)
Acute abdomen *N (%)*	43 (18.9)
Operation in epigastric region *N (%)*	8 (3.5)
Complication of prior operation *N (%)*	41 (18.0)
Embolectomy, bypass, amputation *N (%)*	10 (4.4)
Carotisendarteriectomy	1 (0.4)
Elective correction Aneurysm of the abdominal aorta *N (%)*	20 (8.8)
Rupture of Aneuryms of the abdominal aorta *N (%)*	19 (8.3)
Others *N (%)*	19 (8.3)
CVVH *N (%)*	70 (33,7)
Antibiotic therapy during ICU stay *N (%)*	209 (91.7)
Mortality *N (%)*	27 (11.8)

N = number SD = standard deviation ; % = percentage of total patients; SIRS = systemic inflammatory response syndrome; CVVH = coninouos veno-veneouos hemofiltration

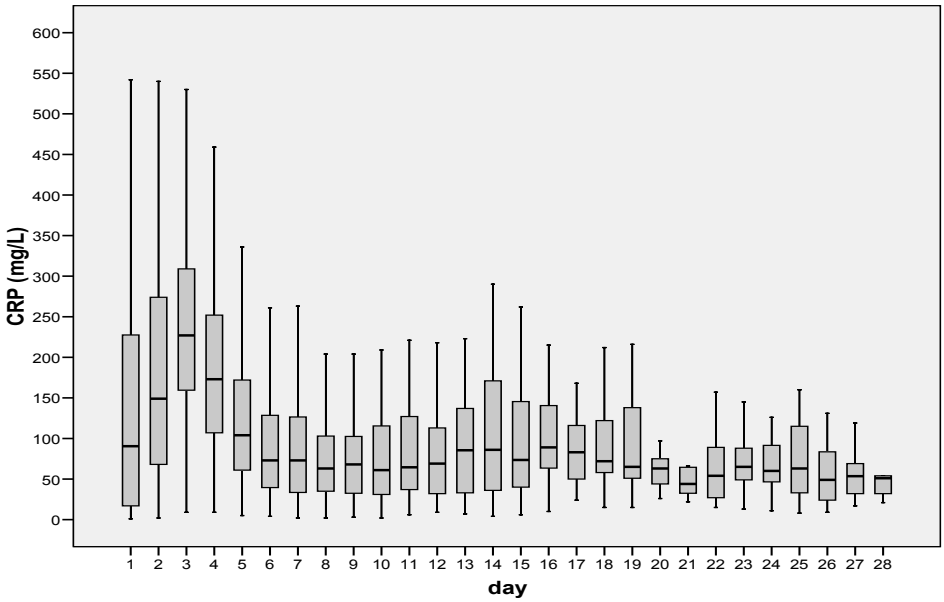

Figure 1. Summary statistics (Box plots) of CRP by ICU day
Distribution of the variables CRP presented in the form of Box by ICU-day

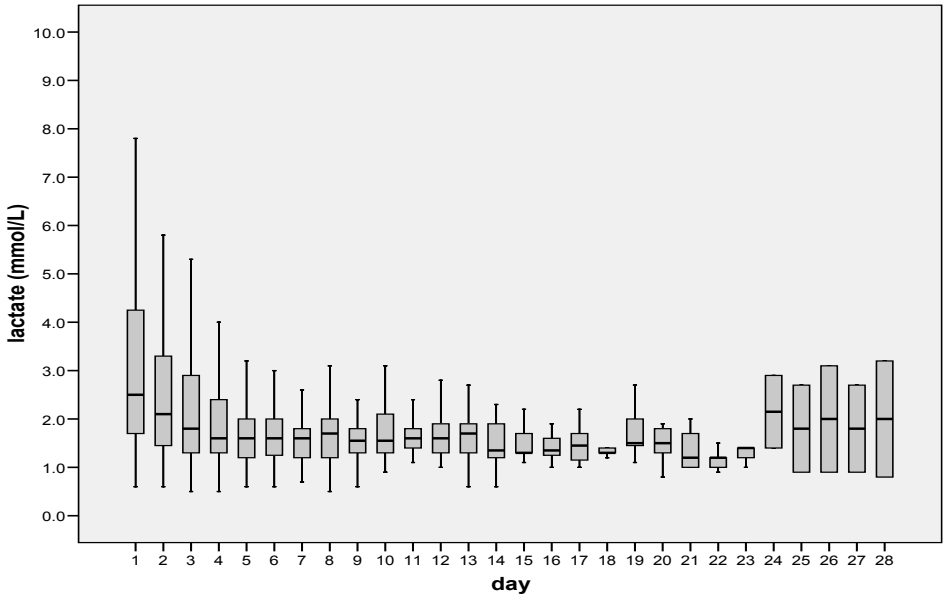

Figure 2. Summary statistics (Box plots) of lactate by ICU day
Distribution of the variables lactate presented in the form of Box plots by ICU-day

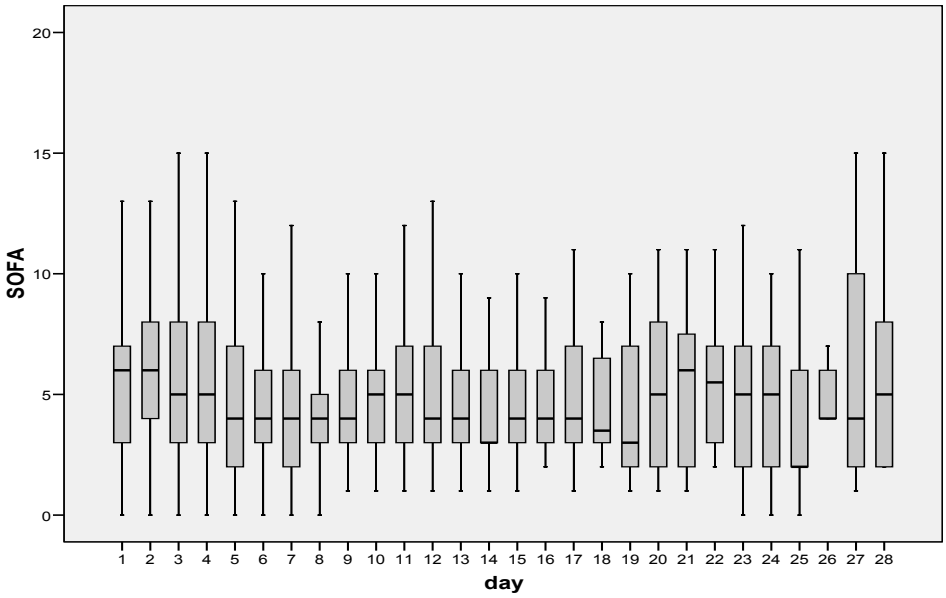

Figure 3. Summary statistics of SOFA score by ICU day
Distribution of the variables SOFA score presented in the form of Box plots by ICU-day

Table 2. Type of complication.

Complication	Frequency	Precentage
Anastomotic leakage	12	12.8
Ischemia	22	23.4
Bleeding	11	11.7
Abscess or infection	35	37.2
Perforation	3	3.2
Ileus	11	11.7
Total	94	100

Out of the 167 events a total of 94 complications were observed. This table describes the complication type.

Table 3. Results of a conditional logistic regression analysis with event or complication as outcome, stratified by day of the event.

variable	estimated β-coeff.	p-value	estimated OR	95 % CI of OR	
Event					
CRP: twofold increase of change factor	0.07791	0.63	1.055	0.848	1.313
CRP: twofold increase of level	-0.04236	0.78	0.971	0.791	1.191
Lactate: twofold increase of change factor	0.119	0.65	1.086	0.762	1.549
Lactate: twofold increase of level	0.2072	0.45	1.154	0.795	1.677
SOFA score change (1 point increase)	0.08605	0.20	1.090	0.956	1.243
SOFA score level (1 point increase)	-0.02986	0.55	0.971	0.881	1.070
Complication					
CRP: 20% increase of change factor	-0.7791	0.011	0.868	0.777	0.968
Lactate: 20% increase of change factor	-0.583	0.20	0.899	0.764	1.058
Lactate: 20% increase of level	0.7576	0.18	1.148	0.939	1.404
SOFA score level (1 point increase)	0.17556	0.11	0.839	0.675	1.043

The overall p-value of the fitted event model is 0.67 (chi-squared = 4.017; df = 6).
The overall p-value of the fitted complication model is 0.014 (chi-squared = 12.427; df = 4).

When we studied the relationship between variables and complications only 84 events were included. Forty-seven of these events were actual complications. Again the six independent variables are: the difference and sum of both measurements of SOFA, CRP (log-transformed) and lactate (log-transformed). However, the number of events involved here (especially the number of 84 – 47 = 37 non-complications) is smaller than anticipated when we established the number of ICU-episodes to be included. With this number of 37 patients without complications out of 84 events the subset of independent variables entering the conditional logistic regression model was restricted to a maximum of four out of the total of six. Using a forward stepwise selection process of independent variables entering the model, the eventually fitted conditional logistic regression model containing four variables was significant (p = 0.014). The only significant variable (p = 0.011) was the change in log CRP (Table 3). However, the effect of this variable was negative in contrast to what was expected. If a CRP change factor of e.g., 1.1 (or a 10 % CRP increase just before the event) becomes 1.2 times larger (or increases by 20 %), then the change factor becomes 1.1 × 1.2 = 1.32 (or a 32 % increase just before the event). The resulting event odds ratio is then estimated as 0.868 (or a 13.2 % lower odds of an event; 95 % CI: 22.3 % lower to 3.2 % lower). This significant result is adjusted for the other variables in the model and, because of the conditioning, optimally adjusted for day of the event. All four variables in the model have a p-value below 0.200.

Prior to the analyses above for predicting an event or a complication, linear mixed model analyses were performed in order to investigate how preceding (changes in) mean CRP, lactate or SOFA were associated with an event or with a complication across

the maximally 28 follow-up days, while adjusting for follow-up day as a categorical variable with 28 categories. Also in these inverse analyses allowing taking account of multiple events per patient the only significant effect found was that of complication on the change in log-transformed CRP. The change factor in CRP immediately preceding an event with complication was 31 % lower (p = 0.004; 95 % CI: 46 % lower to 11 % lower) than that preceding an event without complication. Also here the association was opposite to what was expected.

For a better understanding of this opposite effect of CRP we calculated for each event-day the preceding mean change in CRP (mg/L) in the group of patients with a complication at that day and in the group of patients with no complication at that day. It appeared that the main cause of the opposite effect is the mean CRP-increase just before the third ICU-day (with relatively many events) which is much higher in the no complication group than in the complication group of patients.

DISCUSSION

Our research model was an attempt to develop risk stratification with three commonly used (clinical) parameters for the prediction surgical complications in the critically ill surgical patient on the ICU. In our model the combination of CRP, lactate and SOFA score showed no statistical significant association with events and a theoretically implausible relationship with complications.

This finding is in contrast to what might be expected from literature. First we evaluated the usefulness of CRP in diagnosing surgical complications. CRP has been studied thoroughly in the diagnosis of anastomotic leakage after colorectal surgery. Intra-abdominal infections caused by an anastomotic leak after colorectal surgery were diagnosed when prolonged CRP concentrations over 125- 190 mg/L on the third postoperative day were observed [10, 11]. Many studies confirmed these findings and emphasize the use of an increase in CRP level in surgical patients with postoperative infectious complications compared to those without any complications[10, 11, 19-21]. Yet, not much is known about the clinical value of CRP in diagnosing overall complications in critically ill general surgical patients in the ICU. Many clinicians still rely on this marker to evaluate the clinical course of these patients. Recently our group concluded that an increase in C-reactive protein is a poor parameter for early detection of surgical complications in the critically ill surgical patient in the ICU[12] [12]. In this large study we did not find any statistical significant association from CRP with surgical patients either, confirming our prior results. There even appears to be an implausible inverse relationship between CRP and the occurrence of complications. If CRP decreases, we noticed

more complications. Maybe a decrease in CRP is a predictor for complications in the first few days of admission in the ICU.

Secondly, we added the SOFA score to our analysis as marker for deterioration of the patient during the ICU stay. The usefulness of the SOFA score in critically ill patient has been validated in large cohorts demonstrating its prediction for mortality and outcome[2, 22]. When using this score in clinical practice for diagnosing complications, we also focused on the extent of multiorgan dysfunction rather than the severity or type of complication itself as the presence or absence of this specific complication cannot always be specified.

The third parameter that we studied and added to our model was lactate. Lactate increases whenever the oxygen delivery is inadequate and therefore can be used as marker for clinical deterioration[23, 24]. In addition, lactate has been associated with a high sensitivity (90%) in diagnosing acute mesenteric ischemia in patients undergoing emergency laparotomy [25]. Jansen et. al. also showed that blood lactate measurement act as a real-time marker for the severity of organ failure [5]. We expected that lactate can be a useful marker in diagnosing clinical deterioration and therefore also complications. However our prior study on lactate also showed no relations between lactate levels and surgical complications in this population[13]. This regression model study confirm these findings and emphasizes that even in combination with CRP and/or SOFA score, lactate showed no prediction of surgical complications in the critically ill surgical patient.

This study showed a heterogeneous sample of currently admitted surgical patients into a tertiary heath care institute. The exclusion of surgical patients with short stay on the ICU may cause selection bias. However, as our objective for this study was to mimic the clinical practice on the ICU with those patients prone for complications, we could only included those with a long ICU stay of more than 3 days. Another limitation of this study is the bias due to exclusion of some complications during the analysis. This was due to lack of availability of all data on lactate or CRP during standardized ICU treatment management. Although standardized ICU managements with antibiotics protocols, the use of continuous veno-venous hemofiltration, ventilator managements and other resuscitation techniques may reverse or blunt clinical response, we believe that these data and patients sample illustrated our daily practice and may not have much influence on our results and overall conclusion. As we did not find any correlation between these parameters (CRP, lactate and SOFA score) or their combination and complications, we suggest that these should be used with caution when predicting surgical severe complications in surgical patients during the ICU stay.

CONCLUSIONS

We conclude that the combination of three parameters (CRP, lactate and SOFA score) as risk stratification can not accurately predict surgical complications in surgical patients on the Intensive Care Unit. Further analysis of newer biomarkers or their combination in predicting postoperative complications are needed.

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CHAPTER 8

Summary, general discussion and conclusions

In this thesis, **Biochemical markers in the surgical intensive care**, we studied the role of the biomarkers C-reactive protein (CRP), lactate and procalcitonin (PCT) in combination with a clinical scoring system, the Sequential Organ Failure Assessment score (SOFA), in relation to the occurrence of surgical complications in critically ill patients during admittance to the intensive care unit. Since these patients are vulnerable and prone to complications, including severe morbidity and even mortality, it is important to diagnose complications in an early stage. Early diagnosis leading to effective treatment may help in reducing mortality in these patients. Until now, the early diagnosis of surgical complications is an ongoing challenge and there is a continuing quest for a more reliable prognostic biomarker or clinical scoring system. The aim of this thesis was to contribute to this field of research by defining the value of markers and scoring systems that are currently used in clinical practice in a large non-university hospital.

Chapter 2 of this thesis presents a review of published data on the use of parameters including CRP, lactate, PCT as well as the SOFA score in relation to early diagnose of surgical complications in surgical patients in the intensive care unit. It is challenging to adequately discriminate those patients susceptible to surgical complications from those who will not develop these during an ICU stay. In clinical practice it can be even more difficult to determine whether or not a patient should undergo an intervention or a re-intervention for an assumed complication. Reoperations for suspected surgical complications increase the inflammatory host response even more and a negative laparotomy may hamper the recovery of a patient by further impairment of organ function. It is therefore important to discriminate those critically ill surgical patients who would benefit from a new surgical intervention from those who would not [51, 52]. Based on this review we conclude that there is a lack of well-designed studies that investigate the use of clinical parameters like the SOFA score and lactate for the prediction of postoperative complications in surgical patients during the ICU stay. The authors of the only well-conducted study we identified concluded that lactate seems to be a poor marker for the diagnosis of ischemic complications in surgical patients on the ICU [20]. As both CRP and PCT are being used to discriminate between those with and without bacterial infection or sepsis, numerous publications confirm the use of these markers for diagnosis of septic complications [18, 30-32, 38, 53]. However, both CRP and PCT may also increase during the early postoperative or post-traumatic period indicating inflammation, regardless of an early infection or developing sepsis [38, 54]. As a consequence, conflicting data on the clinical value of CRP and PCT have been published. We conclude that the use of C-reactive protein does not aid in deciding whether or not to perform a therapeutic intervention. Yet, procalcitonin may be a useful parameter for diagnosing postoperative septic complications until 5 days after general surgery with an estimated predictive area under de curve (AUC) of 0.749[53].

In chapter 3 we present three patients with non-traumatic acute abdominal pain and abnormally high C-reactive protein either with or without high lactate concentrations, who underwent a diagnostic laparotomy to explain the abdominal pain. Physicians in the emergency department commonly use increased biomarkers in combination with clinical symptoms as argument to consult a surgeon for a surgical procedure (e.g. laparoscopy or laparotomy). We could also translate these cases to the ICU and show a characteristic trend among physicians in the ICU in which they tend to use CRP and lactate as markers of an acute deterioration in the critically ill patient. Although using these parameters for an intervention during the "golden hour" in the emergency department is a plausible reason, in surgical patients on the ICU we observe an increase of unnecessary interventions in association with an increase in markers levels. A review of the literature helped to conclude that these parameters can often mislead physicians in the emergency department and contribute to more diagnostic examinations or unnecessary invasive interventions. This was also confirmed in the three cases described in this chapter. We advised to not exclusively use these markers during the decision-making for surgical procedures but to continue considering clinical expertise of the surgeon as it still may be of great importance.

Chapters 4, 5 and 6 describe the outcome of the main aim of our thesis, defining the clinical value of biochemical markers in identifying surgical complications in critically ill surgical patients during the intensive care stay. For this analysis, we prospectively included a heterogeneous group of general surgical patients admitted to a general intensive care unit. This group reflected daily practice, and all the decisions to perform interventions were based on clinical symptoms and changes in biomarkers.

We assessed the prognostic value of C-reactive concentrations as parameters for clinical deterioration and/ or clinical decision-making in chapter 4. Our data showed a significant positive relation between an increase in CRP concentrations and interventions (including management by antibiotics, drainage or surgical procedures). The outcome confirmed our assumption that clinicians often utilize this marker as a parameter for deterioration of the patients' clinical condition and that it triggers the physician to perform an intervention. However, our study showed no significant relation between increase in CRP levels and surgical complications. Various studies reported that persistent CRP increase and levels higher than 140mg/L on postoperative days 3 and 4 after open colorectal surgery were predictive of infectious postoperative complications (reaching sensitivity of 86% and 91%) [30-34, 55-59]. Two laparoscopic colorectal resection trials reported contradicting data. One study showed a low diagnostic accuracy of CRP in detecting anastomotic leakage [60]. The other study by Nason et. al. also showed an increase in CRP concentrations as part of surgical tissue injury, but the infectious complication group was distinguished by the magnitude of the CRP rise and sustained

high levels of CRP [61]. We concluded that although CRP is often regarded as an indicator of adverse postoperative course, including both surgical and non-surgical complications, it responds to infection as well as to inflammation. Therefore, the increase in CRP is unspecific and may be useless for differentiating between types of inflammatory or infectious complications. This explains why CRP should not be used as the only marker for clinical deterioration, as it may have a false negative prognostic value even when increased. Furthermore, it is important to realize that changes in CRP concentrations should not be interpreted independently of clinical data in clinical decision-making.

When the Sequential Organ Failure Assessment score (SOFA) was used to identify patients with clinical deterioration, no differences in SOFA score were observed between patients with and without complications. Even when CRP was adjusted for the SOFA score a significant relation was found with interventions, but none with surgical or infectious complications. Since combining CRP with the SOFA score did not improve its prognostic value, more reliable clinical scoring systems and markers are needed.

In chapter 5 we determined the use of lactate levels for selecting patients at risk for surgical complications during the ICU stay. Elevated lactate levels are associated with a high mortality rate and a high SOFA score [12, 26, 27, 62-64]. Once adequate therapy is implemented, lactate levels may decrease, which improves outcome [48, 65, 66]. Our data confirmed the positive correlation between increased SOFA scores and elevated lactate levels. Therefore, we concluded that a decline of organ function corresponds with an increase of lactate concentrations, indicating clinical deterioration of a critically ill patient. However, we also reported that lactate levels should not be used as a prognostic instrument for surgical complications in surgical patients during the ICU stay. In our study population, a value ≥ 2.5 mmol/L was not significantly related to more complications. We therefore suggested that it does not seem justifiable to use only lactate levels as the basis for decisions to perform diagnostic or therapeutic interventions. First, other causes should be explored to explain the hyperlactatemia besides sepsis including hypoperfusion, inadequate oxygenation and tissue oxygen deficiency. These other causes inducing hyperlactatemia are for example diabetic ketoacidosis, liver coma, renal failure, the use of specific medications (e.g. metformin or HAART), thiamine deficiency or acute pancreatitis. In addition, clinicians need to distinguish between the two different types of lactate, L-lactate and D-lactate. Both lactate forms are used in studies as markers for the diagnosis of mesenteric ischemia [23, 67]. However, the utility of L-lactate concentrations as a diagnostic aid for acute mesenteric ischemia is debatable, as it reflects a late stage of the disease [24, 67]. Furthermore, D-lactate has been proven to have a higher sensitivity and specificity in diagnosing acute mesenteric ischemia [20, 68]. Nevertheless, we can still utilize L-lactate in daily practice. The rapidity at which lactate is cleared from the blood during resuscitation also correlates with mortality and

organ failure [69, 70]. The blood clearance of lactate also has a significant association with improved microcirculatory flow [71]. Previous studies showed that the initial blood lactate level is significantly associated with postoperative complications and mortality [26, 62-64, 72]. Moreover, lactate levels and its clearance after elective abdominal surgery have an independent prognostic value for postoperative complications [73]. However, A recent study on elective abdominal surgical patients admitted into the ICU showed that lactate levels at admission had no prognostic value for postoperative complications [16]. Furthermore, the use of lactate concentrations as predictor for patient outcome is questionable because blood lactate levels may fluctuate during therapy [16, 74] and low cut-off values of lactate levels may also be associated with increased mortality in critically ill patients [64, 75]. Given that in critically ill patients the predictive performance of lactate is dependent on lag time and diagnosis at admittance, lactate may not be the suitable parameter for diagnosing complications. For this, we advise that lactate should not be used as a guide to perform diagnostic and or therapeutic interventions, but that its value may be helpful as an end-parameter of resuscitation [76]. The duration of hyperlactatemia is better suited for determining the reversibility of organ damage and patient outcome [16, 26, 62, 75]. A delay in starting adequate therapy will result in irreversible organ damage caused by hypoperfusion and oxygenation, even after normalization of lactate concentrations [16, 48, 75, 77].

A relatively new, promising indirect parameter for infection is procalcitonin, which has been correlated with the incidence of complications and survival of patients after elective aortic or elective colonic surgery. PCT concentrations were significantly higher in patients with complications than without infective complications, such as pneumonia, ischemia, anastomotic leakage, surgical site infection, sepsis or shock [18, 19, 45, 46, 78, 79]. The increase in procalcitonin concentrations is more accurate and more reliable than CRP in the early prediction of major infective complications after surgery [14, 53]. In chapter 6 we presented our data analysis on the use of PCT for the early detection of surgical complications. Despite the results of previous studies showing positive correlation between increase in PCT and complications, our results showed that PCT does not help to predict surgical complications in critically ill general surgical patients during the ICU admission. As our results indicate, increased PCT levels are also not specific for surgical (septic) complications. Some studies described increased PCT concentrations as a result of surgical trauma, mainly after intestinal surgery and major operations [14, 18, 54, 80]. Although the unspecific increase in PCT levels is lower and much shorter than the increase in CRP levels [38, 54], this increase results in the need to accept higher cut-off values for complications. The reference PCT values for the diagnosis of septic complications in surgical patients with sepsis must be much higher compared to non-surgical patients with sepsis (9.70 ng/mL, sensitivity of 92% and specificity of 74%) [81].

This higher reference value is necessary probably because of the initial increase in PCT levels as part of the physiological immune response to a previous surgical procedure. As a result, it is unreliable to use this parameter as a marker for postoperative complications in critically ill surgical patients. Moreover, recent reports on the use of PCT in homogeneous groups of patients after elective colorectal surgery showed that PCT may not always identify those at risk nor be more sensitive than CRP [15, 82]. We therefore concluded that PCT is not suitable for identifying surgical complications in a heterogeneous critically ill surgical population with very complex postoperative stay in the ICU. PCT levels may be considered as an additional maker next to careful clinical examination to improve the accuracy of identifying those surgical complications in the critically ill.

Finally, in chapter 7 we investigated a model using all biochemical markers to identify ICU patients with surgical complications. In this model we studied the combination of CRP, lactate and SOFA score, as these parameters are more commonly used in the ICU as part of daily practice as compared to PCT. Our regression model confirmed our earlier findings that none of these parameters are adequate for identifying those critically ill surgical patients at risk for complications. In addition, this model emphasized that even a combination of these commonly used markers (CRP, lactate and the SOFA score) will not help to predict surgical complications in a critically ill surgical patient.

In conclusion, we have not been able to identify that biomarker or clinical scoring system that can adequately discriminate critically ill surgical patients with surgical or infectious complications from those without complications. Importantly, we confirmed the hypothesis that clinicians are currently triggered to perform additional investigations when increased concentrations of markers as CRP and lactate are observed. As our data demonstrate physicians tend to responds to increase of current markers (CRP and lactate) leading to unnecessary diagnostic and therapeutic interventions. The patient may not benefit from these interventions and additional costs may have been saved if these interventions were not performed.

It must be noted that the outcome of this thesis accentuates the need for further research to find that marker or scoring system that can serve as a tool to detect patients at risk for early postoperative complications. Most importantly, such a test could aid in reducing morbidity and mortality during the ICU stay. Potential sensitive and valid biomarkers have been suggested and include, among others, TNF-α, IL-1 or IL-6 [78]. As these pro-inflammatory cytokines rapidly increase in response to bacterial lipopolysaccharide release, it must be determined whether they may be used in the diagnosis of early surgical complications. In particular, serum IL-6 has been correlated with the severity of injury, sepsis and multi-organ failure [83]. However, contradictive conclusions

have been drawn on the discriminative power of the serum IL-6 in patients with and without complicated postoperative course. In uncomplicated postoperative course, low IL-6 concentrations have been reported [84], but an increase in IL-6 concentrations was observed in patients following colorectal surgery or aortal surgery with postoperative complications [18]. Consequently, further research is needed to assess the value of IL-6 as a possible marker for the early identification of postsurgical complications.

The scope of our thesis was to define the role of biomarkers or scoring systems in surgical patients at risk for major complications; this means that our findings may not be generalized to specific surgical patient population in the ICU. A subgroup analyses and specific studies should be conducted to extrapolate these findings to a homogeneous surgical patient group. For instance, a recent study already showed that increase in CRP levels in patients following esophagectomy with gastric tube reconstruction was associated with the development of postoperative complications [85]. Furthermore, increase in PCT concentrations in these patients on the second postoperative day predicted respiratory complications on the third ICU day [45]. D-lactate, on the other hand, may identify those patients with mesenteric ischemia following repair of a ruptured abdominal aortic aneurysm [20]. Therefore, we suggest that additional research with subgroup analysis of colorectal patients during the ICU stay should be performed separately, since the admittance of these patients with accessory complications during the ICU stay is relatively high.

It should be realized that doctors are clearly triggered by the increased levels of commonly used biomarkers (CRP, lactate and PCT) to adapt patient's management and that a patient's treatment is partly a reaction to the increase of these parameters. However, we suggest to only use these markers as circumstantial evidence for disease and to weight their changes in relation to the medical history taking and clinical findings.

CONCLUSIONS

At present, clinical decisions are clearly triggered by commonly used parameters like C-reactive protein, lactate, procalcitonin and clinical scoring systems as the Sequential Organ Failure Assessment score. However, these markers are not useful as prognostic test to identify early surgical complications in critically ill surgical patients during the intensive care admission. An ongoing quest for new, more reliable clinical scoring systems and biomarkers is mandatory to improve the care for these critically ill patients.

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Chapter 9

Nederlandse samenvatting

Jaarlijks worden wereldwijd gemiddeld 230 miljoen operaties uitgevoerd, waarbij in Nederland 1,4 miljoen electieve operaties in het jaar 2012 [1, 2]. Geen enkele operatie is zonder risico's, maar gemiddeld hebben operaties een lage kans op complicaties [3, 4]. In Nederland wordt 7,7% van de patiënten na een chirurgische ingreep opgenomen op de intensive care (IC) [4]. De mortaliteit in de postoperatieve periode op de IC varieert tussen de 2% en de 29% afhankelijk van de subpopulatie [5-7]. Patiënten die tijdens deze opname een complicatie oplopen hebben een hogere kans op een fatale uitkomst binnen 30 dagen, namelijk 13,3% vergeleken met 0,8% in patiënten zonder complicaties [8]. Echter, de herkenning van patiënten met een verhoogd risico voor complicaties is niet simpel. Het is lastig om complicaties te diagnosticeren alleen gebaseerd op klinische symptomen (bijvoorbeeld hartfrequentie, ademhalingsfrequentie of koorts) en conventionele biomarkers zoals leukocyten of differentiële telling van witte bloedcellen [9, 10]. Hierdoor wordt dagelijks naast de kliniek en conventionele markers ook andere biomarkers, zoals lactaat en C-reactief proteïne (CRP) gebruikt [11-18].

Een van de meest gebruikte serum biomarkers is lactaat. Het is een bijproduct van het anaërobe metabolisme van glucose en is gerelateerd aan cellulaire hypoxie. Verhoogd lactaat concentraties wordt geassocieerd met sepsis, hypoperfusie en specifiek orgaanfalen zoals levercoma en renale insufficiëntie. In de praktijk wordt lactaat vaak gecorreleerd met de diagnose van mesenteriale ischemie, ondanks de matige betrouwbaarheid en bij gebrek aan beter [19, 20].

Een ander biomaker die zeer frequent in de dagelijkse praktijk gemeten wordt, is C-reactief proteïne (CRP). Het is een sensitieve, maar niet-specifieke acute fase eiwit dat gesynthetiseerd wordt in de lever. CRP concentraties is een slechte voorspeller voor survival, maar kan helpen in het identificeren van complicaties [21]. Tot op heden verschijnen meerdere studies die de associatie tussen CRP-stijging en infectieuze complicaties zoals naadlekkage na colorectale chirurgie bestuderen [22-26].

Een nieuwere interessante biomaker is procalcitonine (PCT). Deze wordt fysiologisch gesynthetiseerd in de C-cellen van de schildklier, maar in sepsis wordt het buiten de schildklier geproduceerd [18]. Plasma PCT zou nauwkeuriger het verschil tussen infectie en sepsis kunnen onderscheiden in kritiek zieke patiënten [9, 18, 27, 28]. Tevens is aangetoond dat PCT een nuttige diagnostische hulpmiddel is voor chirurgische condities zoals acute pancreatitis en secundaire peritonitis [29-31], darmobstructie [32, 33], wondinfectie na colorectale chirurgie [34] en postoperatieve complicaties na oesofageale ingrepen[35, 36].
Naast bovengenoemde biochemische markers, kan dagelijks de Sequential Organ Failure Assessment score (SOFA score) gebruikt worden om orgaanfalen aan te tonen. Een

stijgende SOFA score als teken voor de ernst van orgaan dysfuncties, wordt geassocieerd met hoge lactaat, CPR- en PCT-concentraties [37-39].

Het is onduidelijk wat de diagnostische waarde van de bovengenoemde markers zijn voor de identificatie van algmeen chirurgische complicaties in de kritiek zieke chirurgische patiënt op de IC. De gepubliceerde literatuur hierover geeft tevens tegenstrijdige conclusies. Echter, zowel intensivisten als chirurgen neigen hun behandeling aan te sturen met behulp van deze parameters. Dit leidt vaak tot onnodige diagnostische en therapeutische interventies.

In dit proefschrift, "Biomchemical markers in the surgical intensive care", hebben we de rol van de biomarkers C-reactieve proteïne (CRP), lactaat en Procalcitonine (PCT) en Sequential Organ Failure Assessment score (SOFA) bestudeerd om chirurgische complicaties te identificeren in kritiek zieke chirurgische patiënten tijdens de intensive care opname. Deze patiënten zijn kwetsbaarder voor complicaties, waardoor het belangrijk is om een complicaties in een vroeg stadium te herkennen. Vroegtijdige diagnosis zorgt voor snel starten van effectieve behandeling en reductie van mortaliteit.

Hoofdstuk 2 van dit proefschrift geeft een overzicht van alle gepubliceerde data over het gebruik van de parameters CRP, lactaat, PCT en de SOFA score om chirurgische complicaties te diagnosticeren in chirurgische patiënten op de IC. Helaas zijn er te weinig studies gepubliceerd betreffende de voorspellende waarde van lactaat en SOFA score in het vinden van postoperatieve complicaties in patiënten tijdens de IC opname. Wel zijn er verschillende studies bekend welke het gebruik van CRP en PCT bevestigd als markers om septische complicaties te diagnosticeren tijdens de IC verblijf [17, 22-24, 28, 40]. Echter, door de stijging van de plasma concentraties postoperatief of na trauma zonder infectie, zorgt dit voor tegenstijdige publicaties [28, 41]. We concluderen daarom dat CRP concentraties niet bijdragen in de beslissing om therapeutische interventies te verrichten. Aan de andere kant zou procalcitonine wel een bruikbare parameter kunnen zijn voor het diagnosticeren van septische complicaties tot 5 dagen postoperatief [40].

In hoofdstuk 3 presenteren we drie patiënten met niet-traumatische acute buikklachten met abnormaal hoge plasma CRP en/of lactaat concentraties welke een laparotomie hebben ondergaan. Zowel op de spoedeisende hulp (SEH) als op de IC worden soortgelijke casussen gezien waarbij chirurgisch handelen (bijvoorbeeld laparotomie) gewenst wordt. Analyse van gepubliceerde studies laat zien dat deze parameters vaak zorgen voor onnodige invasieve interventies op de SEH. De drie casussen beamen deze bevindingen. We adviseren daarom om de chirurgische expertise mee te laten wegen in be-

slissingen rondom soortgelijke patiëntenpopulatie en niet direct te varen op deze parameters.

De hoofdstukken 4, 5 en 6 beschrijven de voornaamste uitkomsten van dit proefschrift, waarbij de klinische voorspellende waarde van deze biomarkers in het identificeren van complicaties bij kritiek zieke chirurgische patiënten wordt onderzocht. Voor de analyses hebben we prospectief een heterogene groep chirurgische patiënten geïncludeerd welke opgenomen werd op de IC. Deze groep reflecteerde dagelijkse praktijk waarbij beslissingen voor interventies gebaseerd werd op klinische symptomen en concentraties van biomarkers.

De prognostische waarde van C-reactief proteïne concentraties als parameter voor klinische achteruitgang werd geanalyseerd in hoofdstuk 4. Onze data toont een significante correlatie tussen stijging van CRP en interventies. Dit bevestigd het vermoeden dat artsen vaak getriggerd worden door deze markers om interventies te verrichten. Toch wordt er geen relatie gevonden tussen stijging in CRP concentraties en chirurgische complicaties. Meerdere studies tonen een hoog voorspellende waarde voor infectieuze postoperatieve complicaties bij persisterend hoog CRP boven 140mg/L op postoperatief dag 3 en 4 na open colorectale chirurgie (sensitiviteit van 86% tot 91%) [22-26, 42-46]. Echter, er zijn andere studies die deze bevindingen niet kunnen reproduceren [47, 48]. We concluderen dat CRP een onspecifieke marker voor inflammatie en infectie is en vermeden moet worden als enige marker voor klinische achteruitgang.
De Sequential Organ Failure Assessment score (SOFA) aan de andere kant, laat ook geen correlatie zien met chirurgische complicaties.

In hoofdstuk 5 bepalen we of lactaat concentraties gebruikt kunnen worden om patiënten met verhoogd risico voor complicaties te herkennen. Het is bekend dat verhoogd lactaat concentraties geassocieerd is met hoge mortaliteit en hoge SOFA scores [11, 49-53]. Tevens, na het implementeren van adequaat therapie waarbij lactaat daalt, zal de outcome ook verbeteren [39, 54, 55]. Ondanks deze relatie, vinden we in onze studie geen plaats voor lactaat als prognostisch instrument voor chirurgische complicaties op de IC. We adviseren ook om andere oorzaken voor hyperlactatemie uit te sluiten anders dan hypoperfusie, inadequaat oxygenatie en weefselhypoxie. Andere oorzaken zijn bijvoorbeeld diabetische ketoacidose, leverfalen, renaal falen, medicatie gebruik (HAART of metformine), thiamine-deficiëntie of acute pancreatitis. Tevens moet een verschil gemaakt worden tussen de twee types lactaat, namelijk L-lactaat en D-lactaat. Ondanks dat beide markers in de praktijk gebruikt worden voor het diagnosticeren van mesenteriale ischemie, toch blijkt L-lactaat met name actief te zijn tijdens de late fase van het ziekte beloop [20, 56]. D-lactaat is juist sensitiever en specifieker in dit ziekte-

beeld [57, 58]. Desalniettemin, L-lactaat kan een plaats hebben in dagelijks praktijk gezien zowel de initiële concentratie als de klaring gecorreleerd zijn aan mortaliteit en orgaanfalen [50-53, 59-61]. Echter, recente studies over lactaat als voorspeller voor outcome hebben twijfels laten ontstaan doordat ze aangeven dat plasma lactaat waarden kunnen fluctueren gedurende ingestelde therapie [15, 62] en dat lagere afkapwaardes ook geassocieerd zijn met hoge mortaliteit [53, 63]. Gezien de voorspellende prestatie van lactaat afhankelijk is van inschakeltijd en opname diagnose, kan lactaat geen geschikte parameter zijn voor het identificeren van complicaties. Hierdoor adviseren we ook om lactaat alleen te gebruiken als parameter voor resuscitatie [64].

Een relatief nieuwe veelbelovende indirecte parameter voor infectie is procalcitonine (PCT). PCT concentraties zijn significant hoger in patiënten met infectieuze complicaties dan in patiënten zonder complicaties zoals pneumonie, ischemie, naadlekkage, wondinfectie, sepsis en shock [17, 18, 35, 36, 65, 66]. Het wordt beschreven als een betrouwbaarder marker dan CRP voor de vroege predictie van grote postoperatieve infectieuze complicaties [13, 40]. In hoofdstuk 6 presenteren we onze data analyse voor het gebruik van PCT om vroege chirurgische complicaties te diagnosticeren. Ondanks resultaten in eerder studies welke een positieve correlatie tussen PCT-stijging en complicaties toonden, konden we dit niet reproduceren in onze groep algemeen chirurgische patiënten op de IC. Zoals onze resultaten ook bewijzen, is PCT-stijging niet specifiek en kan ook door chirurgische trauma geïnduceerd zijn [13, 17, 41, 67]. Een mogelijkheid om dit te verhelpen is om hogere afkawaardes voor complicaties te gaan accepteren in chirurgische patiënten, zoals ook bij sepsis in deze patiëntencategorie [68]. Hogere afkapwaardes zijn nodig gezien de eerste stijging van PCT het gevolg is van fysiologische immuunrespons op de operatie. Bovendien, zelfs in homogene groep postoperatieve patiënten na electieve colorectale chirurgie is PCT niet sensitiever dan CRP om diegene met verhoogd risico te herkennen [14, 69]. We concluderen dat PCT geen geschikte marker is om chirurgische complicaties in een heterogene kritiek zieke postoperatieve groep patiënten op de IC te identificeren.

Tenslotte, in hoofdstuk 7 onderzoeken we een model waarbij alle biomarkers gebruikt worden om chirurgische complicaties te voorspellen. De meest dagelijks gebruikte markers CRP, lactaat en SOFA score worden geanalyseerd. Dit regressie model bevestigt onze eerdere bevindingen waarbij geen enkel parameter afzonderlijk adequaat blijkt te zijn om die kritiek zieke patiënt met verhoogd kans op complicaties te identificeren. Tevens benadrukt dit model dat zelfs bij een combinatie van parameters geen betere voorspellende waardes voor chirurgische complicaties worden bereikt.

Conclusies

Tot heden worden artsen duidelijk getriggerd door parameters zoals C-reactief proteine, lactaat, procalcitonine en het klinische scoringssysteem Sequential Organ Failure Assessment score. Echter, deze markers zijn niet geschikt als prognostische testen voor de vroegtijdige identificatie van chirurgische complicaties in kritiek zieke chirurgische patiënten tijdens de intensive care opname. Nieuwe betrouwbare klinische scoringssystemen of biomarkers zijn nodig om de behandeling van de kritiek zieke patiënt te bevorderen.

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APPENDIX

Dankwoord
Curriculum Vitae
Scientific Output

DANKWOORD

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CURRICULUM VITAE

Zainna Carolina Meyer was born on January 26th 1985 on the beautiful island of Curaçao. During her childhood she lived on the island where she attended primary school and high school.

After graduation from high school at the Radulphus College Curaçao in 2003, she moved to the Netherlands to continue her studies as a medical student at the Maastricht University, Faculty of Health Medicine and Life Sciences. Her first steps in scientific work were with dr. Sara-Joan Pinto-Sietsma of the department of internal medicine of Maastricht University Medical Centre (MUMC+) doing research on premature arteriosclerosis.

During her medical studies she developed an interest in surgery as she worked as a "kidney-racer" at the Department of organ donation and transplantation also at the MUMC+ (2004-2006). This resulted in an internship and research program at the department of surgery of this academic hospital (2008-2009).

After obtaining her medical degree in December 2009 she started working at the intensive care unit of the Sint Elisabeth hospital in Tilburg (till 2011). As her interest in the surgical field continue to increase, she applied for a residency at the surgical department of the Amphia Hospital Breda (2011-2012). She continued her scientific work with encouragement of dr. L. van der Laan and dr. J.M.J. Schreinemakers, which formed the basis for this PhD project under their supervision and that from prof. dr. J.N.M. IJzermans (Erasmus University, Rotterdam).

A short introduction to Anesthesiology resulted in a career change. In August 2012 she started her residency in Anesthesiology at Maastricht University Medical Centre+ (MUMC+) under supervision of dr. H.F. Gramke and dr. M.M.J. Snoeck.

SCIENTIFIC OUTPUT

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